Steffanie Strathdee

Hi, I'm Steffanie Strathdee, people call me Stef. I'm the Associate Dean of Global Health Sciences at the University of California San Diego and I now co-direct the new Center for Innovative Phage Applications and Therapeutics known as IPAT, that's the first phage therapy center in North America. But that's the end of the story, you wanna hear how I got there, right? Well it's a crazy story, people often don't even believe that it's true but it really is. My husband and I went on vacation in Egypt in the fall of 2015 and we're scientists, we travel together and we always do off the beaten path kinds of things. We had a dream of going to see King Tut's tomb and we floated down the Nile River in a wonderful ship.

So everything went great until the night before we were supposed to see King Tut's tomb and Tom and I had this wonderful meal on top of a cruise ship and he got violently ill afterwards, I mean he was throwing up all over the place. And I just thought he had a bad mussel or something like that but actually he got very sick, we had to call a doctor to the ship, the doctor said he's going into shock. There was no hospital in Luxor where the ship was docked so we ended up having to go to a community clinic. There they diagnosed him with pancreatitis which is essentially an inflammation of the pancreas but when I called back home to our colleagues who are leading the Department of Infectious Diseases at UC San Diego, they said, 'Hey, that's just a symptom of something else because you're the wine drinker in the family, Tom doesn't drink nearly as much as you and that's usually one of the causes of pancreatitis.' They said something else is going on.

And luckily we had travel insurance so we were able to get him medevaced to Frankfurt, Germany because he was too sick to be medevaced home. And there they did a CT scan and saw that he had a giant abscess in his abdomen the size of a football. And the doctors came to me and said, 'You know there's something lurking inside this abscess.' And they showed me this putrid flask of fluid that they'd taken from this abscess and they said, 'Something's growing in there and we've had to culture it, it's gonna take a couple of days but let's hope it's a garden variety microorganism because there's a lot of multidrug-resistant bacteria in Egypt.' Well I was getting a little bit worried but I thought hey, we have antibiotics, anything that's growing in there, we can handle it.

Well the doctors came back in a couple days and they showed me the name of this organism was Acinetobacter baumannii and it's something that I used to plate on my petri dishes back in the 1980s when I was taking a rusty old degree in microbiology at the University of Toronto. Again I really wasn't that worried but they said, 'Look, this is actually the worst bacteria on the planet.' I thought what? How can this be the worst bacteria on the planet because 20 years ago we just had to use goggles and a lab coat and that was it, it was not worrisome at all. Well turns out that the antimicrobial resistance crisis had crept up on us and Tom was essentially the poster child for this post-antibiotic era that we've entered now. So the doctors did what's called an antibiogram to find out the antibiotics that could be used to hopefully treat this thing and they came back and they were even more alarmed because it was only a couple of antibiotics that it was partially sensitive to and it was resistant to 15 right off the top.

Well I started to get worried now and this is right before Christmas of 2015. Luckily they stabilized him, got him sent back to San Diego where my colleagues in the Department of Medicine were looking after him and I thought oh okay, we're fine, we're home now, right. Everything's gonna be fine, we'll find some antibiotics to cocktail together to cure this thing. And they repeated the culture and they found out that now, even though only a few weeks had passed, this organism was resistant to all antibiotics, I mean even the last resort antibiotic colistin that was developed in WWII. Well they said, 'You know he's too weak for surgery, we have no choice but to use interventional radiology that essentially stick holes in his abdomen and put these catheters in there to try and drain out this infected fluid out of the abscess and hopefully it would shrink, and then he'd be better, right.'

	Well not so fast because even though he had started to improve, one day he sat up in bed and this tube inside his abdomen slipped and it just dumped all that infected fluid into his abdomen, into his bloodstream, and immediately he went into septic shock right in front of my eyes. And I'm telling you it was one of the scariest moments of my life. We were actually supposed to get discharged to an acute care facility the next day but that wasn't happening anytime fast. In fact he was rushed back to the ICU in the same hospital and put into an induced coma for a couple days to get his body to rest. And he did wake up from that but now this organism is now in his whole body, he was fully systemically infected. And from that moment on he was dying a little bit more each day and it was just horrible to watch. He lost 100 pounds off of his frame, he was in and out of a real coma that he wasn't waking up from.
	And one day I heard some colleagues on a conference call when I was trying to keep one tether back to the real world and they said, 'Does anybody realize, you know, has anybody told Stef that her husband is gonna die?' And I thought oh my god, nobody has. And I cradled the phone in my arms like a baby and I thought they just didn't wanna tell me and I'm gonna lose him unless I do something. So I had this conversation with Tom and asked him if he wanted to live and I didn't know if he could even hear me. But I said if you wanna live, please squeeze my hand and I'll leave no stone unturned. And he squeezed my hand. Now I mean I was thrilled but I thought what am I gonna do? I'm not a medical doctor, I don't know how to cure this thing. But I did what anybody would do in my shoes cause I'm a scientist, I went home and I hit PubMed, you know the Google Scholar for scientists that the National Library of Medicine has developed.
	And I found this ancient 100 year old therapy called phage therapy which are essentially these bacteria phages or viruses that have naturally evolved to attack bacteria. And I'd heard about them in ym microbiology classes way back in the 1980s but I never knew that they'd been used to treat bacterial infections. Well turned out that they had but they were considered experimental treatment in the west and they were only being used in the former Soviet Union and in parts of Eastern Europe. So I asked the colleagues that were treating Tom, I said can we use phage therapy to treat Tom? And the lead infectious disease doctor, Dr. Chip Schooley who's a close colleague of mine, he said, 'What an interesting and intriguing idea. If you could find phages that match to Tom's bacterial isolate, I'll call the FDA and request compassionate use permission for us to use phage therapy to cure him but I've never done this before and I don't know anybody who has. So it's a long shot.'
	Anyway, long story short, a global village of researchers from all over the world stepped up including researchers from Texas A&M University, San Diego State University, and even the US Navy chipped in and we found phages in the nick of time to match Tom's bacteria. And we injected them into his body a billion phages per dose every 2 hours. We didn't know if they were gonna kill him or cure him but 3 days later he lifted his head off the pillow and kissed his daughter's hand. And I'm telling you it was the happiest day of my life. So that's our crazy story, I left a lot of it out but it's in our book 'The Perfect Predator' if you wanna hear more details. You wanna say hi, Tom?
Thomas Patterson	Hi, Tom.
Steffanie Strathdee	(laughs) How are you feeling these days?
Thomas Patterson	I'm feeling great, can't complain. Well I could but nobody's gonna listen after I got saved like this.
Steffanie Strathdee	Well it's better than the alternative, right?
Thomas Patterson	You're damn right.

TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	That was amazing, thank you so much Steffanie, we really appreciate you taking the time to come on the podcast and share your story with us.
Erin Allmann Updyke	We really, really do. Oh man.
Erin Welsh	Yeah.
Erin Allmann Updyke	What a bonkers story.
Erin Welsh	I really, really, and we'll mention this again but I really really encourage everyone to go out there and read 'The Perfect Predator' which is the book that she wrote about this experience, it was unputdownable in that's a word. I couldn't put it down, how about that?
Erin Allmann Updyke	(laughs) I really hope that that's a word.
Erin Welsh	Yeah, I don't think it is. 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	So today we're talking about antibiotic resistance.
Erin Welsh	Yes. You thought you heard all that you wanted to know about antibiotics in the last episode?
Erin Allmann Updyke	No way.
Erin Welsh	Nope, not so fast.
Erin Allmann Updyke	Wrong. There's so much more.
Erin Welsh	There is so much more in the world of antibiotics to learn about, to read about, to hear about and that's what we're doing this episode.
Erin Allmann Updyke	We promise it's not all depressing. It's mostly depressing.
Erin Welsh	Yeah we're gonna end it on a hope for the future note I think.
Erin Allmann Updyke	Absolutely, yeah.
Erin Welsh	A couple of things. We completely forgot, Erin, in our excitement to do the episode last week to talk about why we were so excited beyond just the fact that it was antibiotics. It was our 50th regular season episode.
Erin Allmann Updyke	I totally forgot about that, oh my gosh.

Erin Welsh	I know.
Erin Allmann Updyke	I can't believe we made that many episodes.
Erin Welsh	I really can't. I remember going back to one of the earlier ones and I remember how we used to be like, 'Oh my gosh, Episode 7! Can you believe we've made it this far?'
Erin Allmann Updyke	(laughs) To be fair I was shocked that we made it to 7 episodes.
Erin Welsh	That's fair, that's fair.
Erin Allmann Updyke	It was a true sentiment at the time.
Erin Welsh	(laughs) The other thing is that I completely forgot to mention where the firsthand account came from in the antibiotics episode. And that was - it's like we're amateurs at this, on our 50th episode we failed to do the most important things.
Erin Allmann Updyke	Sometimes the days just get to you.
Erin Welsh	So the firsthand account from our last episode on antibiotics came from a book called 'The Youngest Science' by Lewis Thomas. Okay so Erin, to accompany our quarantini for the antibiotics episode which was Penicillin, the classic cocktail, what are we drinking this week?
Erin Allmann Updyke	This week we're drinking The Plasmid. If that's not funny to you now it will be funny as soon as I explain the biology of antibiotic resistance.
Erin Welsh	Exactly, exactly. They're like, 'Why are they laughing so hard?'
Erin Allmann Updyke	Erin, what's in The Plasmid?
Erin Welsh	Great question. It is mezcal, like a honey mint simple syrup, and lime juice. It's kind of like a Penicillin but it's a take on a Penicillin.
Erin Allmann Updyke	It's a plasmid of a penicillin.
Erin Welsh	Exactly.
Erin Allmann Updyke	That's not right.
Erin Welsh	It's a plasmid containing resistance to penicillin. We will post the recipe for the alcoholic quarantini and the nonalcoholic placeborita on our website thispodcastwillkillyou.com as well as all of our social media channels.
Erin Allmann Updyke	Any other business?
Erin Welsh	I don't think so. Let's get right to it.
Erin Allmann Updyke	I can't wait. We'll take one quick break first.

TPWKY	(transition theme)
Erin Allmann Updyke	Antibiotic resistance. Okay. It's a big topic so we're gonna break it down. Here's how. Flirts of all hopefully everyone's listened to the antibiotics episode so you have a framework for how antibiotics work. As a very brief overview, antibiotics are designed to either kill or halt the growth of bacteria and they do so by targeting various elements of bacterial cell walls, protein synthesis, DNA replication, or metabolism. That's our whole episode in 10 seconds.
Erin Welsh	Well that's a lot shorter than what the episode actually turned out to be, Erin.
Erin Allmann Updyke	Okay so the question first on a basic level is what are the mechanisms of antibiotic resistance? How do bacteria actually resist these antibiotics?
Erin Welsh	Just sheer force of will.
Erin Allmann Updyke	That's the answer, episode over. Once we understand that, then we can ask two bigger picture questions: what drives antibiotic resistance and how does this resistance spread through populations? Okay. Are you excited?
Erin Welsh	I'm super excited.
Erin Allmann Updyke	All right so what are the mechanisms of resistance? First of all you can have intrinsic resistance and you can have acquired resistance, 'you' being bacteria.
Erin Welsh	Right. I'm a bacterial cell.
Erin Allmann Updyke	You're a bacterial cell.
Erin Welsh	Okay.
Erin Allmann Updyke	So very broadly, intrinsic resistance makes a lot of sense in the context that a lot of our antibiotics come from bacterial products, right. So it makes sense that a streptomyces bacteria for example will be naturally resistant to streptomycin.
Erin Welsh	That makes sense, yeah.
Erin Allmann Updyke	So that is intrinsic resistance which is neither the interesting nor the concerning part of antibiotic resistance, so that's all we'll say about it. What is both interesting and concerning is acquired resistance. And there are a few big categories of mechanisms by which bacteria can evade the effects of antibiotics. Let's go through them. Number one, bacteria can resist antibiotics by changing the target enzymes. So what does that mean? For drugs like quinolones that we talked about, fluoroquinolones, or rifampin or the sulfonamides, these are drugs that bind directly to certain enzymes, DNA gyrase or RNA polymerase. So if bacteria modify these enzymes slightly, change their structure just a little bit, then these antibiotic compounds are no longer able to bind to them. Boom, they don't work.
Erin Welsh	Makes sense. And that seems like a relatively easy or like a relatively simple mutation would be necessary, like one little quirk.

Erin Allmann Updyke	Exactly, one little quirk. For sure. Another way that's actually very similar, in the case of the classes of antibiotics that work by binding to ribosomes instead of enzymes, if bacteria evolve mutations to their ribosomes such that antibiotics can no longer bind, then again boom, resistance. That's pretty straightforward, right?
Erin Welsh	Yeah.
Erin Allmann Updyke	Okay, so we can alter our enzymes that the antibiotics bind to or we can alter the proteins such as ribosomes that antibiotics bind to. All right, two other ways that are also related. Remember that gram-negative bacteria especially have a second membrane that surrounds the outside of their cell wall.
Erin Welsh	Right.
Erin Allmann Updyke	And this membrane is less permeable than the cell wall is, so we know that gram-negative bacteria are already harder to target with antibiotics because of that. So for gram-negative bacteria, the way that antibiotics enter the cells is through pores, porins, channels in the membrane. Well if antibiotics can only enter certain porins and bacteria then evolve changes either to the type of porins or sometimes just to the number of pores on their surface, that can make them more resistant to certain classes of antibiotics.
Erin Welsh	Makes sense.
Erin Allmann Updyke	Makes sense, right? Basically just changing the way that antibiotics are able to get into the cell, making it harder for antibiotics to get in. Another similar mechanism is you could kick antibiotics out at a faster rate. So these are called efflux pumps.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah. Bacteria have efflux pumps because especially gram-negative bacteria that have two layers of membrane plus a cell wall, they have to be able to get stuff in and out of their cells. So efflux pumps are a way that they can shuttle molecules outside of their cells. And it turns out that genes for these types of efflux pumps aren't turned on all of the time because they can be quite costly, they can lead to bacteria exporting too much stuff and that can change the membrane potential of their cells and ultimately lead to cell death.
Erin Welsh	Oh okay, that's interesting. That makes sense too, I like that though.
Erin Allmann Updyke	Yeah. But in the face of antibiotics, if you can upregulate those efflux pumps then you can ship the antibiotic molecules out of the cell before they have time to kill you.
Erin Welsh	Right. So it's worth it even though it's costly, it's worth it in the face of something that is actually going to kill you.
Erin Allmann Updyke	That's like antibiotic resistance in a nutshell. It's worth it if the antibiotic is going to kill you.
Erin Welsh	Yeah. I mean that's evolution in a nutshell.
Erin Allmann Updyke	Yes, 100%. Okay so those are the two other ways, you can change your efflux pumps and you can change your porins, right, make it harder for antibiotics to get in or export them out even faster. And then the last way that you can evade antibiotics is by changing the antibiotics themselves. This is my personal favorite mechanism.

Erin Welsh	Ooh.
Erin Allmann Updyke	Right? So bacteria can evolve ways to alter the antibiotic compounds themselves and render them useless. So for this I'm gonna actually go through a couple of examples. There's a lot of different ways that bacteria can do this, so we'll go through two examples of it. The first are aminoglycosides which you might remember from our last episode, these are streptomycin, tobramycin. These act on bacterial protein synthesis, they bind to ribosomes, okay. So bacteria can produce enzymes, naturally produce enzymes that bind to these antibiotics and add stuff to them whether it's a phosphate or just a little carbon group. And that changes the structure of the aminoglycoside itself so that it no longer works, it basically inactivates it.
Erin Welsh	That seems like much trickier to pull off.
Erin Allmann Updyke	Maybe but they do it really well.
Erin Welsh	It's really cool.
Erin Allmann Updyke	All right. The other most famous example of this are of course the beta lactamases. Have you heard of this?
Erin Welsh	Yes, they're enzymes that actually break down the beta lactam ring, right?
Erin Allmann Updyke	Yes! And the beta lactam ring is how beta lactam antibiotics like penicillin and cephalosporin actually work. So many bacteria especially gram-positives produce these enzymes called beta-lactamases that bind to and inactivate that beta lactam ring. It is so common, like beta-lactamases are so common and ubiquitous that we actually have a whole other set of drugs that we call beta-lactamase inhibitors. And these drugs inhibit or reduce the activity of those enzymes so it's actually really common that when we give a beta lactam antibiotic like amoxicillin, we give it in combination with a beta-lactamase inhibitor like clavulanic acid. That combination is called Augmentin.
Erin Welsh	It's sort of like the lactamase inhibitors hold back the little guards and they're like, 'No, no, you can invade the castle!'
Erin Allmann Updyke	Okay so there's a series of videos that any med student listening is gonna laugh really hard at that because we watch these videos called Sketchy Micro and they show beta lactams are these rings and then the beta-lactamases are these little laser shooters that shoot away the beta lactams and then you have the clavulanic acid that has armor that comes in. Anyways.
Erin Welsh	(laughs) I like it, I like it.
Erin Allmann Updyke	It's really great.
Erin Welsh	I mean it's very easy to envision all of these as little cartoons for sure.
Erin Allmann Updyke	Yes. And they help you learn it a lot easier. Yeah so it's very cool. We've known that beta-lactamases exist for so long that we already have drugs that specifically target those. But what's scary is that now many bacteria are what we call extended spectrum beta-lactamase producers. So they are making even stronger beta-lactamases that can break even more of our drugs essentially.

Erin Welsh	Yeah I mean that's sort of the theme, like this is the same story over and over again with just tiny variations.
Erin Allmann Updyke	Exactly. So then that kind of gets to the next question which is what actually drives this resistance? Why is it that we have resistance cropping up again and again? And we've kind of already touched on it but the basic answer is mutation and selection.
Erin Welsh	Right, it's a numbers game.
Erin Allmann Updyke	Yeah. So for resistance to happen, first a gene for that resistance, any one of those types of resistance that I already mentioned, a gene for that has to appear in the population. And often this happens by random mutation which seems like it should be very unlikely, right?
Erin Welsh	Well given the generation times and how many generations even within a year or something a strain of E. coli will have, it becomes surprising that there's not resistance rather than surprising that there is.
Erin Allmann Updyke	Would you like to put some hard numbers on that, Erin?
Erin Welsh	You know that I would, Erin.
Erin Allmann Updyke	So mutations like this that can provide resistance occur about once every 10 million cells. And because many bacterial species divide so frequently, like once every half an hour, it would only take 6 hours to get to 10 million cells.
Erin Welsh	(laughs) And all it takes is one.
Erin Allmann Updyke	All it takes is one. Okay? Okay so that's the first step, right, mutation. You have to mutate your DNA in such a way that you produce one of those changes. And then the second thing that has to happen is selection pressure which essentially means you have to wipe out most but not all of the bacteria in a population. So let's put some numbers on this again. Let's say you have 10,000 bacteria living in a wound on your hand. If you killed 9000 of those bacteria by any means, antibiotics or otherwise, you have selected 1000 survivors. Those 1000 survivors will go on to reproduce and oftentimes those 1000 survivors aren't representative of that whole 10,000 group of bacteria, right. They all have their own little mutations that are slightly different. But those are the ones that are going to go on and reproduce. So if any of those 1000 had the ability to resist and antibiotic, those are going to be the ones that now grow and proliferate.
Erin Welsh	Right.
Erin Allmann Updyke	Okay? Because remember like I mentioned especially with efflux pumps but this is true for many of those other mechanisms of resistance, a lot of the genes that confer resistance to antibiotics are not useful and in some cases they're harmful in the absence on antibiotics.
Erin Welsh	Right. So you can see over time if you don't put any selection pressure on a bacterial strain as they replicate and replicate and replicate, then the resistance genes might drop out cause it's more costly to maintain.
Erin Allmann Updyke	Exactly, right. Okay so then how does this gene that's present in let's say a couple of those 1000 bacteria that are left, how does it spread through a population? Because we see antibiotic resistance growing at very rapid rates, right.

Erin Welsh	Right.
Erin Allmann Updyke	So to understand this we basically just have to know that bacteria don't just reproduce by fission, right. That's how they mainly reproduce but they also can transfer genetic material between cells, okay. I just get so excited about this.
Erin Welsh	I think we talked about this in E. coli right with Joshua Lederberg who discovered this?
Erin Allmann Updyke	I think so.
Erin Welsh	Yeah.
Erin Allmann Updyke	So there are three ways that bacteria can introduce some variety into their genes besides just mutation: conjugation, transformation, and transduction. Conjugation is kind of like bacterial sex. So basically two bacteria get together, they pull out their pilus, and then they attach their pilus to their partner's pilus and then they can share plasmids. Plasmids are circles of DNA, just little round nuggets, pieces of DNA, and they can transfer them. So they can hand a plasmid to their partner and they can grab a plasmid from their partner and sometimes, oftentimes, those little plasmids have super useful things on them like a better efflux pump or a new types of beta-lactamase for example. Okay. That's conjugation.
	Transformation is when bacteria pick up DNA from the environment, so if their neighbor dies and explodes and leaves a bunch of DNA floating around, another bacterium can swim by and pick some of that up. And finally transduction is when viruses get involved. So bacteriophage which are viruses that infect bacteria okay, these are important, these bacteriophages have to use host cell machinery in order to reproduce. So what they do is they inject their DNA into a bacterium and then some of that DNA can get incorporated into the bacterial DNA. So then every time a virus picks up and infects a new bacterium, they might transfer a little bit of that bacterial DNA to a neighboring cell.
Erin Welsh	That is super cool. Also we forgot to mention this early on but you will hear a lot more about phages and their potential role as treatment for antibiotic resistance infections later on in the episode from Steffanie as well.
Erin Allmann Updyke	Oh yeah, big time. Big time, big time. So I mean that's pretty much how resistance works, okay. So if we go back to that population of 10,000 bacteria that lives in your festering hand wound, okay, just to kind of sum all this up. Actually let's call it 10 million bacteria.
Erin Welsh	Okay, now my hand wound is really, really just oozing with bacteria.
Erin Allmann Updyke	It's pus-y. Yeah, okay. So you've cut yourself, now you have 10 million bacteria in the cut on your hand and one of them happens to be resistant to penicillin and that's when you went to the doctor and that's what they're gonna use to treat your hand infection, okay. So you take the penicillin and it wipes out all but one of those bacteria, right. You have just one lone bacterium left. That's not a problem for your hand wound necessarily but that single bacterium is going to continue to multiply and multiply. And now inevitably your hand is exposed to tons of other bacteria all the time, right, everything you touch is covered in bacteria.

	So eventually that one bacterium that was left and now reproducing, that colony that's growing, is going to come into contact with some new bacteria. And he'll probably go, 'Hey, just so you guys know, if you're planning on making a home here, all my friends just got wiped out by penicillin recently and I have this little plasmid, it seems really helpful, like I survived. So do you want this? It's just a little beta-lactamase. Do you want one?' And all of the new bacteria are gonna be like, 'Yeah! Heck yeah, gimme one of those.' So they'll get together, conjugate, and share that plasmid with their friends. Et voila, antibiotic resistance.
Erin Welsh	I feel like we have this idea of an antibiotic resistant bacteria to be completely bulletproof basically. But your body can still fight off that infection.
Erin Allmann Updyke	Oh for sure, yeah. For sure, for sure. The other thing too though is that many of these antibiotic resistance genes come from environmental bacteria. So they don't necessarily have to originate by mutation in that one bacterium that was left behind, they could have been introduced from outside populations to begin with and then they can spread because of selection pressures.
Erin Welsh	Oh yeah, and I'll talk about some of those sources of resistance.
Erin Allmann Updyke	Excellent. I can't wait. So yeah, that was a lot but that was antibiotic resistance in a nutshell.
Erin Welsh	I loved it. I loved it.
Erin Allmann Updyke	Oh good, I'm so glad. So Erin, how the heck did we get here?
Erin Welsh	I can't wait to tell you.
Erin Allmann Updyke	Should we take a quick break first?
Erin Welsh	Let's do that.
TPWKY	(transition theme)
Erin Welsh	So Erin, you might think that this story, the story of antibiotic resistance, maybe it starts with the first sulfonamide or penicillin-resistant strains of bacteria that were found in hospitals in the 1940s.
Erin Allmann Updyke	Are you gonna tell me it's way further back than that?
Erin Welsh	Oh way, way, way further back, like millennia, millions of years even.
Erin Allmann Updyke	Erin.
Erin Welsh	Okay, okay. So even today like you said many of the antibiotics that we use are compounds produced by microbes, fungi or other bacterial species. And in the early years of antibiotics they were all like that, like synthetic antibiotics really only started to become developed in the past few decades. And so I think it's easy to take it for granted sometimes that these antibiotic compounds are just produced by these soil microbes or fungi and not question why exactly they might have evolved to produce substances that can kill bacteria. Because like you said, when you're producing something like that it can be a costly thing, like it can be a costly thing to kind of go above and beyond just simply replicating yourself and getting food.

Erin Allmann Updyke	I feel like we talk a lot about this in our plant crossover episodes with Matt.
Erin Welsh	Yes.
Erin Allmann Updyke	It takes a lot for plants to make these compounds that kill us, it takes a lot for bacteria to make these compounds that kill other bacteria.
Erin Welsh	Yep. It was just like that with the botulism episode, like why does this toxin exist?
Erin Allmann Updyke	Yeah.
Erin Welsh	So why do these compounds exist in nature? They didn't just arise in the 1940s with penicillin, like they've been there for millions of years. Okay so what do these compounds do in nature?
Erin Allmann Updyke	Yeah.
Erin Welsh	So let's just think about a little hand full of soil.
Erin Allmann Updyke	Okay.
Erin Welsh	You go outside and you grab some soil.
Erin Allmann Updyke	Okay.
Erin Welsh	In that soil you have this beautiful, complex, rich world of microbes even though it looks just like a handful of soil it's really teeming with microbial life.
Erin Allmann Updyke	Wow.
Erin Welsh	And each one of these microbes are all pushing and pulling and fighting for space and basically doing what it takes to continue on to the next generation. This is a battle that has been going on for millions of years and over that time some microbes have evolved strategies to help them stay one step ahead of the race, to gain just a little more ground. And antibiotic is one example of this type of strategy. In nature these antimicrobial compounds actually help the bacteria or fungi that produce them in any number of ways like to make super durable biofilms or to more easily invade an animal cell, type 3 secretion system, or to clear the competition in a particular area or to also better work alongside another group of bacteria. So they actually can help some groups of bacteria. And it's also important to remember that in nature the amount of antibiotic compounds produced by some of these bacteria or fungi, especially those that make something like tetracycline for example, is super small. Like nowhere near what a therapeutic dose would be for humans.
Erin Allmann Updyke	That is really important to keep in mind, yeah. Wow.
Erin Welsh	Really important.
Erin Allmann Updyke	Yeah.

Erin Welsh	And so when we make antibiotics in a lab or in an industry setting, you are farming penicillin, like you are farming the fungi, the bacteria, you're making gobs and gobs and gobs of it which wouldn't happen in nature.
Erin Allmann Updyke	IRL, yeah.
Erin Welsh	Yeah. Or IRL. (laughs) okay so yeah, make a mental note of that.
Erin Allmann Updyke	Okay.
Erin Welsh	So even though we may tend to think of these antibiotic compounds as these brute force drugs that punch holes in cell walls or tear apart ribosomes, their role in nature is much more nuanced and much more longstanding. So it makes sense then that if these microbes have evolved the ability to produce antibiotic compounds over thousands or millions of years, the bacteria that they are targeting with those antibiotics have also evolved a trick or two: resistance genes.
Erin Allmann Updyke	Yeah.
Erin Welsh	And this isn't a guess, this isn't just the logical flow, antibiotic resistance is ancient which is actually the word for word title of a paper that I read. Peer-reviewed paper. And in this paper they analyzed 30,000 year old permafrost sediment to look for genetic traces of antibiotic resistance. And guess what they found? They found genes that gave resistance to beta lactams, tetracycline, glycopeptides, even vancomycin antibiotics.
Erin Allmann Updyke	Yeah, wow.
Erin Welsh	So at least roughly 29,030 years before penicillin was discovered these resistance genes existed.
Erin Allmann Updyke	Just 29,000 years, no big deal.
Erin Welsh	Well I think that this at least helps to a small degree in understanding just how quickly some of these resistance genes have popped up.
Erin Allmann Updyke	Yeah.
Erin Welsh	Because like you said, some have arisen just through mutation, so some you could start in the lab or on a human body and start with a colony of a particular type of bacteria and then you could evolve resistance just by applying that selection pressure. But I think it's also important to remember that some of these mutations, maybe the ones that are a little bit more complex, some of the genes that provide resistance to more complex antibiotic structures, they might have roots already just in nature.
Erin Allmann Updyke	Right and many, many bacteria already have these genes, they might just not be turned on until they face the selection pressure.
Erin Welsh	Right.
Erin Allmann Updyke	So that's the other thing is they might be there, they're just not using them yet.

Erin Welsh	Right, exactly. You know what's funny, Erin? You say 'exactly, right' and I say 'right, exactly'. I've noticed this when I'm editing. (laughs) Its very funny to me. Okay, now I'm gonna be self-conscious about it. okay. All right so now we have a little bit better idea of the ancient roots of some of these resistance genes but how do they spread so far and so wide, so quickly?
Erin Allmann Updyke	Yeah.
Erin Welsh	and you talked about the mechanisms of this, so like the transfer of genetic material through all these different strategies but humans have been a huge helping hand in the geographic spread of this.
Erin Allmann Updyke	Oh for sure. Bacteria can only move so far, Erin.
Erin Welsh	It's true, it's very true. Okay so Erin, you asked how did we get here?
Erin Allmann Updyke	Yeah.
Erin Welsh	Like you always do.
Erin Allmann Updyke	I always do.
Erin Welsh	And I think that's really the perfect question to ask about antibiotic resistance because only by understanding what has driven the rise of resistance are we going to be able to have a chance of slowing it or stopping it. And you're gonna talk a little bit about what 'here' actually looks like in terms of how did we get here.
Erin Allmann Updyke	Right.
Erin Welsh	But spoiler alert, it is absolutely terrifying.
Erin Allmann Updyke	Yeah, it's not great. That's an understatement.
Erin Welsh	It's an understatement, yeah. So we see widespread multidrug-resistant bacterial species across the world and for many microbes our options have completely run out, like we are back in the age of before antibiotics. So far with maybe one or two exceptions, this seems to be a one-way street, so resistance seems to be only increasing. And we've stopped asking the question will antibiotic resistance emerge against a particular antibiotic? And now it's just a matter of when will it emerge. And this state of things has been a long time coming and this massive increase in antibiotic resistant bacteria should not have come as a surprise to anyone and for many people it didn't. So in 1945, the same year that he was awarded the Nobel Prize for his discovery of penicillin, Alexander Fleming warned about how easy it was to make microbes resistant to penicillin. And I don't know if I quoted this directly in the MRSA episode...
Erin Allmann Updyke	I think that you did cause we have definitely quoted this before.
Erin Welsh	Okay.
Erin Allmann Updyke	It's a great quote.

Erin Welsh	Okay. I don't know if it's the same one cause there were a few that I was choosing between, so we'll see if I was consistent in my choices. Okay. So he said specifically about improper use, quote: "The greatest possibility of evil in self-medication is the use of too small doses so that instead of clearing up infection, the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and from them to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save." This was in 1945, this was a couple years after penicillin was introduced to soldiers and a year after or the year it was released to the public. So you know, we saw it coming.
Erin Allmann Updyke	We saw it coming.
Erin Welsh	Despite these warnings, penicillin was everywhere. It was available over the counter in the US until the mid 1950s and like we said is still available without a prescription in many places. It was put in cough drops, throat sprays, mouthwashes, soaps, you name it.
Erin Allmann Updyke	Oh my gosh.
Erin Welsh	At one point Erin, it was even available as a powdered daily dose human growth promoter.
Erin Allmann Updyke	Stop it.
Erin Welsh	Yep. You could buy powdered penicillin.
Erin Allmann Updyke	Like Emergen-C penicillin?
Erin Welsh	Emergen-C, protein powder, just whatever.
Erin Allmann Updyke	Oh no.
Erin Welsh	Just pop that into your antibiotic-laden milk.
Erin Allmann Updyke	Oh dear.
Erin Welsh	Yeah. And even though regulations slowly increased, it didn't do so uniformly, right. And even today antimicrobials or antibiotics can still be found in products you never would have expected them to and their use is still incredibly widespread and not as well monitored especially in some places.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. And as we've said 1000 times on this podcast, pathogens don't respect political boundaries. So the rise of an antibiotic resistant strain of bacteria somewhere is a rise everywhere.
Erin Allmann Updyke	Right.

Erin Welsh	The story of the rise of antibiotic resistance itself is pretty simple and pretty repetitive. You develop a new antibiotic and then depending on how effective it is and how broad its targets are, it becomes the hot ticket item and is widely used. And then there's a ton of selection pressure and so resistance developed and then resistance spreads quickly as well. And then that antibiotic is no longer the miracle drug that was promised and gets resigned to the back shelf. The microbes win. Another antibiotic comes along, resistance develops, it gets shoved to the back shelf. Another antibiotic, more resistance. Rinse and repeat. Like this has been going on since the creation of penicillin.
Erin Allmann Updyke	Right.
Erin Welsh	And since that time there have been more than 150 antibiotics that have been developed and resistance has been found for all or nearly all of them. I watched a documentary called Resistance that I really enjoyed and I'm gonna borrow one of the graphics that they presented and put it in audio form as a way of illustrating the rise of resistance cause it's kind of amazing to see just how quickly it became widespread.
Erin Allmann Updyke	Okay, yeah.
Erin Welsh	So okay. Sulfonamides introduced 1935, resistance detected 1940. Penicillin 1942 introduced, resistance 1945. Streptomycin introduced 1944, resistance 1958. Tetracycline introduced 1948, resistance 1954. Chloramphenicol introduced 1949, resistance detected 1956. And so on and so on, I could list this with 10 more antibiotics that you would recognize by name. It's incredible. And so it became increasingly apparent, obviously as we are aware today that resistance is inevitable, it's just like Thanos. Just kidding.
Erin Allmann Updyke	Another reference.
Erin Welsh	Another Marvel reference.
Erin Allmann Updyke	Marvel reference.
Erin Welsh	But resistance is what we expect. And the discovery of plasmids and the ability of bacteria to transfer genes not just within species but across them, in the 1950s is when those things were kind of discovered or developed, that helped us a lot in terms of understanding the mechanism and how these bacteria were able to gain resistance so quickly and how it could spread so rapidly. But still enthusiasm for these miracle drugs and maybe like our own hubris that we'll just keep digging in the soil or we'll go here and there and we'll just keep finding new soil bacteria to make new antibiotics, that maybe also blinded us to the horrific implications that these discoveries carried, right. The development of antibiotics in the 20th century was arguably the most impactful or at least one of the most impactful medical advancements that we have ever seen. Like it must have been incredible.
Erin Allmann Updyke	Yeah.
Erin Welsh	But within a matter of decades we seem to be witnessing the rise and fall of these wonder drugs. So the big question is where did we go wrong? The short answer is through overuse or improper use in both medical and agricultural settings.
Erin Allmann Updyke	Yeah.
Erin Welsh	So let's dive a little bit deeper into each.

Erin Allmann Updyke	As we are wont to do.
Erin Welsh	Let's start with the medical side of things. As I mentioned before, once they came onto the scene antibiotics were indiscriminately used for anything that might be, could be, possibly was a bacterial infection. And they were even used preventatively, right. They still are used preventatively.
Erin Allmann Updyke	That's true actually, we still...
Erin Welsh	In surgery and stuff?
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	In surgery though it really reduces mortality.
Erin Welsh	Right, right, right. Yeah. So I think one thing that I wanna get across is that antibiotics still should be used, like they're not bad things, they're still hugely important.
Erin Allmann Updyke	No, yeah.
Erin Welsh	But we need to really consider how we used them so that we save them for when we really need them, right. So it's sort of proper use, right. It's reducing their overuse and turning improper use into proper use.
Erin Allmann Updyke	Right. Yeah, yeah, yeah. Totally.
Erin Welsh	Because resistance will continue to happen but at least we can slow it down a bit. Okay so on the medical side of things I see this falling into three different issues. So the first lies with proper prescription. And so particularly in the earlier days of antibiotics this was a huge issue but it also has continued to be a huge issue because there sometimes might be a thought that okay, there's a 95% chance that an infection is viral and a 5% chance that it's bacterial. You might just wanna prescribe that antibiotic anyway because if it's bacterial then you can wipe out that infection, reduce the suffering of your patient, and if it's not, well what's the harm to that patient? It's thought on an individual patient level scale, right, and that makes sense.
Erin Allmann Updyke	Yeah.
Erin Welsh	And jumping ahead a bit, a study showed that in 2010 80% of primary care doctors and 70% of emergency room doctors were prescribing antibiotics for acute bronchitis which is viral.
Erin Allmann Updyke	Almost always viral, yeah.
Erin Welsh	Almost always. And so then that's where we get into the 'almost always' issue.
Erin Allmann Updyke	Right, yeah.

Erin Welsh	So it's sort of a matter of treating the individual vs considering the group as a whole. It's a very tricky decision, it's a very tricky situation.
Erin Allmann Updyke	This is a thing I think a lot about because my whole background is in public health and thinking about these things on a population level and now I'm going into medicine where you're concerned about the patient in front of you and there's often a conflict between what's best for the individual patient and what is best for the public.
Erin Welsh	Right.
Erin Allmann Updyke	And it is a tricky landmine.
Erin Welsh	Yeah. And I'm not gonna talk about what we should do and the ways we should change it but I think the consensus is that we do need to change sort of the directives of this, yeah, we need to change how we use them.
Erin Allmann Updyke	Antibiotics are also not benign, right. We talked about this in the last episode, they have side effects, right, they're wiping out your microbiome, they're going to cause side effects. So they're also not benign to give a patient, to give a person antibiotics if they don't really need them.
Erin Welsh	Right. And this is something that we're becoming more and more aware of as we talk about the microbiome.
Erin Allmann Updyke	Right.
Erin Welsh	And some antibiotics, like you said, are also toxic in themselves, they damage certain organs. So yeah. And there there's also just sanitation issues within hospitals.
Erin Allmann Updyke	Yeah.
Erin Welsh	When you're in a hospital the rate of people that have infections, it's high, infections are very high there, very prevalent and this is talking about drug resistant and antibiotic susceptible infections.
Erin Allmann Updyke	Right.
Erin Welsh	And this makes transfer between patients really easy. And this just speaks to the nature also of how equipped these bacteria are to keeping their foothold in a place and surviving. Some of these are really, really difficult to get rid of.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so a hospital just provides tons of opportunities for bacteria to exchange info and to settle onto the skin or into the surgical incision site or into the intestine of someone who happens to be in the hospital. Finally there's the third issue which is that people who are prescribed antibiotics might not take them properly, so they might not finish their course. By that I mean if you're prescribed 10 days of an antibiotic and you only take 5 because you start feeling better, all you've done is kind of trained the bacteria in your body to become resistant. And so if that happens and you get severely sick and then you have to go to the hospital and then you're bringing you drug-resistant bacteria into the hospital.

Erin Allmann Updyke	Yeah.
Erin Welsh	Which is like, come on. Which is not good. And then that same 2010 study that I mentioned just a little bit ago, they also showed that up to 40% of people fail to complete their full course of antibiotics.
Erin Allmann Updyke	Oh yeah.
Erin Welsh	And so these three healthcare issues have been a part of what is driving antibiotic resistance in hospital and community settings. And for the most part I have to say that we have made some forward progress in terms of regulating them but we still have a long way to go. Okay that's just the medical side of things, we're only getting started. No, this is horrifying. Because even if tomorrow we enacted all of those changes, it might slow down the spread of resistance in healthcare settings but it wouldn't stop the problem entirely. And a small part of that is due simply to the nature of resistance, it's due to this arms race of bacteria and antibiotic compounds. Resistance will always evolve but another huge part is improper antibiotic use in agriculture. And we talked a bit about this in the last episode but I wanna go more into the history of this since it's such an integral part of the story of resistance. So this history starts with yet another chance discovery when a researcher was looking for a natural source of B12 to supplement the food of chickens to help them grow better.
Erin Allmann Updyke	Okay.
Erin Welsh	So he learned that Streptomyces aureofaciens produces vitamin B12 during the fermentation process for making streptomycin so he was like, 'Hey, can I have some of that waste from fermentation, just like the leftover gunk or whatever. I'm gonna mix it into the chickens' food and just see what happens.'
Erin Allmann Updyke	Okay.
Erin Welsh	And the results were remarkable. The chickens grew tremendously, much faster than he expected due to just B12 and so did the piglets that he also tried it out on. He was like okay, is it actually the B12 that's in the fermentation waste or is it trace amounts of the antibiotic that's causing this growth? And he was like well maybe it's suppressing harmful gut bacteria or something else. Regardless of the reason, he couldn't deny that they were actually having an effect. So on average livestock that were fed these growth promoters grew 3-11% faster than their non-antibiotic ridden counterparts but I've seen actually much higher rates quotes, particularly early on in these experiments.
Erin Allmann Updyke	Oh.
Erin Welsh	And this led to because you could make more meat faster, you could sell more meat and so consumption overall really grew and then it kind of in that way firmly established these growth promoters, so-called growth promoters as a necessary part of agriculture. And so I'm gonna use the term 'growth promoters' a lot and that basically means these trace amounts, so nontherapeutic doses of antibiotics that are included in food for animals, like agricultural animals, livestock.
Erin Allmann Updyke	Okay.

Erin Welsh	Okay. So these antibiotic-laced foods plus preemptive treatment, so not just as growth promoters but actually like oh we're gonna dose you so that you don't get this or that ulcer or whatever, that led to some farmers just packing them all in, all these animals in as tightly as possible because they were secure in the knowledge that the crowd diseases that they had previously been worried about wouldn't be much of a concern with these antibiotics. And so it really led to the rise of the industry, some of the nastier sides of the industry that we see.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	I did not know that part of it. But that makes so much sense.
Erin Welsh	And the drug companies that were producing these antibiotics ate it up or rather they were enthusiastic about the livestock eating up their antibiotic fermentation waste products. Cause this was all stuff that they were just throwing away anyway. So it's great for them.
Erin Allmann Updyke	Wow.
Erin Welsh	So subtherapeutic doses of antibiotics were sold as growth promoters starting in the 1950s and the huge threat of antibiotic resistance had been known and discussed for at least a decade before that. And this basically provided the perfect breeding ground for antibiotic resistance because if you think about an industrial farm full of pigs packed in all close to one another and then they're all dosed with antibiotics, bacteria, they can move so easily that way, resistance can move so easily that way. And manure is one of the best sources for antibiotic resistance bacteria, apparently.
Erin Allmann Updyke	Gosh.
Erin Welsh	And then there's runoff. Okay, anyway. And it wasn't just restricted to growth promoters in food. Farmers began toying with different ways to deliver the antibiotics to the animals so they were like in the water before they were slaughtered, like here's some water, injected into the areas for prime cuts-
Erin Allmann Updyke	What?
Erin Welsh	Painting raw steak with antibiotics or mixing them in with ground beef.
Erin Allmann Updyke	I'm sorry, why would you mix it in with the meat that you're selling to humans? What is the purpose of that?
Erin Welsh	Well because then it has a longer shelf life.
Erin Allmann Updyke	Are you kidding me?
Erin Welsh	I'm not kidding you. Dude, spinach was even washed in streptomycin. So serious!
Erin Allmann Updyke	I don't ever wanna eat anything again.
Erin Welsh	Chickens were literally sold soaking in antibiotics because that would lengthen their shelf life.

Erin Allmann Updyke	My face.
Erin Welsh	So you could squeeze out the chicken juices from a raw chicken at the grocery store back then and you could get antibiotics in those juices. The world got its first taste of how the use of antibiotics on farms bled into human life in the 1950s, around the same time when it first started to ramp up.
Erin Allmann Updyke	Oh my god.
Erin Welsh	Around this time penicillin had been made prescription-only in the US and in Britain, partly because the rates of penicillin allergy were just skyrocketing.
Erin Allmann Updyke	Okay, yeah.
Erin Welsh	And so with these increased regulations, physicians and epidemiologists expected to see fewer penicillin allergies crop up. Makes sense, right? No, that's not what they saw. Instead they saw an increase, they saw a surge and it turns out that the source of the penicillin, this was done through a lot of detective work, the source of the penicillin was in the milk that people were drinking. Some milk contained so much penicillin that it could have been sold as a drug. It was therapeutic doses.
Erin Allmann Updyke	Milk.
Erin Welsh	Yes.
Erin Allmann Updyke	Grody.
Erin Welsh	So this finding led the FDA at least to rule that you could no longer treat meat with antibiotics prior to it being sold.
Erin Allmann Updyke	Okay so my steaks are not washed in antibiotics anymore?
Erin Welsh	No, no, that's all done.
Erin Allmann Updyke	Okay. Whew. Small blessings.
Erin Welsh	Yeah. This did nothing to stop the addition of antibiotics in feed for animals as a growth promoter. And then there was a series of studies in the 1960s that clearly demonstrated that growth promoters led to the rapid development of resistance in microbes, colonizing both the animals as well as the people working with the animals. So this was kind of a cut and dry, very eye-opening experiment. Fortunately this was taken somewhat seriously by governments. So the UK took action early on in limiting antibiotic use in agriculture starting in 1971, the banned antibiotics as growth promoters if those antibiotics were used to treat disease in animals and humans.
Erin Allmann Updyke	Okay. So you can no longer use tetracyclines because we use those to treat disease.
Erin Welsh	For example, yeah.
Erin Allmann Updyke	Okay, got it.

Erin Welsh	And you had to have a prescription for them if you wanted to use them therapeutically.
Erin Allmann Updyke	Okay.
Erin Welsh	And the US was like this close to following suit.
Erin Allmann Updyke	Oh dear.
Erin Welsh	But you know, we didn't. A little bit after this decision in the UK, the FDA was like, 'I'm gonna lay down the law and we're gonna limit the use of antibiotics purely to therapeutic purposes.' But then the mighty dollar of the agricultural industry overruled. Representative Jamie Whitten, who was like part of the spokesperson for this industry basically, said that he would hold hostage the budget of the FDA if the regulations passed. Because somehow he had that power, Erin, I don't know.
Erin Allmann Updyke	Oh my god.
Erin Welsh	So the White House gave in since the budget hold up would have also hurt many other important projects. And so Whitten, this representative, insisted that the data in support of banning the use of nontherapeutic antibiotics in agriculture was incomplete and biased against farmers. And so then they were like okay well we want the agricultural industry to design their won projects and do their own research to figure out what the truth is.
Erin Allmann Updyke	Oh there's no bias there at all.
Erin Welsh	Right? I mean the burden of proof has been on epidemiologists and researchers to find that antibiotic use in agricultural settings leads to antibiotic resistance that is clinically important in humans, right.
Erin Allmann Updyke	Right, yeah.
Erin Welsh	But this insistence that those studies were inaccurate or that the research was incomplete was just a flat out lie. Because in the 1970s a researcher named Dr. Stuart Levy wanted to see how rapidly resistance could develop or spread in livestock given these growth promoters. So he tested out some young chickens who were given tetracycline. Within 36 hours of first being given the feed laced with tetracycline, their gut E. coli was resistant. 36 hours.
Erin Allmann Updyke	Wow.
Erin Welsh	So that's scary enough. And tetracycline was a broad spectrum, just awesome, widely used drug.
Erin Allmann Updyke	It's a good drug. Was.
Erin Welsh	Was. And so that's scary enough on its own. But what made it even scarier is that over the next 3 months the E. coli also added to its arsenal genes that made it resistant to ampicillin, streptomycin, and sulfonamides. And the chickens had never even received any of those drugs.
Erin Allmann Updyke	Whoa!

Erin Welsh	The tetracycline had acted like a call to arms for these bacteria. Like we've faced and defeated one antibiotic so we need to be prepared for any others that might come our way.
Erin Allmann Updyke	Man oh man.
Erin Welsh	And I bet you didn't think that this study could show even more concerning results but it did. And you're not gonna be surprised by them. But Levy found the same antibiotic resistance in the gut E. coli of the farmers and the families of those farmers that had kept the chickens. None of them had received tetracycline.
Erin Allmann Updyke	Oh dear. Right.
Erin Welsh	There have been literally dozens, dozens and dozens of peer-reviewed articles demonstrating clearly that antibiotic use in animals impacts humans. To epidemiologists and physicians and microbiologists and biochemists, whether or not rampant use of subtherapeutic levels of antibiotics was leading to a huge increase in resistance and resistant organisms, that wasn't a scientific question, it was firmly established that it was.
Erin Allmann Updyke	Right.
Erin Welsh	Instead it was a political one. Does it sound familiar?
Erin Allmann Updyke	Sounds too familiar, Erin.
Erin Welsh	Yeah. And despite this strong evidence that growth promoters also promoted antibiotic resistance and all of the terrifying implications that came along with it, the US declined to ban tetracycline as a growth promoter. It along with many other antibiotics continued to be used freely for decades in livestock.
Erin Allmann Updyke	You said for decades. Are you gonna tell me some happy news at the end of this? Like no longer or what?
Erin Welsh	There are some bright moments.
Erin Allmann Updyke	Okay.
Erin Welsh	And some really cool little case studies that I won't go into but I'll mention and I'll mention places to read further about them because... Denmark and Netherlands, woo woo! Okay. (laughs) And just because a country had stricter regulations doesn't mean that they weren't also contributing to the resistance problem. A lot of the time there wasn't much regulatory oversight into just how much antibiotics were being sold to agriculture and when there was sort of a retrospective look at the amount over time, like number of tons or millions of pounds sold over time, there actually wasn't really a decrease after some of these bans were put into place. Because the labeling just changed for a lot of these things. Another issue was that these bans, like I mentioned, often limited use of antibiotics to those that weren't also used to treat animal or human infections. But this is also a problem and that's because as resistance to the most common antibiotics grew, doctors had to reach increasingly to the back of that cabinet for the third and fourth string antibiotics that had been deemed too toxic or too specific or too expensive to be used.

	Vancomycin was one of these antibiotics. It was one of the earlier ones that had been discovered and developed but it was deemed to be too expensive and had some nasty side effects. So people were like, 'Nah, nah, we'll just use methicillin instead.' And so in the 1980s it was dusted off and increasingly used to treat stubborn, resistant infections. And it seemed to be remarkably effective in that microbes weren't showing resistance towards it, so that was promising. And some researchers were like okay well how exactly does it work? And they were like it's so complex that it would be nearly impossible for a bacterium to develop all of the genetic changes needed to overcome this mechanism. It's like an unsinkable ship, like why do we say these things? It's just tempting fate. In 1989 the first strains of vancomycin-resistant Enterococci, VRE, starting popping up in hospitals in the US and by 1993 it was close to being endemic in many hospitals.
Erin Allmann Updyke	VRE, baby.
Erin Welsh	VRE, baby. It's really bad. Within 5 years of first showing up, VRE was widespread in the US, something that it took MRSA, methicillin-resistant Staph. aureus, about 15 years to do. So they were like, 'What the heck? This is super complex. So how could there have been enough time that has passed for these mutations to actually emerge? What is going on here? What happened?' Turns out the answer is in agriculture. A vancomycin-like antibiotic had been used as a growth promoter in livestock for decades.
Erin Allmann Updyke	Oh gosh.
Erin Welsh	And so when physicians started to reach into the back of that cabinet for vancomycin, the resistance genes were already long-present and quite prevalent. And then with that added selection pressure of being used in a clinical setting, it just spread like wildfire. And bad turned to worse when in 1996 the first vancomycin-resistant Staph. aureus, VRSA, infections emerged in Japan. At this point in time about 50% of all hospital Staph. aureus infections were methicillin resistant, treatable only by vancomycin. Within the next few years, VRSA was basically everywhere. And again there was still lobbying for the continued use of vancomycin and other antibiotics as growth promoters in the US and those lobbyists still refused to acknowledge how those practices could lead to resistance. So Robert Carnevale who is one of those lobbyists is quoted as saying: "I'm sure VRE can transfer from animals to people and it might be resistant but is it of clinical importance?" Yes.
Erin Allmann Updyke	Yes.
Erin Welsh	Yes it is. Yes.
Erin Allmann Updyke	Oh gosh.
Erin Welsh	And it wasn't just vancomycin resistance that agriculture was promoting, colistin was another one of those antibiotics that had been put aside in favor of more sensitive drugs in the past and it had also been used in agriculture and so resistance was already super high there. And it wasn't just resistance genes that spread from agricultural settings to hospitals or communities. People realized it was also the bugs themselves. Epidemics of exPEC, which I can't remember what that one is but it's some sort of E. coli, toxic E. coli, yeah, these UTIs caused by exPECs, they seemed to be coming from food, specifically chicken.
Erin Allmann Updyke	Oh gosh.

Erin Welsh	Quinolone-resistant Salmonella typhimurium strain DT104, that's a bad one, that spread through fresh dairy and can kill you and that came directly from animals. And quinolone-resistant Campylobacter, that was found in grocery store chicken.
Erin Allmann Updyke	Gosh.
Erin Welsh	So quinolone had been used in agriculture for years but the sharp, alarming rise of resistance to it prompted the FDA finally to propose a ban, propose a ban, for their use in animals. But a proposal is just a proposal, some drug companies including Bayer declared that it would not comply voluntarily. So it would fight the proposal and ask for a hearing where it could show that quinolone use in animals was of no harm to humans.
Erin Allmann Updyke	I'm just getting too depressed, Erin.
Erin Welsh	I know. Okay. But in the late 1990s, this is a little shining sun-
Erin Allmann Updyke	Okay.
Erin Welsh	The European Union moved to ban antibiotics as growth promoters, like all of them.
Erin Allmann Updyke	Okay.
Erin Welsh	But preventative use was still allowed which still promoted resistance. Again there didn't seem to be any decline in the amount of antibiotics sold for farm use. So from 1999-2006 and beyond it stayed at 606 tons per year. This is after the ban, right. However some countries did actually do it on their own and some countries like in Denmark, the industry did it on their own themselves.
Erin Allmann Updyke	Wow.
Erin Welsh	They just decided amongst the community and the farmers that they were going to do this because they were like it's right for everyone.
Erin Allmann Updyke	Social responsibility kind of a thing?
Erin Welsh	Yeah. So the Netherlands for example, they really doubled down and started policing the use of antibiotics much more and the result was that antibiotic use on farms actually declined dramatically starting in 2013 and really cool, the occurrence of antibiotic-resistant bacteria found in meat also declined. And similar things happened in Denmark as well. And all of the horrible repercussions that had been promised like a drop off in the weight of livestock, sky-high meat prices, more disease among livestock, none of these things happened. The weight dropped a bit, a little bit, but it had been recognized for quite a while that growth promoters were no longer achieving the same dramatic gains that had been seen when they were first used.
Erin Allmann Updyke	Oh now that's interesting.

Erin Welsh	That is very interesting. So somewhere in the 5 or 6 decades since antibiotics were first used in agriculture, they had lost their magical ability to promote growth. So a couple of different things. It's probably likely that when they were first used the antibiotics were compensating for some of the negative ways that the farms were run, so like as hygiene and monitoring and nutrition and breeding had changed, it had eliminated that gap that growth-promoting antibiotics had made up.
Erin Allmann Updyke	That makes sense.
Erin Welsh	It's also possible that if it was affecting the harmful gut bacteria or whatever gut bacteria, that resistance had emerged and so antibiotics were literally just doing nothing.
Erin Allmann Updyke	Doing less, yeah.
Erin Welsh	And by removing antibiotics from agriculture, places like Denmark and the Netherlands incorporated animal welfare into the business model and with that they improved quality. Quality of life for the animals, quality of meat for consumption, quality of their investment, etc. But once again the US failed to make similar regulatory progress as Europe. In 2015 34.3 million pounds of antibiotics were sold for use in animals compared to approximately 7.7 million pounds for humans. But even though the US government agencies were slow to stop the overuse and misuse of antibiotics, some companies actually voluntarily stopped using growth promoters because they realized that antibiotics for growth promotion may not be worth the cost for human health or the cost of the constant legal battles. This industry shift paralleled many others that were going on in food supply arenas. So it was one after another, both from the meat-providing side of things, so these big name chicken farms to the food supply aspect, so like fast food restaurants, stuff like that. They were all starting to offer antibiotic-free meat options and the market seemed to be responding positively to these changes. But that's all on the industry side.
	So even though starting in 2012 the US has put in some regulations for monitoring the use of antibiotics in agriculture, for many years the amount of antibiotics has actually increased rather than decreased. 2017 did see a decrease but it doesn't seem 100% clear why that decrease happened, maybe it was because of these bans and that would be great. But antibiotic resistance and its association with agriculture is a perfect example again of why a one health approach is essential. Humans and animals share one bacterial and viral world and fungal world and protozoal and parasitic, whatever, so the rise of antibiotic-resistant bacteria on farms means a rise of antibiotic-resistant bacteria everywhere.
	Just like with the medical side of things, there is such thing as proper use of antibiotics in agriculture but there has been overuse in terms on growth promoters and in terms of preemptive treatment and it has remained a debate and a challenge to kind of see what the cost and benefits are. And I think we're only becoming more and more aware of the cost to humans. And it's also not going to just be antibiotic-resistant infections in humans, it's also going to be livestock as well. So it's an interesting thing to think about. Anyway. But it's not just the US where overuse is an issue. So in 2015 a group of researchers tried to predict how much antibiotics Brazil, Russia, India, and China could be predicted to use in the next 15 years as demand for meat continues to increase. If nothing changed, that estimate was 105,596 tons globally.
Erin Allmann Updyke	Oh dear.

Erin Welsh	It's hard to wrap your brain around. The annual numbers of antibiotic-resistant infections and deaths due to those infections are absolutely staggering. The history of resistance is actively still being written and it's not looking good. I mean there are some promising avenues of research ahead of us but I wanna end with a quote from the amazing book 'Big Chicken' by Maryn McKenna: "Antibiotic resistance is like climate change. It is an overwhelming threat created over decades by millions of individual decisions and reinforced by the actions of industries. It is also like climate change in that the industrialized West and the emerging economies of the global South are at odds." Well with that Erin, tell me where we stand with antibiotic resistance today.
Erin Allmann Updyke	Oh gosh.
Erin Welsh	Are we basically on the brink of returning to pre-antibiotic era? Is there any hope?
Erin Allmann Updyke	I mean let's find out.
Erin Welsh	Oh boy.
Erin Allmann Updyke	I need a short break.
Erin Welsh	Yeah, same.
TPWKY	(transition theme)
Erin Allmann Updyke	Well let's start with the depressing things and then we'll end on an at least hopeful note, how about that?
Erin Welsh	Great.
Erin Allmann Updyke	Okay. All right so medically in the US at least the CDC estimates that at least 47 million antibiotic prescriptions in the US each year currently are unnecessary.
Erin Welsh	What?
Erin Allmann Updyke	So we're doing great.
Erin Welsh	Okay what does unnecessary mean?
Erin Allmann Updyke	I don't know for sure because that was just a stat taken off their antibiotic resistance general page but in general 'unnecessary' means either not the right antibiotic for the infection or using an antibiotic to treat a nonbacterial infection, right.
Erin Welsh	You wouldn't expect ever to see zero, right? Because if somebody comes in and they have some infection but you don't know what it is yet or you suspect it's a bacterial infection, you're gonna try different antibiotics, right.
Erin Allmann Updyke	Right.
Erin Welsh	So that would be included in that? I'm just trying to wrap my brain around this 47 million whatever.

Erin Allmann Updyke	Yeah, it's a good question. I don't know if that includes every time that you give vanc and zosyn in the E.R. which like everyone who comes into the E.R. gets those two antibiotics at first right, when we don't know what they have yet.
Erin Welsh	Right.
Erin Allmann Updyke	So I don't know if that's included or if that's just prescriptions like outpatient, what you get sent home with. Either way it's terrifying. I mean 47 million.
Erin Welsh	Oh yeah.
Erin Allmann Updyke	That's in the US. Also in the US it's estimated that more than, and this is very recent data so this is from a report that came out at the end of 2019, it's estimated that there are more than 2.8 million antibiotic-resistant infections in the US every year that result in more than 35,000 deaths.
Erin Welsh	Wow.
Erin Allmann Updyke	So 35,000 people a year are dying in the US because of antibiotic-resistant infections.
Erin Welsh	Do you have global numbers?
Erin Allmann Updyke	Great question. I tried really hard to get solid global numbers, it is very, very difficult. So the World Health Organization has set up in I believe 2015 they set up the Global Antimicrobial Resistance Surveillance System which is basically every country setting up their own surveillance system. So I think now it's over 60 countries that are reporting their antimicrobial resistance data to the World Health Organization but they don't seem to aggregate that data and present it as overall numbers. Overall World Health Organization estimates that in many parts of the world, over 40% of bacterial infections are with bacteria that are resistant to antibiotics but I don't have numbers on deaths. I do have numbers in the EU. In 2015 an estimate from the European Union was that 671,000 infections were likely antibiotic-resistant and that likely resulted in 33,000 deaths in 2015.
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	So that's in the EU. But a lot of the increase in antibiotic use is in low and middle income countries and we don't really have good data on the number of resistant infections worldwide. But it's bad, it's not good. It's a lot.
Erin Welsh	So I have two questions.
Erin Allmann Updyke	Okay.
Erin Welsh	The first question is about in the US are antibiotic-resistant infections reportable? Like are you required to report them?

Erin Allmann Updyke	That's a really good question, I don't fully know the answer to that. So the CDC, that report that came out in 2019 has a list of the most concerning pathogens, right, and the World Health Organization also has a list of what their pathogens of greatest concern are. And those lists mostly overlap. So I would think that most of those pathogens are going to be reportable in the US.
Erin Welsh	Okay.
Erin Allmann Updyke	But that doesn't mean... Like very time for example someone comes in with a UTI, if you do a urine culture you might send that culture off to see what the resistance profile is and that bacteria might be resistant to a few antibiotics so then we use that to choose what antibiotic we give to that person. But I don't think that we then report that necessarily to the CDC. It probably goes to the local public health district so that we can keep track of what the general antibiotic resistance looks like in our area.
Erin Welsh	Gotcha.
Erin Allmann Updyke	So hospitals keep track of things like that.
Erin Welsh	Okay.
Erin Allmann Updyke	So I will say that a report that came out in 2014 which is earlier than most of the data I was hoping to find estimated that currently worldwide there are 700,000 deaths attributed to antimicrobial resistance worldwide.
Erin Welsh	That is a lot.
Erin Allmann Updyke	It's a lot. And they projected that out and estimated that by 2050 that number would go up to 10 million deaths.
Erin Welsh	Oh my god. If we do nothing, if we just continue on this same pathway?
Erin Allmann Updyke	Yeah.
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	Yeah. And then they also estimated what the overall cost, like the monetary cost of that would be, that it would cost the world up to 100 trillion dollars, antimicrobial resistance.
Erin Welsh	I can't comprehend that number but wow.
Erin Allmann Updyke	Me neither.
Erin Welsh	Wow.
Erin Allmann Updyke	I was really hoping to find more recent hard data on antimicrobial resistance and I came across a paper that came out in 2016 that really highlighted some of the issues that we have in even trying to get a handle on this burden of antibiotic resistance. Because that number, that estimated number of deaths, it's such an estimate, we really don't have solid numbers on that.

Erin Welsh	Well and then also my other question was about how do you attribute cause of death?
Erin Allmann Updyke	Exactly!
Erin Welsh	And so yeah, if you're in the hospital and you go in for a routine surgery like appendicitis and you get MRSA and then you die, is that MRSA? Is that appendicitis?
Erin Allmann Updyke	Right, exactly. That's kind of exactly what they were highlighting in this paper. We can't calculate the number that we really need to calculate to know the number of deaths attributable to the failure of antibiotic therapy due to antibiotic resistance because we don't know enough about the rates of resistance or the rates of infection for so many different infections. You have so many things like diarrhea that can be caused by so many different pathogens.
Erin Welsh	Right.
Erin Allmann Updyke	So yeah, it's a really complicated, big picture question.
Erin Welsh	But there is no question that it is leading to death and is horrible.
Erin Allmann Updyke	Yeah, it really is. And it's a very multifactorial problem. Like you mentioned Erin, there's a number of different factors contributing to this, right, inappropriate prescriptions, misuse of taking those antibiotic prescriptions, agriculture, poor sanitation in hospitals. So I will say that all of the kind of action plans that CDC and WHO and all these different organizations, they're very holistic plans, right. They recognize that this is not going to be solved by just one change or even a few changes, it's a whole bunch of different solutions that are gonna be required for this problem. The one thing that it's definitely going to take are new methods of treatment because for many pathogens resistance is already here, so we need new ways to target these pathogenic bacteria.
Erin Welsh	We do.
Erin Allmann Updyke	And this is where we'll have some shining moments of hope, okay?
Erin Welsh	Yay!
Erin Allmann Updyke	The good news is there are so many people working on the issue of antibiotic resistance from a treatment standpoint. You heard in our last antibiotics episode about a group that's working on new methods of identifying antibiotic compounds using machine learning which is so cool. I love it so much.
Erin Welsh	It's amazing, it's literally unbelievable. So cool.
Erin Allmann Updyke	There are a number of other groups working on alternative therapy strategies as well. There's some really promising data on probiotic therapy which I think is awesome.
Erin Welsh	Oh yes.
Erin Allmann Updyke	So basically boosting gut microbiomes to try and both treat and prevent toxic infections.
Erin Welsh	Fecal transplants!

Erin Allmann Updyke	Fecal transplants! So probiotic therapy is a very cool - I feel like we'll probably talk a lot more about that in a microbiome episode.
Erin Welsh	But you should definitely google 'fecal transplant'.
Erin Allmann Updyke	Oh for sure.
Erin Welsh	It's so cool.
Erin Allmann Updyke	There's also a lot of work being done on combination therapy, so whether that's combinations of an antibiotic and another molecule that blocks a normal resistance mechanism to that antibiotic, like Augmentin, that was an example I gave early on, or whether it's giving a number of different antibiotics in combination that have different mechanisms of action which is how we already treat things like tuberculosis, for example.
Erin Welsh	Right. Which by the way, I know we touched on this in the tuberculosis episode but multidrug or extremely drug-resistant tuberculosis is terrifying.
Erin Allmann Updyke	Oh Erin, tuberculosis is so terrifying that it's not even included on the lists of the terrifying bacteria because it's its whole own version. Like we've known about resistance in TB for so long, we don't even need to include it on our list.
Erin Welsh	Oh gosh. The ESKAPE list, is that what you're talking about?
Erin Allmann Updyke	Oh yeah, I didn't even mention the names of any of them. I got ahead of myself. So some of those pathogens include Enterococcus faecium, Staph. aureus, Klebsiella, Acinetobacter baumannii, Pseudomonas, and Enterobacter. Those are the 6 that are really commonly like the big ESKAPE, I think just because they make a nice acronym. But there's really at least 12 that we need to be concerned about.
Erin Welsh	But we don't care about the other 6 just because they don't make a good acronym?
Erin Allmann Updyke	They don't make a good acronym. H. pylori, meh. Campylobacter, gonorrhea, salmonella, Strep. pneumo. You know? There's a lot.
Erin Welsh	Ooh but there aren't enough vowels in there.
Erin Allmann Updyke	I know, that's why they're not included.
Erin Welsh	We do care about all of this.
Erin Allmann Updyke	Oh especially gonorrhea, man.
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	Yeah. So there's a lot. There's also a lot of work being done on antimicrobial peptides, there's work being done on stimulating the immune response and using our own immune system to better fight off infection. There's the use of things like iron scavenging molecules. One of the coolest areas and one that I've been most excited to talk about for a while now is phage therapy.

Erin Welsh	Phage therapy. We briefly touched on it in the MRSA episode.
Erin Allmann Updyke	Very briefly.
Erin Welsh	Very briefly. Too briefly.
Erin Allmann Updyke	Far too briefly. And so who better to tell you about the status of phage therapy research than the provider of our firsthand account who literally treated her own husband with phage therapy and also studies it, Dr. Steffanie Strathdee.
	Well thank you so much for taking time out of your day to chat with us, we're really excited about this episode and thrilled to get the chance to talk to you. We'd love for you to kind of give us first maybe a brief overview of what phage therapy is for our listeners and kind of how it works.
Steffanie Strathdee	Sure. Well phages are viruses that have naturally evolved to attack bacteria. They're like the perfect predator for bacteria. They've actually coevolved for 4 billion years, they're the oldest and most ubiquitous organism on the planet and it's thought that there's about 10 million trillion trillion, that's 10 to the power of 31 for you numeric math-y people out there. So they're everywhere. They're on our skin, they're in our guts, we poop them out, they're in water. A single drop of water can have trillions of phages in it. We just haven't been able to understand what they're like because they're so small, they're about 100 times smaller than bacteria. And they were discovered in 1917 by a French Canadian named Félix d'Hérelle and he deduced that these must be viruses that are parasites of bacteria even though you couldn't see them until the electron microscope was developed in the early 1940s. And people actually had a big debate as to whether or not these were proteins or whether they were viruses or whatever.
	And d'Hérelle himself was quite a character, he was very egotistical, he wasn't formally trained, and he was really pushed to the margins of society and the medical field. And then when he helped the former Soviet Union develop the first phage therapy center in the world, it got the label as 'Soviet science' and this was around WWII and of course that led to a big geopolitical bias of like 'pinko commie science' and that put a cloud over phage therapy for decades. And so that's one of the reasons why the West really abandoned it and of course penicillin came on the scene in 1942 even though it was discovered in 1928 it took some time to come into the field and that was because it was needed on the war front. And so people though antibiotics are wonder drugs. And of course they were for a while but antimicrobial resistance has just continued to outpace us and nobody's really been paying attention to that until we get these people who are having minor scrapes or surgeries and we realized oh my gosh, they got a superbug and there's nothing left to kill it anymore.
Erin Welsh	Could you talk us through what a typical course of phage therapy might look like. So how do you even go about finding the right phages and then administering them?
Steffanie Strathdee	Well the thing about phages that's both a blessing and curse is that they're really finicky. They only match to specific bacteria so for an organism like Staphylococcus which one of the strains is MRSA, right, methicillin-resistant Staph. aureus, that's the superbug that was discovered first. Maybe about 20-30 phages will cover the majority of circulating strains around the world and that's pretty good because you don't need that many of them and maybe you could have a cocktail of phages that would cover the majority of those infections. But for superbugs like tOm's Acinetobacter baumannii, it's very, very specific. So the phage doesn't just have to match the genus and the species, it has to match the isolate, so Tom's bacteria. So that means you have to essentially look for a needle in a haystack.

	It's a little worse than that because when you think about where there's a lot of bacteria, that's where you're gonna find a lot of phages. So if you need to go on a phage hunt you have to go to some of the worst places around. And we're talking like sewage, barnyard waste, scummy ponds, that kind of thing. So the phages that were actually used to treat Tom were from (beep). So I can say literally that my husband is full of (beep). I mean who gets to say that about her husband?
Erin Welsh	(laughs) That's amazing. So then once you go in and you dig through all that sewage and you get lucky enough and you find that needle in that massive, massive haystack, do you then take that to the lab, culture it, and then what's the next step after that? How do you actually get it into that person?
Steffanie Strathdee	Well the old fashioned plaque assay, this is something that high school freshmen learn how to do, you have a petri dish say with your bacterial lawn or your bacteria streaked on it and if you wanna see if you have phages that are matching to that bacteria you put a drop of sewage on the petri dish and you incubate it for 24-48 hours. And if it comes back looking a little like Swiss cheese because there's holes literally in the petri dish, then you get really excited because even though you can't see the phage because they're smaller than the naked eye and even smaller than the light microscope can detect, you know that it worked because they've gobbled up a bacterial colony.
	So then you can pluck it out and add it to more bacterial suspension and then you need to purify it and that's the tricky part, there's different techniques to purify phage suspension but if you're gonna treat with phage intravenously, you wanna get it as pure as possible because if there's a lot of bacterial debris in the suspension, it could elicit septic shock in the patient and could kill them. And that's what we were worried about with Tom's situation and nobody really knew what the threshold for safety was so we were taking a big risk.
Erin Allmann Updyke	Yeah. So you mentioned kind of how difficult it is to even be able to identify and find these phages, especially when you're dealing with bacteria where you maybe have to find a very specific phage. So could you talk maybe a little more broadly about some of the pros and cons of using phage therapy maybe in comparing and contrasting that to antibiotics that we have currently?
Steffanie Strathdee	Yeah well the good news about phages is that again there's 10 million trillion trillion phages on the planet so there's almost an inexhaustible supply of them, it's just you need to find the right phages to match the bacteria that you wanna kill. So if you have to go back to sewage or barnyard waste or whatever every single time you need to treat somebody, that would be a real pain and obviously it's very labor intensive and you may not find phages in time and we've been in that situation with other patients. But if you have a phage library or a phage bank, it's essentially like a walk-in cooler where you have thousands of phages and they're already identified and characterized and sequenced, then you could just kind of go in there and see if the bacteria that you wanna kill has phages in the library. So that problem about how do you find the phages to match the bacteria that you wanna kill can be overcome.
Erin Welsh	Gotcha. So one of the questions I had was about dose and sort of one of the negative consequences or potential consequences of phages. So how do you know how much, many phages to give? And also when those phages break apart those bacterial cells, what are some of the risks associated with that?

Steffanie Strathdee	Well to be honest nobody really knows the right dose for phages in most cases and that's part of the translational basic science research that needs to go on so that we can get ready for clinical trials. In Tom's case we just took an estimate based on his weight and the fact that he had a systemic infection where the bacteria were in every cavity in his body and we knew that if you underdose, if you get too few phages, the body's own immune system can eliminate them and the phages might not ever reach their target. And we thought well is there a risk of overdosing him or whoever you're treating? And we talked to experts and they said we haven't actually seen any side effects of this as long as the endotoxin which is essentially the bacterial debris that is caused when you're growing up a lot of phage in the context of a lot of bacteria. That endotoxin, if there's a lot of endotoxin left, that could kill the person. So again we haven't seen that though, we've treated over a dozen patients at UC San Diego and dozens other internationally.
Erin Welsh	Gotcha, yeah. So you talked a little bit about some of these challenges moving forward with phage therapy but let's talk about the bright future. So since the publication of your book there's been a lot of forward progress in phage therapy and in new initiatives. So can you talk a little bit about what you see as the future for phage therapy? And also are there going to be genetically engineered phages for specific infections?
Erin Allmann Updyke	Yes!
Steffanie Strathdee	Well yes, there's been a lot of really exciting developments since then. The first is that the first genetically modified phage cocktail to be used successfully to treat a human bacterial infection was published in May of 2019, so a year ago from now. And it was an incredible case, just as fantastic as Tom's. This is a young girl, her name's Isabelle, I happen to know her now through our connections and Facebook and social media. She has cystic fibrosis and she'd had a double lung transplant and had acquired what's called Mycobacterium abscessus. And people who are familiar with tuberculosis will know that Mycobacterium tuberculosis, a cousin to this Mycobacterium abscessus is the biggest bacterial killer in the world, it almost kills 2 million people per year. And so this is a very difficult to treat pathogen and she was literally dying, she was in hospice and he mother heard about Tom's case, contacted her doctor, the doctor contacted some of our colleagues. And we happened to know that there was a fellow named Graham Hatfull at the University of Pittsburgh who runs this wonderful training program called SEA-PHAGES, teaches students how to find phages and essentially they're doing this phage hunt that I described earlier.
	And all the phages that they find go into a giant phage bank and they have about 15,000 Mycobacterium phages, they never even dreamed that they could be used therapeutically. And when asked they said, 'Wow, we'll certainly see if any of our phages will be a match for Isabelle's bacteria.' And three of them were and one was perfect, its name was MUDDY, it was found on a rotting eggplant from South Africa by a student there and all the students who find these phages get to name them right, that's part of the bonus. And two of the other phages were the sleepy kind. In our book I describe them as hitting the snooze button, they actually don't kill the bacterial cell. But that's all they could find. So what they did was the genetically manipulated those two phages by clipping out the repressor gene in a technique called recombineering which is a prequel to CRISPR gene editing. It forced those sleepy phages to become the phage rage kind of phages that actually kill the bacterial cell.

And then they had to convince the UK government where she was living in the UK that this was okay to use. And luckily they went along with it because they said, 'Well it's not a GMO because you took away a gene, you didn't add a gene.' And Isabelle received phage therapy intravenously because based on Tom's protocol, we convinced them that it was safe. She left the hospital within a week. It was just stunning. And she's made a great recovery, I believe she's still receiving phage therapy now but she's working, she's finished her A level exams, she's learned to drive a car, she's dyed her hair purple. I believe she's 18 now and she's doing great. So that case is a landmark because that's the first time that genetically engineered phage has been used to treat a bacterial infection in a human being successfully. And also it's the first time that a Mycobacterium infection in a human has been successfully treated with phage therapy. And it lends hope that maybe someday we could treat tuberculosis with phage therapy, wouldn't that be awesome?

Erin Allmann Updyke

That would be incredible.

Erin Welsh

That is so exciting. Wow, that is amazing. And it seems like it's coming at just a highly, highly needed time. We need to do something about this huge and continuing to grow problem of antibiotic resistance. And so how have you felt the receptivity of phage therapy in academic circles for instance? Do you feel like people are being fairly receptive or is there still some pushback?

Steffanie Strathdee

Well initially when Tom's case was starting to become publicized about a year after he was treated, it was presented at the 100 anniversary of the discovery of bacteria phages at the Pasteur Institute and then the story went viral. I mean literally I was getting contacted by people from all over the world wanting phage therapy but it was mostly patients and their families, doctors were very skeptical. And until Chip Schooley started making presentations to infectious disease physicians, that's when they started to realize wow, this isn't just a one-off, there's several other cases and it's looking really exciting.

And they're very well documented and Tom's case is published and several other cases have been published. And of course the Georgians and the Poles have been doing this phage therapy for years now and there's also interest in their work and they have extraordinary clinical experience. But it had been really kind of poo-pooed because it was thought of as this 'Soviet science'. And so it's really been a watershed moment for reasons that I don't completely understand but the story itself has kind of led to a lot more interest in phage therapy, pharmas and biotechs have started to get into the space because they realize too that will genetically engineered or even synthetic phages, they'll be easier to patent.

The NIH which had traditionally not funded any phage therapy, they funded now two clinical trials of phage therapy. The first is going to be undertaken by our center, IPAT, in collaboration the Antibiotic Resistance Leadership Group, a network of research institutions around the US that have predominantly focused on new antibiotics but since there's not antibiotics in the pipeline to speak of, they've embraced phage therapy. So we're very excited by that because that's what we need now, we need clinical trials to advance phage therapy and to first show efficacy and then we can hope that the FDA will license it alongside antibiotics. We don't think that phage is ever gonna replace antibiotics altogether but it will be an important adjunct and it will allow us to reduce the amount of antibiotics that we're using. We've even seen that phage can be synergistic with antibiotics, we saw that in Tom's case and in several other cases. So if we can leverage the power of phage, we'll be using antibiotics more wisely.

	I'm just happy that our story can kind of take a rightful place in medical history, I mean Tom and I are really privileged, if we had been living anywhere else or if I didn't have the connections that I did and wonderful colleagues at our University hospital, I'd be holding an urn with his ashes instead of his hands. So that was one of the reasons we decided to tell our story because we realized how privileged we are and that most people die from superbugs around lower and middle income countries and they don't have the resources we have. So my dream someday is to have an open source phage bank that can be accessible to anyone, anywhere and I'm fundraising for that through IPAT, that's our Center for Innovative Phage Applications and Therapeutics and hopefully one of these days we'll be able to say goodbye to superbugs.
TPWKY	(transition theme)
Erin Welsh	That was amazing, we were so excited to speak with you. Thank you so much for taking the time to chat phages.
Erin Allmann Updyke	So cool, so cool, so cool.
Erin Welsh	The coolest! The coolest. Erin do we have anything else or is it time for sources?
Erin Allmann Updyke	This was such a fun episode, let's cover sources.
Erin Welsh	Let's do it. I think I might have mentioned a couple of times the book 'Big Chicken'.
Erin Allmann Updyke	Just a few.
Erin Welsh	(laughs) Just a few, by Maryn McKenna. It's great, it's about the use of antibiotics in agriculture, particularly the chicken industry. And I also read a few papers that I will put on the website. But another book that I read is called 'The Killers Within: The Deadly Rise of Drug-Resistant Bacteria' by M. B. Shnayerson and M. J. Plotkin. And finally you guys should definitely check out Dr. Strathdee's book called 'The Perfect Predator: A Scientist's Race to Save Her Husband from a Deadly Superbug: A Memoir'. So good, you guys, seriously.
Erin Allmann Updyke	So good, so good. I heavily used actually the same book that I used for the antibiotics episode edited by Rosaleen Anderson et al called 'Antibacterial Agents: Chemistry, Mode of Action, Mechanisms of Resistance, and Clinical Applications'. And then there's another great paper from 2016 called 'Mechanisms of antibiotic resistance' that I will link to plus a whole bunch of papers on the kind of current status of antibiotic resistance. We'll link to all of our sources from this episode and every episode on our website.
Erin Welsh	Yes. Thank you again so much to Dr. Strathdee for coming on and chatting with us and telling her story, we really appreciate it.
Erin Allmann Updyke	So, so much. Thank you so much for taking time to speak with us. And thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Welsh	Yes. And thank you to you, listeners, for listening. We appreciate it.
Erin Allmann Updyke	51 episodes long!
Erin Welsh	51 episodes. Now we can continue our excitement. (laughs) Awesome.

Erin Allmann Updyke	Oh wow.
Erin Welsh	Well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals!