

TPWKY

This is Exactly Right.

Erin Welsh

"I am one of the increasingly rare old-timers who lived during the pre vaccination era. I am the second to the last of 13 siblings, 5 of whom died of vaccine preventable diseases in infancy. Born to poor immigrant parents, I remember well my mother's account of the causes of their deaths. Three from pertussis and two from measles. Even after many years had passed she spoke of the death of her angels with a great deal of emotion. Imagine losing not one, two, three, or four but five babies. It was common in the pre-vaccine era. Like our family, many families lost several children to these diseases. We forget, time blurs our memories of these common tragedies of yesteryear. I remember well during the winter and spring of each year hearing the whoop of pertussis in movie theaters, school assemblies, and assorted gatherings. Today few have ever heard this and those who have forget. I remember the summer outbreaks of polio, the crippled children who could no longer walk or walked with limb-distorted limbs.

As a third and fourth year medical student I remember answering the appeals of hospital administrators who could not find the nursing staff for special duty tending to the needs of polio patients in iron lungs. We forget. I remember the awful cases of measles my own children experienced. I remember the children with smallpox during the years my family lived in Pakistan. I remember those who lost their sight from lesions in their eyes. I remember those who died. We forget."

TPWKY

(This Podcast Will Kill You intro theme)

Erin Welsh

So that was a letter to the Immunization Action Coalition by E. J. Gene Gangarosa who was a professor emeritus from Emory University and he wrote that letter in 2000.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah. It is amazing, he's very right. We do forget.

Erin Allmann Updyke

Forget.

Erin Welsh

And those of us who've never heard it don't know.

Erin Allmann Updyke

Right, yeah.

Erin Welsh

We don't know what it's like.

Erin Allmann Updyke

Right.

Erin Welsh

My name is Erin Welsh.

Erin Allmann Updyke

And I'm Erin Allmann Updyke.

Erin Welsh

And this is This Podcast Will Kill You.

Erin Allmann Updyke

Vaccines today!

Erin Welsh

Yes. This is the first episode of a two part series on vaccines and all about the history of vaccines, the biology of vaccines, how they work. And we are also so thrilled for this episode because we got to talk to two real life vaccine experts!

Erin Allmann Updyke

Woo!

Erin Welsh

Dr. Gail Rodgers and Dr. Padmini Srikantiah who are both senior program officers at the Bill and Melinda Gates Foundation. We chatted with Dr. Srikantiah and Dr. Rodgers about how vaccines are developed, some of the different vaccine-preventable diseases that are targeted around the world, and the challenges faced in some global vaccination initiatives. We had such a great time talking with them, seriously aspirational.

Erin Allmann Updyke

Yeah, they've like lived lives that we want to live someday.

Erin Welsh

It was so cool. And we know that your gonna love them too. So stay tuned.

Erin Allmann Updyke

Woo woo!

Erin Welsh

Okay so what are we drinking today? It's vaccine time. (laughs) No, it's quarantini time.

Erin Allmann Updyke

(laughs) It's quarantini time. We're drinking - wait for it - Ender's Fame.

Erin Welsh

Finally.

Erin Allmann Updyke

Finally.

Erin Welsh

Yes. So this quarantini is named for John Enders who is the recipient of a Nobel Prize for his work on cultivating the poliovirus which really paved the way to create polio vaccine, he also created the measles vaccine. I'm talking too much about the history, tell me what's in the drink.

Erin Allmann Updyke

(laughs) It's cognac, orange liqueur, and lemon juice. It's basically a sidecar.

Erin Welsh

Yeah.

Erin Allmann Updyke

Fancy little fun drink. And we'll have the full recipe for that quarantini as well as our nonalcoholic placebortia on all of our social media channels as well as our website thispodcastwillkillyou.com.

Erin Welsh

Yeah, check it out.

Erin Allmann Updyke

Ch-ch-check it out.

Erin Welsh

We also really quick need to make a fun little announcement. We are working on an episode where we answer questions you send us about us or about disease ecology or epidemiology or podcasting or cocktail techniques or honestly whatever you can think up.

Erin Allmann Updyke

Anything you want to know. So send us your questions by email to thispodcastwillkillyou@gmail.com.

Erin Welsh

And if you decide to send us a question that you want us to answer for this episode, please put 'Ask the Erins' or something to that effect in the subject line and let us know whether you're okay with us saying your name on the episode.

Erin Allmann Updyke

We can't wait to hear from you!

Erin Welsh

All right.

Erin Allmann Updyke

Should we just jump right into it?

Erin Welsh

I think we should.

Erin Allmann Updyke

Okay. We'll take a quick short break.

TPWKY

(transition theme)

Erin Allmann Updyke

So vaccines are often called one of the greatest public health inventions of all time and I agree, they totally are. But it's partially because they work at two different levels. Vaccines work both on an individual level, so when you get vaccinated you are protected against whatever infection you just got vaccinated against which is great, who doesn't want to be protected? But they also work at the population level. So when you get vaccinated, you're actually protecting all of those around you as well. So you can pat yourself on the back for doing a public service every time you get vaccinated. So to understand exactly how vaccines can be so awesome and work on these two totally different levels, I'm gonna get into some serious detail about the biology and epidemiology of how they work. And I'm gonna do it so that you can A) understand how awesome our immune systems are, B) understand how cool it is that vaccines exist, and C) be the one who explains this to Aunt Martha at Thanksgiving this year.

Erin Welsh

Oh yeah. (laughs)

Erin Allmann Updyke

Okay. (laughs)

Erin Welsh

Excellent.

Erin Allmann Updyke

All right. So to first understand how vaccines can protect you specifically, dear listeners, we first have to understand how our immune system works and how our bodies fight off infection. So immunologists, don't hate me, I'm gonna break this down in the simplest possible way. It's more complicated but these are the basics. There are two major parts to our immune system. There's a nonspecific which is called the innate immune response and then there's a specific response which is called the adaptive response.

Erin Welsh

Okay.

Erin Allmann Updyke

The innate immune response, it's very fast on the uptake. When you get exposed to viruses or bacteria it can find them and start to get to work really quickly. But it's not that powerful, it doesn't last that long, and it can't destroy everything. So we have a second immune response, the adaptive immune response. This is something that allows us to target very specific individual pathogens but it takes some time, it's a little bit slow to get started. So what that means is that before your adaptive immune response kicks in, you usually get sick. You feel crappy. And then your adaptive immune system needs time to kick in and actually fight off that infection but the good thing about this adaptive immune response is that it has a memory like an elephant. It never forgets. So anything that the adaptive immune response has responded to once, the second time it's exposed to that same virus or bacteria, it can respond much more rapidly and much more effectively.

Erin Welsh

Right. Right.

Erin Allmann Updyke Okay. So here's how it works in four acts, we're gonna have a play.

Erin Welsh Oh my god, my mine's in four parts too!

Erin Allmann Updyke Really?

Erin Welsh Yeah!

Erin Allmann Updyke Oh my god we didn't even plan that!

Erin Welsh No we didn't. (laughs) Okay.

Erin Allmann Updyke (laughs) That's thrilling, oh my goodness. Okay. So our biology play, first four acts. Here we go. So we have three main characters. Do you have three main characters too?

Erin Welsh I have a host of characters.

Erin Allmann Updyke Okay well we're just simplifying it to three. We're gonna have three main characters in our immune system play: the macrophages, the T cells, and the B cells.

Erin Welsh Okay.

Erin Allmann Updyke All of these three characters are types of white blood cells and in your body you have a lot more than just these three but these are our three main characters and all of the rest of your white blood cells are gonna be the ensemble.

Erin Welsh Okay.

Erin Allmann Updyke All right.

Act I: You Breathe.

Okay? In your breath you inhale an antigen. This might be a virus, a bacteria, a toxin, your neighbor's boogers, aerosolized poop, whatever.

Erin Welsh Gross.

Erin Allmann Updyke Yeah well, that's life. It's a foreign substance that doesn't belong in your body. And in your body just waiting at the ready are thousands, nay, millions of these white blood cells ready to jump into action. First in comes the macrophages. The macrophages are gonna see this antigen, this virus or bacteria, and they're going to eat it. They're gonna gobble it up. And they're gonna take that and take a part of it and they're gonna bring it over to their friends who enter stage left, the T cells. And the T cells walk in and they're like, 'Hey! Macro! How's it going? Whatchu got? What do you have for us today?' And the macrophage is like, 'So I don't know exactly what this is but I found it over there and I know it doesn't belong here. I recognize it, I'm not sure what to do with it.' And the T cells are like, 'Don't worry, we got you.'

Act II: We Got You.

Erin Welsh

Oh! (laughs)

Erin Allmann Updyke

So the T cells, they recognize that antigen, there's a whole group of these T cells. And they're like, 'We can do two different things.' Some of these T cells, they're a little wacky, they're a little wild, okay? They're called the cytotoxic T cells. They probably have like a mohawk and motorcycle.

Erin Welsh

Sweet.

Erin Allmann Updyke

They recognize that antigen, they're like, 'I know, I know how to take care of this. Don't worry.' So they're gonna exit and they're gonna go start replicating like wildfire. And they're gonna go out and just find anything that has that same antigen, any virus that looks the same, any bacteria that looks the same as that antigen and they're gonna go out and kill it. They're just gonna start murdering things throughout your body.

Erin Welsh

Oh, okay. Shoot first, ask questions later?

Erin Allmann Updyke

Exactly. So those are the cytotoxic mohawk T cells. The other T cells, they've got like bangs and a short bob, they're the helper T cells. They're a lot calmer. They're gonna take this antigen and swing their way over to their friends who hang out at the lymph node bar, the B cells. And as they walk into the lymph node bar, they call out amongst the thousands of B cells just hanging out and they're like, 'Hey! Hi everybody! Does anyone recognize this antigen? Macrophage just dropped it off. Do you guys know what to do with it? This is kind of your thing.' And in through the swinging... What do you call those old-timey western doors?

Erin Welsh

Swinging doors?

Erin Allmann Updyke

The swiny western doors. You hear the clink-clink-

Erin Welsh

Saloon doors!

Erin Allmann Updyke

Saloon doors, there you go. You hear the clink-clink of spurs and in walks, wearing a 10 gallon hat, a B cell. And he says, 'I sure do. I sure do recognize that antigen.' And then they get to work.

Act III: Immunity.

So 10 gallon hat B cell, he knows what to do. He starts replicating and replicating, making more and more copies of himself and inside he's making antibodies. These antibodies are super specific. They're gonna target just that one antigen that the T cell brought over. And these B cells are making millions of these antibodies and what they do is they throw them out into your bloodstream, they travel throughout your whole body and they find and attach to that antigen anywhere that they find it, whether it's in your cells that have been infected, whether it's on the bacteria or on the outside of a virus, anything that has this specific antigen is gonna get an antibody attached to it. It's kind of like a flag that you put on buildings when you say this one's gonna get demolished and this one's gonna get demolished. That's what an antibody is. So these antibodies go out and mark all of these cells so that the ensemble, the rest of the cast, the rest of your white blood cells can recognize it and now they can come in and clean up the mess.

Erin Welsh

Little soldiers.

Erin Allmann Updyke Exactly.

Erin Welsh Okay.

Erin Allmann Updyke So they come in and destroy that infection.

Erin Welsh Okay so can I just review?

Erin Allmann Updyke Absolutely.

Erin Welsh Okay so the macrophage picks something up weird and then they bring it over and they're like, 'Okay everyone, T cells, B cells, what is this?' So the T cells, the killer ones, they go and they just kill anything that remotely resembles that antigen?

Erin Allmann Updyke Anything that specifically resembles that antigen.

Erin Welsh Okay. Specifically resembles that antigen.

Erin Allmann Updyke Yes, yes.

Erin Welsh What does that mean, specifically resembles?

Erin Allmann Updyke It means anything that is that exact same antigen. So it's not gonna go out and just kill anything that looks similar to it, it'll just be that exact antigen.

Erin Welsh Okay. And then the helper T cells, they go and find the B cells and say, 'Hey, this is what we're looking for, can you go and tag everything?'

Erin Allmann Updyke Exactly.

Erin Welsh And so then that makes the killer T cells job easier?

Erin Allmann Updyke Absolutely, yeah.

Erin Welsh Okay.

Erin Allmann Updyke And it also brings in the rest of the white blood cells so that it's not just the T cells out there killing things.

Erin Welsh Right. Okay. Cool.

Erin Allmann Updyke Act IV: Memory.

So once your body has done all this work and cleared the infection, it's not done. Old 10 gallon hat B cell and a few of those wild cytotoxic mohawk T cells, they're going to develop into memory cells. These cells hang out and persist. They no long run around making antibodies or killing cells, they're gonna go backstage and wait until it's their time again. Maybe they'll play cards, they'll bide their time. And if that same antigen ever shows their face again, these B cells and T cells, the memory cells, will be able to jump right back into action. They won't have to go through the whole rigamarole or Acts I, II, and III, they'll just be able to use the antibodies they already have in the memory cells to make more copies and identify and target that antigen and quash the infection before it ever takes hold.

So this is the principle that vaccines exploit. They expose you to an antigen which is a virus or a bacteria or part of a virus or bacteria and that triggers your immune system to develop this memory response so that if you're ever exposed to that virus or bacteria in real life, you've already got a response ready to go. You don't have to take the time to build that immune response.

Erin Welsh

And so the difference between that first exposure and then seeing that same pathogen again is a state of disease and then a state of rapid immune response and no disease.

Erin Allmann Updyke

Exactly.

Erin Welsh

And then a vaccine just bypasses that whole disease, you don't have to actually endure the disease symptoms.

Erin Allmann Updyke

Exactly. So if you imagine that your immune cells, in a lot of cases if they're dealing with a live virus, a full-on fully-loaded measles virus, it's not like they're just dealing with something passive. That virus has come in guns blazing. It's replicating, it's going full force while your immune cells might be kind of like tripping over their lines and getting things wrong and trying to figure out what to do about it. Right? So immunization is kind of like a dress rehearsal for the play. It's real, there's people in the audience still and you're going to develop the exact same response at the end of it but you don't have a live virus trying to kill you while you develop this immune response the very first time. Cool?

Erin Welsh

Yeah.

Erin Allmann Updyke

Cool.

Erin Welsh

It's fantastic. I mean vaccines are the best.

Erin Allmann Updyke

They're the best! So that's how vaccination can protect you as an individual. How does it protect an entire population? This is something we've touched on before but it's called herd immunity and it goes something like this. Every infectious agent, bacteria, virus, fungi, whatever, in order to survive it has to spread from person to person, that's how they reproduce. And in order to do so, in order to spread from person to person there have to be susceptible people in the population for that virus or bacteria to get into.

So if a population has a high level of vaccination, let's say like 97% of 100 people are vaccinated, that means that those 97 people have developed this immune response already. They're already protected. So if you happen to drop an infected person in the middle of that population, the chances that that infected person would run into somebody who's still susceptible to that disease are really, really low. So you'd have that one infected person who will get sick and then hopefully they'll recover or else they'll die from their infection and then that's it. Nobody else gets sick because that sick person didn't run into anyone who was susceptible to that disease.

But if you imagine that maybe only 50% of people are vaccinated, then only 50% of people are immune and the other 50 are susceptible. And you dropped an infected individual in the middle of that population, there's a pretty good chance that that infected person will run into somebody who happens to be susceptible. And maybe they cough or they shake their hand or lick their face and now you have two infected people. And then that second infected person, they have a pretty good shot, like 49 more people, that they might run into another susceptible individual and lick their face and now you have three infected individuals.

Erin Welsh

Right.

Erin Allmann Updyke

And so on and so on. So this is the principle behind herd immunity. If the entire herd, the entire population or enough of it is immune to infection either because they've already been exposed and recovered from the disease or they were vaccinated and they developed immunity, then the infection can't spread.

Erin Welsh

Right. So the more people that are immunized against something or immune to something by whatever means, the less chance a pathogen has of establishing in a population or being transmitted.

Erin Allmann Updyke

Exactly. So by getting vaccinated you are protected yourself from getting that infection but you're also protecting that tiny baby on the train who's too young to get vaccinated, your grandma who's frail and immunocompromised, whoever. You're protecting literally everyone around you when you get vaccinated. So that's how vaccines work. They're pretty dang cool.

Erin Welsh

Yeah, I love 'em. Big fan.

Erin Allmann Updyke

Me too. Major. (laughs) If you can't tell already. So there are a lot of different types of vaccines and we're gonna talk a little bit about the differences between them. Not a full-on immunology lecture but just a quick rundown. But I do wanna say at the very top of this that all vaccines that are used are extremely safe, they're extensively tested, and very highly regulated. And all the different types of vaccines that we have are very effective. And part of the reason that we have different types of vaccines is because different viruses and bacteria behave differently and so we have to come up with different types of vaccines to target those specific pathogens.

So some vaccines, for example the MMR vaccine, that's measles, mumps, and rubella which we talked about before and also the varicella which is chickenpox, these are made from what we call live attenuated viruses. So that means the vaccine itself has a live virus in it but that virus has been modified so that it's super, super weak. It's not strong, virulent virus that actually makes you get sick. It's a weak little infantile virus. So this type of vaccine elicits a really good immune response because it's just like getting a real infection in that you have virus replicating in your body. But because it's such a weak virus, you don't get sick from it. However it does mean that some people who are immunocompromised, who have very weak immune systems might not be able to get these live virus vaccines cause their immune system might not be strong enough to fight off even a very weak virus.

Erin Welsh

Gotcha.

Erin Allmann Updyke

Okay. We also have whole killed vaccines. So these are vaccines that are a whole entire virus, so all of the different parts of the virus but we kill the virus before we make the vaccine out of it. So that's the inactivated poliovirus, the one that is an injection or the influenza vaccine.

Erin Welsh

And so are there also killed bacteria vaccines?

Erin Allmann Updyke

There are. So there's a killed bacteria vaccine for typhoid and there's also a live vaccine for typhoid. Hey, there's both.

Erin Welsh

Cool.

Erin Allmann Updyke

So these whole killed vaccines, you still develop a really strong immune response but you might need to get more boosters with this type of vaccine because it might not be quite as strong of a response as you get from a live vaccine. But people who are immunocompromised can still get these killed virus vaccines because there's no live virus in these vaccines that's replicating.

Erin Welsh

So going back to the flu vaccine.

Erin Allmann Updyke

Yes.

Erin Welsh

This means that-

Erin Allmann Updyke

(laughs) This means that you cannot get the flu from the flu vaccine!

Erin Welsh

Correct.

Erin Allmann Updyke

Absolutely not ever.

Erin Welsh

Nor can you pass on the flu to someone if you have gotten the flu shot.

Erin Allmann Updyke

Exactly, it's not possible. It's a killed, dead virus.

Erin Welsh

Okay.

Erin Allmann Updyke

Sometimes you might get a slight fever or muscle aches, especially in the arm that you got the shot in or the butt cheek where you got your vaccine. Do you know why, Erin, that you might get a fever and feel achy?

Erin Welsh

Is it some sort of innate immune response?

Erin Allmann Updyke

Oh, you're so good! (laughs) It's your actual immune system actually doing its job. So you might feel a little bit cruddy after you get a vaccine but it's a lot less cruddy than you would feel if you got that actual infection.

Erin Welsh

Right. And also you wouldn't die.

Erin Allmann Updyke

You won't die.

Erin Welsh

Like you might if you got the actual infection.

Erin Allmann Updyke

Right, exactly, yeah. No again, adverse events are extremely, extremely rare for vaccines. They're very safe. The other thing about live virus vaccines and the reason why some vaccines that we used to use as live virus vaccines we no longer use live virus vaccines is that there is a small chance that people can actually get sick, essentially, from the vaccine itself. Because it is a live virus there is a chance that either the virus can change a little bit or mutate or your immune system, even if you have a good immune system and you're not immunocompromised, might not just be strong enough to fight off that vaccine strain.

So for example with the oral polio vaccine which is a live version of the polio vaccine that isn't really used much around the world, it's only used in places where there is still a chance of polio infection, like wild-type polio still circulates. In about 1 in 2.5 million doses someone would end up getting polio from the polio vaccine. So it is theoretically possible that with a live virus vaccine that you could end up getting sick or end up for example, if you get the varicella vaccine and then end up getting a rash, you could potentially then pass varicella to somebody who is immunocompromised from that vaccine strain. Again it's very, very, very rare. These would be considered adverse events and those are all reported to a system called the vaccine adverse events reporting system.

Erin Welsh

And those would be detectable as vaccine strain so the infection would be milder than if it were wild-type?

Erin Allmann Updyke

Exactly, right. Yeah.

Erin Welsh

Okay.

Erin Allmann Updyke

Okay there's a few other kinds of vaccines. There are toxoid vaccines which are very fun. Toxoid vaccines are an inactivated version of a bacterial toxin. So do you remember one that we covered already?

Erin Welsh

Diphtheria?

Erin Allmann Updyke

Diphtheria! Also tetanus, okay.

Erin Welsh

I think that toxoid vaccines are my favorite and I don't know why.

Erin Allmann Updyke

You know actually they're my second favorite, I'll tell you my favorite in just a second.

Erin Welsh

Oh I can't wait.

Erin Allmann Updyke

So because some bacteria don't actually make you sick themselves but they produce a toxin that makes you sick, then we can just take that toxin and give you a vaccination with that inactivated toxin which is called a toxoid. And that way you're protected against any strains of that bacteria that contain the toxin. Very cool.

Erin Welsh

Question.

Erin Allmann Updyke

Answer.

Erin Welsh

Cholera produces a toxin. Is the cholera vaccine toxoid or is it...?

Erin Allmann Updyke

That's a good question. I'm pretty sure that it is. I was just looking at the cholera vaccine. I think I wrote it down.

Erin Welsh

No I have it right here, hold on. Okay so the one that was produced in 1896 was killed whole and then the second one that was in 1991 is also killed whole cell.

Erin Allmann Updyke

Killed whole cell vaccine.

Erin Welsh

And then the one in 2009 was also killed whole cell.

Erin Allmann Updyke

Okay. Killed whole. So cholera is a killed whole cell vaccine, maybe that's why it's not a super excellent vaccine. (laughs)

Erin Welsh

Yeah.

Erin Allmann Updyke

It's not the most effective. Anyways. There are also what are called component vaccines. This is as an example the hepatitis B vaccine. So a component vaccine, instead of having an entire killed virus it has just a small part. Just the part that you would need to be able to quash that infection. In the case of hepatitis B we have a single antigen, the surface antigen, so that's like what's on the surface of the hepatitis B virus aka what your body needs to be able to see to prevent that virus from ever getting into your cells. So we have some vaccines like that that are just made of a single component of a virus.

Erin Welsh

Okay. And are there also component bacterial vaccines?

Erin Allmann Updyke

Yeah, there are. For sure. But what's more common for bacterial vaccines are my favorite vaccine, the conjugate vaccine. So this is what is really commonly used against bacteria. The reason is - okay, this is where we get back into some immunology.

Erin Welsh

Oh good.

Erin Allmann Updyke

It turns out bacteria are very good at evading our immune system, they're very clever, they've been with us for millions of years so they know how to get around our immune responses. So a lot of bacteria on their surface have sugars, polysaccharides. These polysaccharides specifically evolved in order to evade our immune response because as it turns out that whole amazing immune response that I told you about with the B cell 10 gallon and the helper T cells, those only work if the antigen is a protein. So what we figured out to outsmart these bacteria who have polysaccharides, not proteins on their surface is that we can take these polysaccharide sugars and we can conjugate them which means attach them to a protein antigen, for example the tetanus toxoid which we know is safe because we use it in vaccines. Conjugate a bacterial polysaccharide to that protein and use that as a vaccine and then our body will make antibodies to fight off that bacterial sugar.

Erin Welsh

My brain is tingling.

Erin Allmann Updyke

Isn't it?

Erin Welsh

That's so fascinating.

Erin Allmann Updyke

I know, they're my favorite.

Erin Welsh	What the heck?
Erin Allmann Updyke	So very cool, that's how we got vaccines for Haemophilus influenzae, Neisseria meningitidis, etc. So those are definitely I think the newest vaccines are conjugate vaccines. Well even newer are DNA vaccines which I'm not gonna talk about today. But how fun, right?
Erin Welsh	That's amazing.
Erin Allmann Updyke	It's very cool.
Erin Welsh	Question. How exactly are vaccines developed?
Erin Allmann Updyke	Great question. I'm not going to answer it. (laughs)
Erin Welsh	Okay. (laughs)
Erin Allmann Updyke	But that's because we were fortunate enough to chat with Dr. Gail Rodgers who is a senior program officer at the Bill and Melinda Gates Foundation which is the world's largest private charity foundation that focuses on improving health and reducing poverty around the world. And Dr. Rodgers has worked on several vaccine initiatives at the development and deployment stages and she shared with us her expertise on vaccine development. So I'ma let her answer.
Erin Welsh	Take it away, Gail.
Erin Allmann Updyke	(laughs)
TPWKY	(transition theme)
Erin Allmann Updyke	So Dr. Rodgers, thank you so much for chatting with us today.
Gail Rodgers	Oh you're very welcome, I'm excited to do it.
Erin Allmann Updyke	We're really excited to talk with you about vaccine development and the future of vaccines so let's jump in.
Gail Rodgers	Great.
Erin Allmann Updyke	Can you introduce yourself and tell us a bit about your background and your role now at the Gates Foundation?
Gail Rodgers	Sure. I'm a pediatric infectious disease physician and I worked in academic in a children's hospital for many years and then went into industry working on vaccines, specifically in the area of pneumonia. And from there I moved on to work where I currently work at the Gates Foundation also in the pneumonia group to really both develop and make countries that are low resource countries have better access to vaccines, in particular to vaccines for pneumonia.

Erin Welsh

Fantastic. So on this episode we're trying to give listeners information about the process of vaccine development. So when we hear that a new vaccine has just been licensed like the recent malaria or dengue vaccines, that vaccine has gone through rigorous development and clinical trials before it gets to the licensing stage. Could you explain the general process of vaccine development from when a vaccine is just someone's idea to when it's actually being distributed around the world?

Gail Rodgers

Sure. So it's a pretty lengthy process and that's something and I think the right word is rigorous as you mentioned. So it starts out and it's somebody's idea of doing this and usually there is a preclinical stage which is when it is looked at in the laboratory, it might be looked at against different strains of what you're trying to protect against. And then tested in some forms in animals usually to start off with before it goes into what's called first in humans studies. And first in humans studies are an adult even though the vaccine may not ultimately be used on adults, always to start off in the first phase in adults. And that really is for safety reasons.

And then it goes into the second phase of testing to see if it would work against the target as well as being safe in other populations. And those are rather small studies where you start looking at it in the populations that you want to target, in my case it's babies, it's pediatrics. So it would start off in adults and then move maybe to toddlers and then move to infants where it is tested for safety and whether it is useful and whether it works. And then there is what is the big studies which are called the phase 3 studies in which it's tested in many more children in different schedules sometimes, in different countries, and really rigorously tested under many circumstances to make sure that they're safe. And then this is the one that you wanna make sure that it works against the germ that you're preventing. So after that all the evidence is looked at, all this data is looked at by really committees in the countries that are made of committees of experts, of vaccine developers, of physicians, of safety experts, etc where all the data is looked at. And based on those data then licensure is given and from when a license is given then it can go and be used by doctors as well as by countries themselves.

Erin Allmann Updyke

Excellent. So as we talk about on the episode, the past 100 years have been incredibly productive for vaccine development especially the past 40 years, even the past 10 years. Yet there is still so many other pathogens for which there is no vaccine. So what makes a pathogen a good target or a more challenging target for vaccine development?

Gail Rodgers

Yeah I guess it really is interesting. Part of it is what you look to prevent. So a lot of the times one looks to prevent the worst of the worst, the deadliest. So certainly there is a focus on very serious pathogens being targeted. And then what makes one more successful than others I think is the wide variety of the pathogens and how often they can change which is pretty daunting. For example, I know you talked to Padmini and she runs influenza but influenza changes so frequently that the target for getting one vaccine to cope against all types is really challenging. And I can tell you a specific case of the pneumococcus which is the most common cause of pneumonia and common cause of death in children less than 5 for which there is a vaccine. And there had been a vaccine many years ago that was geared to adults and it was only in the 90s when the technology became available to know how to actually compose the vaccine to make children's immune system react to it that a vaccine became available for children.

So the challenges are in the pathogen itself, it's in how our immune system reacts to it and what type of protection can be elicited at different ages. And then for pneumococcus for example there's over 90 serotypes they're called that cause pneumonia. And it's hard to envision trying to do this for all 90. So it started out with doing it for several, for 7 initially and when that worked and those were the 7 that were picked as being the most commonly cause of disease and then it got expanded. So currently we have 10 serotypes and 13, two different vaccines that target those serotypes and more on the way as technology advances.

Erin Welsh

Well speaking of technology, so there is as you mentioned a lot of very interesting future avenues for vaccine development. So what do you see as some of the most exciting future prospects for vaccine technology? Where do you think we're going with vaccines?

Gail Rodgers

Oh I think we're aiming to challenge and really try to control the worst of the pathogens as they become more prominent. So I think that for one technology is helping us to try to get to a universal influenza vaccine so old pathogens that we know of. But what I'm kind of really interested in and not directly involved with the development but really see as new diseases come up that are truly worldwide threats such as Ebola, such as Zika, that it's pretty now clear that advances can be made pretty quickly in these fields with new technologies that will lead us to having vaccines for example for Ebola in a timespan that was really unreachable or inconceivable before. So I guess I'm kind of hopeful for a response time. In the future I'm hoping for antimicrobial resistance, a vaccine for that that would be multi pathogen, I mean this is really a dream. And as organisms they're pretty smart and they can outdo antibiotics quite quickly. I think that potentially going the vaccine route is gonna be important.

Erin Welsh

That's really exciting. The idea of a vaccine for multiple pathogens that are antimicrobial resistant, I just...

Erin Allmann Updyke

It's thrilling.

Erin Welsh

My mind just went poof.

Erin Allmann Updyke

I got chills.

Gail Rodgers

Well that's a dream but you gotta dream big.

Erin Allmann Updyke

Right.

Gail Rodgers

Yeah and you know just seeing for example there are other things as well that I think I can point towards that are really interesting on a different realm which is trying to get what we strive for at Gates which is trying to get vaccines that are available or are in development to be aimed toward pathogens for countries that have lower limited resources, so developing countries for example. And before we had vaccines that were really good but we had no way that low resource countries could afford them. And now there are innovative financing mechanisms involving tiered pricing, etc. So at the same time that they're licensed in the U.S. and Europe and used in middle income countries, they can be used in low income countries as well. And that's particularly exciting to have that kind of equity being built throughout the world for prevention.

Erin Allmann Updyke

Yeah that's amazing. So for some of our listeners who want to dive even deeper into the future of vaccine development, can you help direct our listeners on where they can go to find more information about some of the vaccines that are being developed by the Gates Foundation and elsewhere?

Gail Rodgers

Yeah sure. So I think that always a really good resource is the cdc.gov website. They have what's available as well as what's up and coming. There's also clinicaltrials.gov that tells you all the trials that are being done with vaccines as well as with other drugs. So those are really good resources for you to look for what's up and coming.

Erin Welsh

Fantastic, thank you so much. Well Dr. Rodgers I think those are all the questions that we have for you today. Thank you so, so much for taking the time out of your busy schedule to chat with us today, we really appreciate it. We had a great time.

Gail Rodgers	No problem, this is great. Thank you so much.
Erin Welsh	That was so awesome, we learned so much.
Erin Allmann Updyke	Oh my gosh, so much.
Erin Welsh	How cool was it to talk with her?
Erin Allmann Updyke	Amazing. Okay so that's vaccines, finally.
Erin Welsh	(laughs) Yay.
Erin Allmann Updyke	That's all I have for the biology. It was like a whole immunology course.
Erin Welsh	Yeah. I feel armed with knowledge.
Erin Allmann Updyke	Great, great. Arm me with some knowledge then. (laughs)
Erin Welsh	Okay well get ready to learn.
Erin Allmann Updyke	I can't wait.
Erin Welsh	There's a lot of history here.
Erin Allmann Updyke	Let's take a quick break.
Erin Welsh	All right, let's do it.
TPWKY	(transition theme)
Erin Welsh	For this episode I'm going to give an overview of the history of vaccine development and the observed effects in disease prevalence after vaccines were widely adopted. I'm not gonna go heavily into the various anti-vaccine movements yet, I'm saving that for next episode so hold on, hold tight.
Erin Allmann Updyke	Excellent. Hold onto your butts.
Erin Welsh	Hold onto your butts. And I'm also not gonna go into the details of every single vaccine that has been created because if I were to do that we would be here forever. But I am going to touch on the highlights of vaccine developments and what I see as the biggest stages of vaccine history.
	Act I: Blossom.
Erin Allmann Updyke	I love it.

Erin Welsh: As we know, the word 'vaccine' itself tells us its roots. Edward Jenner developed and tested the first vaccine against smallpox in 1796 in England from a cowpox sore, 'vacca' means cow. Even though cowpox is no longer used in the smallpox vaccine or any vaccines, the name stuck and is used for all diseases. Okay so that much we know. Technically speaking though, the smallpox vaccine really is the first vaccine but that's not exactly where the history of vaccines begins. Some of this is a bit of a refresher from past episodes, by the way. So the history of vaccines starts over 1000 years ago in China where writings tell of a tradition called inoculation used to prevent smallpox infections. This practice may even go back to as early as 200 BCE.

Erin Allmann Updyke: Wow.

Erin Welsh: Yeah, it's amazing.

Erin Allmann Updyke: It's totally amazing.

Erin Welsh: Basically you were supposed to grind up scabs from people who had recovered from a mild form of the disease and then blow them into the noses of healthy children. Gross.

Erin Allmann Updyke: So gross.

Erin Welsh: This would usually result in some mild symptoms but it would also ensure that the child would not come down with severe smallpox later in life. Sidenote, the earliest immunization might be even older than variolation against smallpox. So apparently people used to try to prevent severe or disfiguring leishmaniasis infections by scraping an active lesion of someone with the disease and putting it on a child's arm or butt.

Erin Allmann Updyke: Really?

Erin Welsh: Yeah.

Erin Allmann Updyke: Ugh.

Erin Welsh: I know. So there isn't a licensed leishmaniasis vaccine today but people at the Texas Children's Hospital Center for Vaccine Development are working on it.

Erin Allmann Updyke: Ooh! Spoilers.

Erin Welsh: Yeah. (laughs) Back to variolation/inoculation. Because the Silk Road allowed for exchange not just of good but also ideas, Turkey picked up this practice as well. So this concept was starting to pick up steam in Eastern Europe around the same time that people were starting to travel to the New World, bringing with them smallpox along with other killer microbes like measles and influenza that would wipe out the majority of the native populations.

Erin Allmann Updyke: (trumpeting sound) Yep.

Erin Welsh: In Turkey the practice was refined a bit. So instead of snorting ground up scabs-

Erin Allmann Updyke: (laughs) Snorting.

Erin Welsh: (laughs) Just like do a line of ground up scabs.

Erin Allmann Updyke

Just like a line, yeah. (laughs) It's so gross.

Erin Welsh

So people actually injected the infectious material just under the skin, so this is variolation. And so even though smallpox was a deadly killer that could devastate communities, people outside of Turkey and China were super hesitant to take up the practice because they viewed it as dirty despite numerous reports of its efficacy. This is also the same people who would just dump poop right into the streets but cool.

Erin Allmann Updyke

(laughs) That's fine.

Erin Welsh

Cool. A few people went against this thinking and I mentioned some of them on the smallpox episode such as Lady Mary Montague and Cotton Mather. And it's not surprising that variolation was slow to catch on really because stories of its effectiveness were largely just stories. At that point clinical trials weren't yet a thing. But these iconoclastic thinkers definitely helped pave the way for the acceptance of variolation and eventually vaccination. Okay, smallpox vaccination as we all know was developed by Edward Jenner in 1796 in the story we all know and love. Jenner, who already knew about variolation, had his revelation when he realized that milkmaids never got smallpox because they were protected against it after being exposed to cowpox which is another infection.

Erin Allmann Updyke

Blah, blah, blah, see Episode 3.

Erin Welsh

Blah, blah. Yep. I do wanna include this part. He tested this out on a child named James Phipps.

Erin Allmann Updyke

Little Jimmy Jim.

Erin Welsh

Inoculating him first with cowpox on May 14th, 1796.

Erin Allmann Updyke

That's the day this episode's being released!

Erin Welsh

Yes!

Erin Allmann Updyke

Oh my god, did we do it on purpose? 100% no.

Erin Welsh

No definitely not.

Erin Allmann Updyke

This is my favorite.

Erin Welsh

Just serendipity.

Erin Allmann Updyke

Wow.

Erin Welsh

I love it. 223 years ago today on the day that hopefully a lot of you are hearing this is the day of the first vaccine.

Erin Allmann Updyke

Oh my gracious. Oh I feel so excited in my heart. (laughs)

Erin Welsh

Good, good. (laughs) Okay so anyway we got Phipps with this cowpox injection thing, he's protected from smallpox. The Royal Society of London is like, 'Okay this looks great, I love it.' Okay so I don't remember if I mentioned this in the episode of smallpox but apparently the cow that was the source of the cowpox used in this vaccination was named Blossom. Hence the title of Act I.

Erin Allmann Updyke

The title of Act I. (laughs)

Erin Welsh

So her hide, Blossom's hide is displayed at St. George's Hospital in London. So if there are any London listeners that are out there-

Erin Allmann Updyke

Send us pics!

Erin Welsh

Please send us a pic. Okay, was Jenner actually the first to come up with this idea of cowpox preventing smallpox? Probably not. We know of at least one other person who 20 years before Jenner's vaccine amidst a smallpox outbreak decided to infect his family with cowpox and no one became infected. But word got around and the community was like very angry and anxious, they were like, 'This family is gonna grow horns and udders and they're gonna mutate so you all need to get out of here.' So the family moved to avoid the constant physical and verbal harassment from their wonderful neighbors.

Erin Allmann Updyke

Wow.

Erin Welsh

And they lived out a long and smallpox-free life.

Erin Allmann Updyke

Alone forever.

Erin Welsh

Alone. (laughs) So it seems not so much that Jenner was the first to make the logical leap about cowpox protecting against smallpox but rather the first to conduct trials on multiple people and bring his results to the attention of a large and legit medical society. And this first vaccine would light the way for the development of so many more.

Act II: Chance Favors the Prepared Mind.

Erin Allmann Updyke

(laughs)

Erin Welsh

Even though vaccination... God I'm such a dork.

Erin Allmann Updyke

I love it.

Erin Welsh

Even though vaccination clearly saved lives by preventing severe cases of smallpox and decreasing epidemics, people didn't really know exactly how it worked. For about 60 or 70 years after Jenner first vaccinated Phipps, germ theory which is the idea that microorganisms can cause disease and can be transmitted from person to person hadn't really been developed, much less widely accepted. Luckily for the world, Louis Pasteur had had it up to here with sour wine and spoiled beer.

Erin Allmann Updyke

(laughs) Haven't we all?

Erin Welsh

I'm kidding though about that probably, I don't know for sure if that's what motivated him. In the 1850s and 1860s, Pasteur who's one of our favorite microbiologists was investigating fermentation in alcohol, specifically wine and beer and found that yeast, a microorganism was responsible for the production of alcohol and that when exposed to certain other microorganisms the wine or beer could spoil. He made the logical jump from microbe spoiling wine to microbes causing disease in humans and animals and switched his research focus from alcohol production to the field that we now call microbiology. Where do vaccines come into this? Okay. In the summer of 1880, so almost 100 years after Jenner's vaccine, Louis Pasteur was going on vacation. He packed his bags, double checked the stove was turned off, and told his assistant to finish up a chicken cholera study they had been working on. So chicken or avian cholera is caused by *Pasteurella multocida* or something like that for those of you who might be curious.

Erin Allmann Updyke

Oh, all right. I'm curious.

Erin Welsh

Apparently it's extremely high mortality rate.

Erin Allmann Updyke

In the chickens?

Erin Welsh

Yeah in wild and domestic fowl.

Erin Allmann Updyke

Oh poor babies.

Erin Welsh

Yeah. So Pasteur just set off for holiday, leaving his research in good hands. Or so he thought. It turns out the assistant was busy getting ready for his own vacation and completely forgot about the experiment. Luckily he returned before boss Pasteur did and when he got back he saw the test tube with avian cholera broth still sitting on the bench and the chickens were running around blissfully unaware that they had narrowly escaped a horrible death. The assistant was like, 'Well better late than never' and injected the chickens with the stale broth. Nothing happened to the chickens.

Erin Allmann Updyke

Oh my gosh!

Erin Welsh

Right?

Erin Allmann Updyke

I didn't know this little story, this is so cool!

Erin Welsh

Isn't it fun?

Erin Allmann Updyke

Yeah!

Erin Welsh

So he tried again with a fresh batch of avian cholera, again nothing. At this point the assistant, Chamberland, is like oh god, he's in full panic mode.

Erin Allmann Updyke

Chamberland.

Erin Welsh

He's like, 'I'm about to get fired but I have to tell the boss.' So he fills in Pasteur on the results and Pasteur is like, 'Oh my gosh, are you kidding me? This is the most exciting thing, what do you mean? Do this same exact experiment, leave the broth out for a long time and then just do the whole thing all over again.'

Erin Allmann Updyke

I love this. I feel like I would love to work for Pasteur. You're like, 'Okay gotta tell me boss I really screwed up.' And they're like, 'This is the best news!'

Erin Welsh

Yeah he's like, 'What? Genius!' So then that's what Chamberland does and again the chickens remain healthy and cholera-free.

Erin Allmann Updyke

Oh my gosh.

Erin Welsh

Both Pasteur and his assistant realize that their stale cholera was acting to protect the chickens from disease in a similar way as to how the smallpox vaccine worked. But even cooler, unlike that smallpox vaccine this avian cholera vaccine was made from the same species of bacteria themselves. So you didn't have to find a milder strain or species to create a vaccine like the cowpox virus and the smallpox virus, you just had to weaken the existing one.

Erin Allmann Updyke

Right.

Erin Welsh

So this opened this door in Pasteur's mind, hence the phrase commonly attributed to him, 'chance favors the prepared mind.' But he began to test various ways such as chemicals to weaken or attenuate different bacterial species to make more vaccines. This itself was a contentious issue because many scientists believed that bacteria were static, they were either virulent or not and they didn't change over their lifetime. According to them, adding chemicals to weaken the bacteria was not possible. But Pasteur's avian cholera vaccine was not a fluke. In the summer of 1881 Pasteur successfully produced an anthrax vaccine by attenuating the bacteria using phenol. He demonstrated the effectiveness of his vaccine on various farm animals and it was pretty widely accepted, especially by farmers because anthrax was a huge killer of cows and sheep and goats and so on. Pasteur decided to keep the name vaccine as a nod to Jenner and the story of vaccines was about to enter its heyday.

Act III: Low-Hanging Fruit

Erin Allmann Updyke

Ooh.

Erin Welsh

Pasteur's development of the avian cholera and anthrax vaccines using chemical inactivation marks a pretty big turning point in the history of vaccines. There was now a template or road map that scientists could follow to try to develop vaccines against other diseases. First identify the causative agent, then weaken it using chemicals or through multiple passages, try it out on animals, and then try it out on humans if things look good. In 1885 Pasteur developed the rabies vaccine which I talked about in the rabies episode and then Almroth Wright, Richard Pfeiffer, and Wilhelm Kolle developed the first typhoid vaccine in 1896. That same year Waldemar Mordechai Haffkine developed a cholera vaccine-

Erin Allmann Updyke

Whoa.

Erin Welsh

Yeah, what a name. Which he promptly tested on himself and then narrowly escaped with his life apparently.

Erin Allmann Updyke

Oh dear.

Erin Welsh

Yeah.

Erin Allmann Updyke

Not as perfect a vaccine, there?

Erin Welsh

Well he thought good enough so he tested it out on a bunch of friends and fortunately it worked and then he went big time with trials in India. So while he was in India testing out his cholera vaccine, Haffkine witnessed the third plague pandemic and the death and chaos it had brought. He was tasked with developing a plague vaccine which he did in 1897 and which he in typical fashion tested on himself first. He experienced a mild fever but survived and figured it was good enough to test on other people, such as prisoners.

Erin Allmann Updyke

Naturally.

Erin Welsh

Fortunately the vaccine did work without serious side effects and his quick work probably saved thousands of lives. However his fame and accolades were short-lived. In 1902 after being given the plague vaccine, a bunch of people developed tetanus symptoms and 19 died.

Erin Allmann Updyke

Oh!

Erin Welsh

Yeah. So the deaths were traced to a bottle of plague vaccine manufactured by Haffkine and he was fired and exiled and remained unemployed for at least 4 years. And this whole time he was begging to read the entire report of the inquest. Like what exactly happened? How could this have gone wrong? I don't understand. So he finally got his wish and as he read it, he learned that the specific bottle had been handled by a lab technology who dropped his forceps in the dirt and didn't bother to clean them or get a replacement. Tetanus loves soil, loves to live in soil.

Erin Allmann Updyke

That's where it hangs out, man.

Erin Welsh

Yeah.

Erin Allmann Updyke

Oh that's so awful.

Erin Welsh

Right? Yeah. Sterile technique, important.

Erin Allmann Updyke

Very.

Erin Welsh

So eventually Haffkine was publicly exonerated but the damage to his reputation was already done and would never fully recover. Haffkine's contaminated plague vaccine is a perfect illustration of the lack of oversight on vaccine development during this time. While all of these vaccines and antitoxins were being produced in the late 1800s, there wasn't really any government regulation. So a classic example of technology outpacing the law. And as you might expect, things took a tragic turn or rather they took several tragic turns. Around 1901, the year before the Haffkine incident, some smallpox vaccines and diphtheria antitoxin were contaminated with tetanus and 24 people died. Following these tragedies people were like, 'We demand that the government look over the manufacturing of vaccines.' And they got their wish. So right after this in 1902 Teddy Roosevelt signed into law the Biologics Control Act which would require that health commissioners oversaw vaccine production which was some much needed legislation.

Vaccine development didn't slow down with these new regulations, if anything it spurred researchers to create safer, more potent, more stable vaccines. And there were still plenty of devastating diseases for which there was no effective treatment or protection. In the 1920s researchers started to experiment with adjuvants, which comes from the Latin for 'to help', adding them to increase the efficacy of a vaccine by eliciting a stronger immune response that lasted longer and provided better protection. The French scientist Gaston Ramon discovered that the chemical formalin, which had been used just to preserve antitoxin, also actually inactivated the toxins. So this allowed him to develop the diphtheria vaccine in 1923 as well as a tetanus vaccine a few years later.

Erin Allmann Updyke

Gosh it seems like they need it since all their vaccines keep getting infected with tetanus. (laughs)

Erin Welsh

Right? (laughs) His contributions to vaccine development have resulted in over 60 million lives saved estimated.

Erin Allmann Updyke

Wow, jeez.

Erin Welsh

Next was pertussis. Pertussis aka whooping cough was an infamous child killer alongside measles, still is and it will definitely have an episode all of its own eventually.

Erin Allmann Updyke

Yeah.

Erin Welsh

And because it was so feared and killed so many children so horribly, it was high on the list for vaccine development. But it was a tough nut to crack. First of all it had been a real struggle getting the bacteria isolated. And even once it was isolated it was nearly impossible to culture. But eventually a broth was developed which allowed Pearl Kendrick, Grace Elderling, and Loney Clinton Gordon to develop, test, and implement a pertussis vaccine in 1940 that would be used up until the 1990s.

Erin Allmann Updyke

Wow.

Erin Welsh

Which is pretty dope.

Erin Allmann Updyke

Yeah.

Erin Welsh

Go ladies. During the 1930s vaccines against influenza, tuberculosis, the BCG vaccine, and yellow fever were developed with Max Theiler earning the only Nobel Prize to be given just for the discovery of a new vaccine, the yellow fever vaccine. Okay. It wasn't always sunshine and rainbows in the vaccine world, there some dark turns including the unethical experimentation on human volunteers that was rampant throughout this entire period.

Erin Allmann Updyke

Quote unquote "volunteers"?

Erin Welsh

Right, yeah, sorry I forgot to include the air quotes. (laughs) The contamination of a batch of yellow fever vaccine that led to 50,000 military personnel getting infected with hepatitis B during WWII.

Erin Allmann Updyke

Holy crud!

Erin Welsh

Yeah, yeah. This was when they didn't know that hepatitis B can survive in plasma. And also the Cutter polio vaccine incident in which a batch of polio vaccines were contaminated with the live virus resulting in a paralysis of 56 people, mostly children. We talk about this a bit in the polio episode. But for each of these either new laws or regulations were put into place to prevent additional suffering. Most of the vaccines that I've mentioned so far could almost be looked at as king of the low-hanging fruit of the microbiology world. Of course it was a huge leap of technology and scientific thought to develop the concept of vaccines in the first place but once it was there scientists applied it to the most common diseases and in particular those whose causative agent had been identified, those that were culturable, responded well to attenuation, and had low mutation rates or strain diversity because these were diseases that were fairly straightforward to develop vaccines for.

Erin Allmann Updyke

Right.

Erin Welsh

It was almost just a race to see who could publish their vaccine first. In many ways.

Erin Allmann Updyke

It's pretty cool.

Erin Welsh

By the 1950s, even though there was a smallpox vaccine, a rabies vaccine, a diphtheria vaccine, yellow fever vaccine, and several others, many terrible diseases including measles, mumps, rubella, hepatitis, meningitis, homofluous influenza type B, and polio still killed or permanently disabled many, many people, children in particular.

Act IV: Cultured.

Why did vaccine development for diseases like measles, rubella, and polio lag behind that of diphtheria, plague, and cholera?

Erin Allmann Updyke

Tell me.

Erin Welsh

And important part of that answer is the fact that measles, rubella, and polio are caused by viruses that can only replicate in cells while diphtheria, plague, and cholera are caused by bacteria that can replicate on their own which makes them much easier to grow in a lab setting because all you need is a correct nutrient broth. If you wanted to make a lot of bacteria to produce your vaccine or study the bacterium, you would just make a lot of broth. On the other hand, virus need cells in order to reproduce. So if you wanted a lot of viruses you had to have a lot of cells where they could grow and that's trickier than it sounds. Where do you get the cells? Well one solution was to maintain large numbers of lab animals to infect with the virus. Not great. Another was cell culture. Cell culture, which we haven't talked that much about so far-

Erin Allmann Updyke

We haven't.

Erin Welsh

-involves isolating cells from living tissue and growing them under controlled settings in a lab. These cells can come from animals or humans or plants but we're not gonna talk about those, sorry Matt-

Erin Allmann Updyke

Sorry Matt.

Erin Welsh

And they often can continue to replicate indefinitely. All you have to do is just take a little subset of the cells, place them in a new sterile container with the appropriate nutrients, and keep them at a temperature they like. Cell culture is an amazing technology that was really only getting its start in the mid 1900s but huge developments were occurring as researchers kept finding new applications for the cells. One of these applications was growing large quantities of viruses to study and to try to develop vaccines for. Before cell culture vaccines for viruses were made either directly in animal tissue such as chicken embryos in the case of yellow fever or animal nervous tissue such as in the case of rabies. But those were not perfect solutions by any means. Regulating the growth of viruses was more difficult in both cases and maintaining large numbers of lab animals was expensive and logistically challenging. Cell culture went a long way towards solving these problems. And the history of cell culture is fascinating particularly with the ethical discussions but I just can't go into it here.

Erin Allmann Updyke

No.

Erin Welsh

But we are going to cover it someday so keep an ear out for a Henrietta Lacks episode.

Erin Allmann Updyke

Oh definitely.

Erin Welsh

Okay. So cell lines began to be used to culture viruses which greatly advanced the field. One of the most important developments involves our buddy John Enders-

Erin Allmann Updyke

Enders Fame!

Erin Welsh

Of Ender's Fame, who was one of the creators of the measles vaccine. Also I just love his origin story. Okay. While finishing his master's thesis on Middle English at Harvard-

Erin Allmann Updyke

What? What?

Erin Welsh

Yeah so he got a master's in Middle English-

Erin Allmann Updyke

Give me a break.

Erin Welsh

He was all set to do a PhD on Middle English.

Erin Allmann Updyke

Middle English?

Erin Welsh

But he found himself rooming with an Australian bacteriologist, they became close buds-

Erin Allmann Updyke

He was so charming.

Erin Welsh

And Enders would tag along with him to the lab and he was like, 'Whoa, what is this? This is super cool. What are you doing? I love this.' And so he decided to get his doctorate in microbiology instead of Middle English.

Erin Allmann Updyke

That's everyone who studies Middle English who listens to this podcast, right? And then emails us like, 'Now I'm doing epidemiology.' And we're like yes!

Erin Welsh

Yes! (laughs)

Erin Allmann Updyke

By the way those emails literally break our hearts with happiness, they're the most thrilling.

Erin Welsh

Oh yeah, absolutely. Okay so in the 1940s Enders began to doubt the conventional wisdom that poliovirus only grew in nervous tissue and he decided to try to grow the virus on other types of human fetal tissue which was successful. So this was a huge turning point in polio research that would lead to the creation of the vaccine that saved countless lives and prevented so many cases of paralysis. This development also earned Enders and his two research partners Weller and Robbins the Nobel Prize in physiology or medicine in 1954. Using a similar technique but monkey kidney cells rather than human fetal cells, Jonas Salk developed the polio vaccine in 1952. Monkey kidney cells had been used for a while to grow and study viruses but something concerning came to light in the 1950s. Many of these cells which were still being used by people like Albert Sabin and Hilary Koprowski to develop live polio vaccines were found to be contaminated by a virus called SV40. SV meaning simian virus, 40 just being random.

Erin Allmann Updyke

(laughs) The 40th one or something maybe?

Erin Welsh

(laughs) Yeah, I think so. So whether these viruses caused any kind of disease in humans wasn't known but this was really worrisome because many animal cell lines had been found to be contaminated with cancer-causing viruses.

Erin Allmann Updyke

Ooh.

Erin Welsh

The live polio vaccines developed by Koprowski and Sabin which had been widely tested but not yet licensed were found to be contaminated with the virus and Salk's killed polio vaccine which had been administered to millions of people around the world was also found to contain viral particles of SV40.

Erin Allmann Updyke

Whoa.

Erin Welsh

So in those people who had already received the live vaccine, researchers found no antibodies for SV40 which indicated that it didn't cause any major infection but that's still a lot of unknowns.

Erin Allmann Updyke

Yeah.

Erin Welsh

So after this initial study that notified researchers of the presence of SV40, a researcher named Bernice Eddy had been on the hunt for any hidden dangers of the viruses tucked away in these vaccines. And she found some disturbing things. When injected into lab animals such as hamsters the animals developed tumors and died within a few months. Not great.

Erin Allmann Updyke

No.

Erin Welsh

She published her work which contributed to the general controversy and concern that was being raised about the existing Salk and Sabin polio vaccines and she was promptly demoted by her boss who told her that she wouldn't be allowed to speak at any more meetings without him reviewing and approving everything she was going to say.

Erin Allmann Updyke

Rude.

Erin Welsh

Ugh, gross. By that time that regulations were put into place to prevent the contamination of the polio vaccine by SV40, by the time people were like, 'Okay this is actually a big deal', over 98 million Americans had received the Salk vaccine which had at least inactive and very possibly active SV40 particles in it. Okay so another researcher who tried to sound the alarm bell about SV40 was Maurice Hilleman who would go on to become the most prolific vaccine developer ever.

Erin Allmann Updyke

Whoa.

Erin Welsh

Ever. Surpassing even John Enders. His name should be a household name but he was just super modest. He and his team developed vaccines for over 40 diseases, over 40 vaccines.

Erin Allmann Updyke

What?

Erin Welsh

His work is estimated to save 8 million lives every year. Isn't that amazing?

Erin Allmann Updyke

That is amazing.

Erin Welsh

Yeah. I really wanted to shout him out. Okay. So anyway vaccines made from SV40 infected cells could not be considered safe which meant massive and expensive testing as well as throwing away the vaccines already produced. There needed to be a longer term, more stable solution. Enter a man named Leonard Hayflick. Hayflick worked on cell culture at the Wistar Institute in Philadelphia, Pennsylvania under Hilary Koprowski. He had developed a strain of cells from human fetal lung tissue that he believed held great promise for the field of virology and for the development of vaccines overall. This cell strain which he called WI-38 came from a fetus that had been aborted by a woman in Sweden in 1962 where abortion had been legal since 1938. I also want to point out here that tissue from aborted fetuses had been used in scientific research for a while at that point, quite a long while, and is still widely used today with many more legal regulations in place regarding consent. Just FYI.

Erin Allmann Updyke

Yeah.

Erin Welsh

Hayflick wanted to cultivate these lung cells because he believed they would be cleaner and safer for vaccine production compared to monkey kidney cells. The WI-38 cells did not turn cancerous as did many other cell types used in culture and they were shown to be free of any viruses. So most importantly though, Hayflick was able to grow human viruses in these cells and that had powerful implications for vaccine development because if you can culture you can study and you can most likely attenuate. So these cells were shown to be stable, diploid, non cancer-causing and could be maintained in a lab for months. It was a huge deal.

But the medical community wasn't quite ready to embrace WI-38 cells. Many who had spent years developing vaccines using monkey kidney cells like Albert Sabin weren't ready to trash their research program and start anew despite the promise the WI-38 cells had. Others expressed caution. These cells were new, time would perhaps tell whether they were safe but not enough time had passed yet. So WI-38 cells, particularly in the U.S. took a backseat in vaccine development compared to monkey kidney cells. Not everyone though was willing to give up on them. Stanley Plotkin, a vaccine developer, worked at the Wistar Institute along with Hayflick and Koprowski.

Erin Allmann Updyke

These are some great names, by the way.

Erin Welsh: I know, right? (laughs) He had witnessed the rising concern about viruses contaminating monkey kidney cells and became convinced that Hayflick's WI-38 cells were the way to go. A couple years after Hayflick had published on these cells, a devastating rubella epidemic in the U.S. resulted in 12.5 million infections.

Erin Allmann Updyke: What?

Erin Welsh: Which is 1 in 15 Americans.

Erin Allmann Updyke: Holy guac.

Erin Welsh: 2100 people developed encephalitis, 6250 pregnancies ended in miscarriage or stillbirth, 5000 women chose to get abortions because they had been infected during pregnancy.

Erin Allmann Updyke: Congenital rubella is terrible.

Erin Welsh: Yep. 2100 infants died soon after birth and 20,000 babies were born and survived with congenital rubella syndrome.

Erin Allmann Updyke: Ugh.

Erin Welsh: 20,000!

Erin Allmann Updyke: Oh my uterus.

Erin Welsh: These numbers are actually probably an underestimate because physicians weren't required to report rubella cases until a year after this epidemic. So this epidemic was horrible and the urgency for an effective vaccine was keenly felt. Plotkin, who had been working on a rubella vaccine using WI-38 cells, decided to test his out. To be blunt it wasn't great. Didn't work. Many toddlers in the experiment straight up developed rubella while others developed no protection whatsoever.

Erin Allmann Updyke: Oh dear.

Erin Welsh: Yeah. But Plotkin didn't give up on his vaccine. Instead he tried different ways to weaken the virus, growing it over and over again or growing the virus at different temperatures. Eventually he hit the sweet spot. Multiple passages and a low incubation temperature of 86 degrees Fahrenheit or 30 degrees Celsius weakened the injected rubella enough to not cause any disease or side effects but left it strong enough to produce antibodies and lasting immunity.

Erin Allmann Updyke: Wow.

Erin Welsh: Despite Plotkin's WI-38 derived rubella vaccine having super solid experimental results, it was not getting any traction. Instead it was getting overshadowed by a different rubella vaccine developed in monkey cells. When Plotkin's WI-38-based vaccine was dropped from production in 1970 it wasn't noticed by too many people beyond those involved in its development but there was another person who did take notice cause she had serious concerns about the efficacy of the animal cell-based vaccines that had been selected over the WI-38 one. Her name was Dorothy Horstmann and she was a pediatrician and vaccinologist at Yale Medical School. She found that 80% of those who received the commercially available rubella vaccine became reinfected within a few months. Really bad.

Erin Allmann Updyke

Not that good.

Erin Welsh

80%.

Erin Allmann Updyke

That's a lot.

Erin Welsh

Yeah. And even more concerning, they didn't necessarily develop overt signs of the disease but were silently infected, meaning they could shed the virus to pregnant women who were unvaccinated.

Erin Allmann Updyke

Uh oh.

Erin Welsh

So she turned to Plotkin's vaccine, testing it along with the commercially available ones at daycares. And she found that Plotkin's vaccine in contrast to the two commercially available ones produced an immune response and the types of antibodies that mimicked natural infection, making the immune memory last much longer. So there was a clear winner in this race. Following Horstmann's research, Plotkin's WI-38 rubella vaccine was finally licensed in 1978 and the only other competitor, a vaccine made from animal cells, was withdrawn the following year.

Erin Allmann Updyke

Wow.

Erin Welsh

WI-38 cells have gone on to make vaccines that have been given to over 300 million people and similar methods were used to make an additional 6 billion vaccines.

Erin Allmann Updyke

Whoa.

Erin Welsh

These vaccines have saved millions of people from horrific deaths or excruciating infections or debilitating disabilities from infections like rubella, rabies, chickenpox, measles, polio, hepatitis A, shingles, and adenovirus. They've been so integral to the development of vaccines, to laying the groundwork for our understanding of how cells function, and for examining the safety and application of potential pharmaceuticals that they are displayed in little glass tubes at the National Museum of American History in D.C.

Erin Allmann Updyke

Ooh!

Erin Welsh

Yeah.

Erin Allmann Updyke

Aw I was just there and I didn't know those were there or I would've sought them out. Just went straight to Julia Child's kitchen.

Erin Welsh

Oh of course, those high counters, gotta love 'em.

Erin Allmann Updyke

Yeah.

Erin Welsh

These cells which have their origin in a single aborted fetus have prevented millions and millions of miscarriages, infant deaths, and pain and suffering around the world. There's so much more to the story of WI-38 cells if you can believe it and if you wanna learn more I recommend the book 'The Vaccine Race'. The widespread success of various vaccination programs led to record lows in diseases that previously killed or disabled millions each year. Arguably the biggest accomplishment in vaccine history besides the invention of vaccines themselves, happened when the world was officially declared smallpox-free in 1980 with the last known wild case occurring in 1977 in Somalia. The effort to eradicate smallpox left a larger legacy than just eliminating the disease though. So by assembling this global team to target this disease, it had built a vaccine infrastructure that could be used to deliver vaccines all over the world. So the WHO used this already existing infrastructure to deploy additional vaccines which I'm sure we'll hear more about. And the WHO also set up the Expanded Program on Immunizations, EPI, to do this

Throughout the 70s, 80s, 90s, and 2000s and beyond, more vaccines were developed including ones for chickenpox, Strep pneumonia, Neisseria meningitidis, hepatitis B, homofluous influenza type B, Q fever, hepatitis A, rotavirus, typhoid, human papillomavirus. I mean it's amazing. Tick-borne encephalitis, gotta throw that in there.

Erin Allmann Updyke

Yeah!

Erin Welsh

I wanted to illustrate just how many lives vaccines have saved and improved since being developed so this is what I'll call vaccines by the numbers.

Erin Allmann Updyke

Yes.

Erin Welsh

And this just compared U.S. numbers because that's all I could find in a table format. So if anyone has global comparisons between the pre-vaccination era and the post-vaccination era, please send them our way. Diphtheria before vaccines annually: 21,000 cases, 1800 deaths. 21st century annually: 0 cases, 0 deaths.

Erin Allmann Updyke

Whoa.

Erin Welsh

Measles in the U.S. before vaccines annually: 530,000 cases, 440 deaths.

Erin Allmann Updyke

Jesus.

Erin Welsh

21st century: TBD. But let's just say for no tentatively over 100 cases annually.

Erin Allmann Updyke

Yeah, average.

Erin Welsh

Yeah. Pertussis annually before vaccines: 200,000 cases, 4000 deaths. 21st century on average: 15,600 cases annually, 27 deaths. A lot higher than I thought actually.

Erin Allmann Updyke

It's a lot of waning immunity with the pertussis vaccine.

Erin Welsh

Yeah, yeah. Paralytic polio before vaccines annually: 16,300 cases, 1900 deaths. 21st century: 0, 0.

Erin Allmann Updyke

Wow.

Erin Welsh Rubella in 1969, which is the last year before a rubella vaccine was licensed, there were over 55,500 cases reported to the CDC and 10 years later that number was 11,800. So between those years the number of congenital rubella cases in the U.S. declined by 36% but at the turn of the 21st century there were 176 reported cases of rubella and 9 cases of congenital rubella.

Erin Allmann Updyke Wow.

Erin Welsh Isn't that amazing?

Erin Allmann Updyke That is absolutely incredible.

Erin Welsh Yeah. In 2005 the CDC announced that endemic rubella had been eliminated from the U.S. and 10 years later in April 2015 PAHO, the Pan American Health Organization, announced that endemic rubella had been eliminated from the western hemisphere. Just got chills.

Erin Allmann Updyke Me too. And it's hot in this room.

Erin Welsh (laughs) Smallpox. There are so many of these. Smallpox in the first half of the 20th century: 29,000 cases and 337 deaths annually. 0 obviously in the 21st century.

Erin Allmann Updyke Yeah.

Erin Welsh It's gone, it's gone.

Erin Allmann Updyke It's gone.

Erin Welsh Okay. Tetanus in the first half of the 20th century: 580 cases and 472 deaths annually. 21st century: 41 cases, 4 deaths. Before the vaccine homofluous influenza type B caused meningitis, bloodstream infections, and pneumonia in 20,000 children every year, killing 1000 of them and causing permanent brain damage in many more. When fear drove down vaccination rates, outbreaks happened in 2008 and 2009 in Minnesota, Pennsylvania, New York, Oklahoma, and Maine with at least 4 children dying because those parents chose not to vaccinate them. Okay, chickenpox. The incidence of chickenpox and shingles as well as U.S. hospitalizations and deaths, because people do die from chickenpox and shingles-

Erin Allmann Updyke Yes they do.

Erin Welsh It declined by 90% after it became a part of the routine schedule.

Erin Allmann Updyke Wow.

Erin Welsh And when a booster was added, the incidence fell another 81%.

Erin Allmann Updyke Wow.

Erin Welsh No one younger than 20 years old has died of chickenpox in the U.S. since 2010.

Erin Allmann Updyke Wow!

Erin Welsh Yeah.

Erin Allmann Updyke

That's amazing.

Erin Welsh

Okay, two more numbers. It is estimated that the work done by John Enders and his teams, Enders Fame, has saved over 120 million lives as of 2017. And I said it before but I wanna say it again, Maurice Hilleman's work is estimated to save 8 million lives each year. So he has saved more lives than any other scientist. So let's hear it for Maurice. (snaps) I kind of want that to be the title of our episode.

Erin Allmann Updyke

Let's hear it for Maurice? I like it.

Erin Welsh

Okay, good.

Erin Allmann Updyke

(laughs) I really like it.

Erin Welsh

The need for vaccines has never diminished and the recent resurgence in vaccine-preventable illnesses only highlights their importance. Erin, I'm hoping you'll tell me some good news about vaccines today.

Erin Allmann Updyke

All right. After one more short break.

TPWKY

(transition theme)

Erin Allmann Updyke

All right so let's talk about some of the vaccines, what the vaccine recommendations are around the world. Okay?

Erin Welsh

Great.

Erin Allmann Updyke

So the World Health Organization has a list of recommended routine vaccinations. So I'll kind of just go through this, you've already mentioned a lot of these because as it turns out these recommended vaccinations are in general the ones that have had the biggest impact around the world in terms of decreasing the number of disease outbreaks that we see. So the World Health Organization recommends as a blanket statement for all countries with vaccination programs that they include BCG which is the tuberculosis vaccine which I think is interesting because that is one that the U.S. does not vaccinate for but that one the World Health Organization recommends as a general recommendation.

Erin Welsh

Why doesn't the U.S. vaccinate against that?

Erin Allmann Updyke

So the BCG vaccine is a vaccine for tuberculosis that's good at preventing disseminated, so like full body tuberculosis in infants. For some reason that's not entirely clear it's not great at protecting adults so it doesn't protect adults from getting TB.

Erin Welsh

Huh.

Erin Allmann Updyke

Yeah, it's not good in adults, it's just good in kids and it's really just good against disseminated infection.

Erin Welsh

Okay.

Erin Allmann Updyke

And so infants in a lot of countries get BCG like at birth but in the U.S. we don't have high enough rates of tuberculosis to justify giving the BCG vaccine essentially.

Erin Welsh

Interesting.

Erin Allmann Updyke

Yeah. And then some countries only give it to certain subsets of their population if those children happen to be at high risk or something like that.

Erin Welsh

Okay.

Erin Allmann Updyke

All right we've also got hepatitis B which is another vaccine given to infants at birth. Polio, DTP which is diphtheria, tetanus, and pertussis, Hib that's homofluous influenza type B, the horrible one that causes meningitis, the pneumococcal vaccine which there's actually a couple different pneumococcal vaccines but this protects against meningitis as well as pneumonia in children and adults, there's different ones for children and adults. Rotavirus, measles, rubella, and HPV.

Erin Welsh

Cool.

Erin Allmann Updyke

So these are the ones WHO says every country should vaccinate for sure for these at a minimum. There's a few more that we vaccinate for in the U.S. that the World Health Organization has on their list as recommending for countries that have strong vaccination programs where they can generally achieve at least 80% vaccination coverage. And so those are mumps, varicella which is chickenpox, and seasonal influenza.

Erin Welsh

Great.

Erin Allmann Updyke

So that's the U.S. vaccine list. We actually also vaccinate against Neisseria meningitidis in the U.S. which is a truly horrible illness that causes meningitis. And that one is recommended by the WHO for some countries, so the U.S. is one of the countries that has that on their recommendations list. And then there's a whole number of other vaccines that are recommended in certain geographic areas or for certain populations. So for example some countries like China have Japanese encephalitis as a recommended vaccine for all children, hepatitis A is recommended a lot for travelers, it's probably gonna be put on the routine vaccination list here in the U.S. pretty soon. And then there's things like typhoid, cholera, yellow fever, tick-borne encephalitis.

Erin Welsh

Woo-woo! Getting that this week.

Erin Allmann Updyke

Yeah it's thrilling. So yeah, so basically recommendations differ around the world because every country is gonna decide what is the most important diseases that they wanna vaccinate their people against and different geographic regions are gonna have different risk profiles, so they're gonna vaccinate against different diseases. But something that's really important to keep in mind about all of these recommendations is that vaccines are always recommended to be given to the youngest age group that's at risk for developing that disease. So that's a very important part is that we always want to vaccinate before someone has a risk of being exposed to that pathogen.

Erin Welsh

Right.

Erin Allmann Updyke

And in populations whose members we know are going to respond to that immunization. So some vaccines we don't give to infants for example because they might have maternal antibodies still circulating that would neutralize that vaccination. So we'd have to wait to give some vaccines to infants until they're a little bit older.

Erin Welsh

Right.

Erin Allmann Updyke

But in general we give vaccines to people before they're ever exposed because a vaccine doesn't do you any good if you've already been exposed to the pathogen.

Erin Welsh

Yep. Makes sense. What about rabies?

Erin Allmann Updyke

Oh so rabies is an interesting one. We give that after because in that case it actually does help protect you after because when the rabies virus, once it makes it into your central nervous system your body can't produce antibodies against it so by giving you a vaccine that circulates for longer in your bloodstream you have time to actually create those antibodies against it.

Erin Welsh

Right.

Erin Allmann Updyke

So in the case of rabies it does work to immunize after.

Erin Welsh

Okay.

Erin Allmann Updyke

But for most other pathogens it doesn't. Okay so how does coverage actually differ across the globe when we look at all these different vaccines?

Erin Welsh

Yeah.

Erin Allmann Updyke

Honestly it differs so much that it's hard to even get a handle on it.

Erin Welsh

Right.

Erin Allmann Updyke

The World Health Organization has numbers ranging from 50% of all children have gotten the polio vaccine who should have gotten the polio vaccine like in 2018, 85% of children have gotten MMR and DTP and things like that. But the thing is that those numbers don't really tell us much because geographic variation is so high that in some countries you're gonna have over 99% coverage and in some countries you're gonna have extremely low coverage.

Erin Welsh

Right.

Erin Allmann Updyke

And so even for example in the United States, so the way that the U.S. mandates vaccinations is that children have to be vaccinated by the time they enter public school. So by the time you're in kindergarten if you're going to a public school you have to be vaccinated. But every state handles differently how they enforce that mandatory vaccination. So some states make it easier to get exemptions whether for medical or religious or personal reasons you can request exemptions. And some states make it really, really difficult where you basically can only get an exemption from vaccines if you have a very legitimate medical reason, like a serious allergy or immunocompromise or something like that.

Erin Welsh

Right. I think there are just two states that don't allow religious or philosophical exemptions.

Erin Allmann Updyke

I can guess what one of them is although I didn't look up which states they were. But so in 2017/2018 in 49 states that reported their vaccine coverage rates for kindergarteners, while you look at the U.S. overall vaccination rates were very high for things like DTP and MMR and varicella, anything from usually about 95% if you look at the whole United States. In Washington D.C. which had the lowest coverage it was only 81%.

Erin Welsh

Oof, yikes.

Erin Allmann Updyke

And in Mississippi 99% coverage of kindergarteners.

Erin Welsh

Okay. Interesting. Does Mississippi have philosophical exemptions?

Erin Allmann Updyke

No, they do not. You cannot get exemptions for religious, philosophical, or conscientious reasons in Mississippi. Only medical exemptions.

Erin Welsh

Wow.

Erin Allmann Updyke

Yeah I didn't know that. Fascinating.

Erin Welsh

High five Mississippi.

Erin Allmann Updyke

Right? Way to go. So you can see that even within the U.S. which is a very small part of the world we have huge variation in vaccine coverage. And what happens when you have variation in vaccine coverage is that you can have pockets of the population that have very low vaccination rates and this does lead to outbreaks. We can see this in the data.

Erin Welsh

Yeah.

Erin Allmann Updyke

And what we also see in the data and I do think this is really interesting is that a lot of the outbreaks do tend to happen in populations that choose not to vaccinate.

Erin Welsh

Right.

Erin Allmann Updyke

So for example a recent review found that 70% of measles cases that happened in vaccine eligible individuals meaning not including the babies that were too young to be vaccinated, 70% of those cases were among children with nonmedical exemptions. So that's personal or religious exemptions to vaccination. In pertussis outbreaks and what's interesting about pertussis outbreaks is that unlike measles outbreaks we do see pertussis happening in previously vaccinated people because immunity can wane as you get older with the pertussis vaccine.

Erin Welsh

Right.

Erin Allmann Updyke

That's why they recommend boosters for the pertussis vaccine. But even among pertussis outbreaks, between 25 and 45% in some outbreaks of cases were among unvaccinated or undervaccinated individuals. And very often a large percentage of those unvaccinated individuals are what they call intentionally unvaccinated.

Erin Welsh

Yeah. So for the 70% of measles cases that happen among vaccine eligible kids I presume?

Erin Allmann Updyke

Yes, kids.

Erin Welsh: What is the other 30%?

Erin Allmann Updyke: So it was 70% of cases were children with nonmedical exemptions. So then the other ones might've been kids that had either medical exemptions or another reason that they weren't vaccinated.

Erin Welsh: Okay.

Erin Allmann Updyke: Other than being too young.

Erin Welsh: Okay. So that 30% is they may not have been able to or they didn't for some other reason but it wasn't an exemption issue.

Erin Allmann Updyke: It wasn't a nonmedical exemption. Yeah.

Erin Welsh: Okay.

Erin Allmann Updyke: They could've also been undervaccinated. So studies have also found that the kids who tend to be completely unvaccinated and especially intentionally unvaccinated so families who are choosing to not vaccinate their kids, those kids tend to be from families of higher socioeconomic and higher education status.

Erin Welsh: Yeah.

Erin Allmann Updyke: Whereas kids who are undervaccinated, meaning they have some of their vaccinations but not all of them and those kids are still at risk for getting disease, those kids tend to be from families of lower education and lower socioeconomic status which suggests that they might be facing barriers to getting vaccinated. So that's a pretty huge deal.

Erin Welsh: Right. Vaccination should be easy and affordable/completely free in my opinion.

Erin Allmann Updyke: Speaking of, I would agree with you entirely. So let's talk about what the costs of vaccinations are.

Erin Welsh: Fantastic.

Erin Allmann Updyke: What a transition. (laughs) So in the U.S. if you have health insurance vaccines are covered. All of the recommended vaccines are required to be covered by your health insurance provider.

Erin Welsh: Okay.

Erin Allmann Updyke: So you might have co-pays or other out of pocket fees, you might have to pay facilities fees at your hospital. No shade. So much shade. But the vaccines themselves are covered by health insurance in the U.S. However this is only true for recommended vaccines so if you for example are outside of the age range of what is recommended for the HPV vaccine, your insurance is not required to cover that which means it will cost you \$200 out of pocket per vaccine, by the way.

Erin Welsh: And so this also applies to travel vaccines?

Erin Allmann Updyke

Yes.

Erin Welsh

Yellow fever and typhoid and so on.

Erin Allmann Updyke

It does, absolutely. Yep. So those are pretty expensive. What was the yellow fever one? Like \$150 or something?

Erin Welsh

At least, I think it might've been a little more.

Erin Allmann Updyke

Yeah. If a child, so if we're talking about childhood vaccines which is most of what we've talked about so far in this episode, if a child does not have insurance in the U.S. they qualify for the vaccines for children's program which is a federally funded program that covers the cost of all the recommended vaccines for children. It is not always super easy to access, I think in general you have to go to a federally qualified health center to get those vaccines. So for example in Champaign kids can go to some school-based health clinics or the Champaign public health department. But in theory there are programs in place to make sure that kids, even if they don't have insurance, have access to vaccines. Doesn't mean that they're always getting vaccinated. Around the world every different country does things a little bit differently. So some countries have entirely free vaccines, some countries like Australia actually pay people to vaccinate.

Erin Welsh

I love that.

Erin Allmann Updyke

Me too, I think it's so great. Cause some countries also fine you if you're not up to date so it's like ooh. Different strokes.

Erin Welsh

Well positive reinforcement, negative reinforcement.

Erin Allmann Updyke

Right. Both are effective. (laughs)

Erin Welsh

Kind of. One might be more than the other.

Erin Allmann Updyke

Right. And then there's also something called the Global Alliance for Vaccines and Immunization, GAVI. Gah-vi or gavi?

Erin Welsh

I don't know.

Erin Allmann Updyke

Let's say gah-vi cause it sounds fancier.

Erin Welsh

Sure.

Erin Allmann Updyke

GAVI was established-

Erin Welsh

Could be gav-eye.

Erin Allmann Updyke

Gav-eye. I like that, let's go with that. GAVI - they're gonna hate us - was established in 2000 and their goal is improving vaccine coverage around the world. So they provide funding for a number of different vaccines for countries to establish vaccine programs, to keep them up and running and things like that. The Bill and Melinda Gates Foundation helped GAVI get started and in the first 16 years of the program more than 640 million children had access to vaccines because of GAVI and it's estimated that more than 9 million lives were saved.

Erin Welsh	Awesome!
Erin Allmann Updyke	It's pretty great. And then the World Health Organization and UNICEF also have programs in place to help subsidize the cost of vaccines in a lot of countries.
Erin Welsh	Fantastic.
Erin Allmann Updyke	And to bring you even more information about the future of vaccines and vaccines initiatives and what's really going on around the world today we talked with Dr. Padmini Srikantiah who's another Senior Program Officer at the Bill and Melinda Gates Foundation.
TPWKY	(transition theme)
Erin Welsh	Dr. Srikantiah, thank you so very much for taking the time to chat with us today about vaccines. Could you introduce yourself and tell us a bit about what you do as a Senior Program Officer at the Gates Foundation and maybe a bit of your background?
Padmini Srikantiah	Sure. So as you know my name is Padmini Srikantiah, I am an infectious disease physician by training and also an epidemiologist. So I trained in internal medicine but knew I was interested in public health and about almost 20 years ago I trained at the CDC in a program called the Epidemic Intelligence Service which is a training program in applied public health and epidemiology. And since then have been focused on infectious diseases and public health. And I came to the Gates Foundation about a year and a half ago and here I work in the global health division in the pneumonia team which is headed by Dr. Keith Klugman. And I lead three initiatives, our initiatives on three different pathogens or syndromes. One is on antimicrobial resistance or antibiotic resistance, the second is on a virus called respiratory syncytial virus which is a leading cause of pneumonia in young children and especially in infants under 6 months of age, and the third is on influenza which as you know is a major killer globally and here in the United States as well.
Erin Welsh	Very cool.
Erin Allmann Updyke	Yeah. So I think when a lot of us hear about vaccines we usually think about the vaccines that we got as children, like the MMR vaccine or the DTAP vaccine or even sometimes the seasonal influenza vaccine. But there are so many other vaccines out there that are incredibly important and save millions of lives and also help to reduce poverty worldwide. So can you tell us about some of the global vaccine initiatives that are high priorities at the Gates Foundation?
Padmini Srikantiah	Sure. So within the pneumonia team actually I can tell you that we are focused on vaccines as our major lever for preventing the infectious pathogens that cause pneumonia and lower respiratory tract infections which remain among the leading causes of mortality among young children under the age of 5. So within the pneumonia team our focus is on pneumococcus which is a bacteria that cause pneumonia and invasive disease for which there is a very effective vaccine which has been in use in the U.S. for a number of years and has shown remarkable reductions in invasive infections due to pneumococcus as well as what's called herd immunity. In the area that I'm focused on we are very interested and keenly working towards the development of a vaccine for RSV or respiratory syncytial virus as I mentioned a very important and one of the leading causes of pneumonia and an important cause of pneumonia-related mortality in infants under the age of 6 months.

So this population is, particularly because the mortality is seen in very young infancy in the first 3 months of age, this population presents a challenge for how we approach vaccination. And in this case for RSV what we're pursuing with our partners is a maternal vaccination. So in this scenario a pregnant woman is vaccinated in her third trimester of pregnancy, mounts an immune response to the vaccine, and those antibodies are passed through the placenta to the fetus. And so the baby at birth now has levels of antibodies that are protective against RSV or the idea that they would have protective levels of antibodies against RSV and then those young infants would be protected against pneumonia for their first few to several months of life. So RSV is one example and the field is full of a number of other developers who are working on vaccines to protect both young infants as well as elderly populations who are also at greater risk of severe disease and poor outcomes.

The other that I'm focused on or that we are focused on in the Foundation is influenza and as you mentioned right now much of the effort for influenza is on seasonal influenza vaccination. The goal and the focus of our influenza vaccine development efforts is really on a universal influenza vaccine. So this idea is that a vaccine that is effective against the strains of influenza that are circulating and then as well as the strains of influenza that may emerge particularly the concern is for pandemic influenza or influenza that is dramatically different than what the circulating strains are. So this is a tall order and our efforts through our partners are in preclinical stages primarily at this point but I think this is what we're really aiming for with influenza.

And maybe the last thing I'll talk about is the work that I'm doing with our partners again on antimicrobial resistance. Most of the efforts and most of the focus globally when people are talking about antimicrobial resistance has really been on specific bacterial and fast-growing bacterial pathogens but specific to the efforts that I wanna mention today are trying to understand the burden of disease due to resistant pathogens and bacteria in particular. And in our efforts, our focus is really on neonatal or newborn sepsis and pathogens or bacteria that are causing sepsis and mortality in these populations then become our potential target for vaccination. And maybe that's a good point to just mention in terms of how we select what our targets for vaccination, it's really driven by trying to understand where the disease burden lies and where mortality and disease mortality lies. And where there is that significant burden of disease burden and disease mortality will be our focus for trying to figure out what is the best method of preventing this illness and how could vaccines potentially be an important and successful lever. So maybe I'll stop there and turn it over back to you.

Erin Welsh

Yeah. Thank you so much, that was incredibly thorough and you really did raise a lot of interesting and very important points particularly in terms of vaccine development and targets and sort of jumped our questions a bit. That's great, anticipated our needs. (laughs)

Erin Allmann Updyke

(laughs) Yeah.

Erin Welsh

So one of the things about a lot of these global vaccine initiatives in the places where they are targeted, resources might be limited or there might not be a strong public health infrastructure set up yet. So what are some of the challenges that you face on the ground in actually getting vaccines to the people who need them? And how are you at the Gates Foundation working to overcome those challenges?

Padmini Srikantiah

Yeah so within the Foundation there is a large group and team that actually works on vaccine delivery that is really focused on a lot of these issues that you raise. And I think that one of the things is many of the countries where we are focused in South Asia, in Sub-Saharan Africa where health systems aren't that strong, most of these countries do have routine immunization programs. And what we certainly advocate for countries to invest further in their routine immunization programs which lays the foundation not only for a stronger health system but also helps to protect the most vulnerable populations and therefore have a more resilient population as these young children grow up.

So in terms of thinking about these challenges, one for example that I can mention is when we are interested in maternal vaccines and maternal immunization where we have to think about not just the challenges in a routine immunization program where children will be brought at certain time points, you mentioned, for example at birth, at 6 weeks, at 6 months or 9 months and thereafter, at routine immunization time points. Here in a maternal vaccine situation we actually need to target the mother, the pregnant mother in the antenatal care system.

And so our challenge has been together with many experts and colleagues in the field is to figure out when we do have an effective maternal vaccine like for RSV or group B strep or other pathogens that we feel are important pathogens to target with maternal vaccinations, we'll need to figure out and we're working hard to try to figure out how do we access and how do we work with the obstetric and antenatal care populations to leverage those platforms and help to strengthen those platforms to provide immunization to the mother that will ultimately protect the infant. While we see these challenges we also see that many of these interventions, in particular vaccine interventions can be used in and of themselves to help strengthen what might not be the strongest healthcare systems to begin with.

Erin Welsh

Mm-hmm.

Erin Allmann Updyke

That's excellent and kind of really leads into the next question we were gonna ask you which is that we talk in this episode about how the benefits of vaccines includes that you are protected and like you mentioned herd immunity, your neighbor is protected from infectious disease. But vaccines are indirectly tied to a lot of other improvements in health and poverty reduction.

Padmini Srikantiah

Mm-hmm.

Erin Allmann Updyke

So can you talk a little bit more about how this works, how vaccines have had this very multifaceted impact on health and the economy?

Padmini Srikantiah

Yeah. So I think vaccines one of the important things to remember is that vaccines are one of the most cost-effective health tools that have ever been invented. Every dollar spent on childhood immunization returns up to \$44 in economic and social benefits. And while we prevent a specific illness through a vaccine or a specific pathogen, many of these illnesses, RSV is a great example, when an infant contracts RSV not only are they at risk for the poor outcomes of the RSV infection, not only does that lead to the infection and episode of that acute illness but they are also then potentially at greater risk for subsequent infections.

So you can see how for a family where each health shock is a potential for a drop in economic gains, not only are they concerned about the health and wellbeing of that one child but that illness impacts their ability to earn as a family, their ability to provide for themselves and for other members in the family. That is there is a subsequent superinfection or a subsequent pneumococcal infection for example, then there is a whole next shock that actually happens and through vaccination if you're preventing that first instance, you're actually helping to prevent that cascade of events as well.

Erin Welsh: Yeah. So can you tell us, maybe point our listeners in a direction to where they can find more information on the work that you and that the Gates Foundation is doing?

Padmini Srikantiah: Sure. So I think the best place to go is just to our Gates Foundation website which is www.gatesfoundation.org and they'll be able to navigate through the plethora of different global health efforts that the Foundation is engaged on. I've just touched on just a few that I'm specifically involved with in the pneumonia team but within global health there are teams that are focused on TB, on HIV, on enteric and diarrheal diseases, other pathogens within pneumonia, malaria as well as neglected tropical diseases just to name a few. So I hope your listeners have a chance to learn more about all of these different efforts.

Erin Welsh: Great.

Erin Allmann Updyke: We do too. Thank you so much, I think those are all of the big questions that we had for you today. Thank you so much for taking time out of your busy schedule to talk with us, we really appreciate it and I feel like we covered so much ground in a short time.

Erin Welsh: Yeah, thank you.

Padmini Srikantiah: My pleasure. Thanks a lot.

Erin Welsh: That was so amazing, it was so cool to talk with both Dr. Srikantiah and Dr. Rodgers and to get more insight into how vaccines actually are developed and also what vaccines are targeted and what's going on around the world. That was amazing.

Erin Allmann Updyke: We're so lucky that we get to do stuff like this, Erin.

Erin Welsh: I know!

Erin Allmann Updyke: It's been thrilling. Thank you so much to Amber Zeddies for setting all that up.

Erin Welsh: Yes, Amber. Hero, champion.

Erin Allmann Updyke: You're our hero.

Erin Welsh: You know how earlier I kept listing all the different numbers about vaccines and lives saved and so on?

Erin Allmann Updyke: We've had so many incredible numbers in this episode.

Erin Welsh: So many numbers. Okay, I'm gonna add just one more.

Erin Allmann Updyke: Oh good.

Erin Welsh: Sorry about that. But so it's a number related to the Gates Foundation that I came across recently that estimates that since 1990 and estimated 122 million lives, mostly children, have been saved by the work that the Bill and Melinda Gates Foundation has done.

Erin Allmann Updyke: Wow. That's incredible.

Erin Welsh: Isn't that amazing?

Erin Allmann Updyke: That's incredible.

Erin Welsh: Yeah.

Erin Allmann Updyke: So overall vaccines are safe, they're effective, and we know that there's a lot of misinformation out there right now about vaccines so next week-

Erin Welsh: Next week!

Erin Allmann Updyke: You don't have to wait two weeks!

Erin Welsh: Guys this is a surprise. We're doing this a week early.

Erin Allmann Updyke: This is major. Because we don't want you to have to wait a single more day.

Erin Welsh: Yeah.

Erin Allmann Updyke: So next week we will be addressing the history of vaccine hesitancy which as it turns out isn't so modern.

Erin Welsh: No.

Erin Allmann Updyke: And then we're also going to address a lot of the specific concerns that you have that you've written to us about and that many people have about vaccines so that you can feel good about them and you can explain to your Aunt Martha why she should feel good about vaccines too.

Erin Welsh: (laughs) It's gonna be fantastic.

Erin Allmann Updyke: Oh it's gonna be great. And we have such great guests lined up, we can't wait to tell you about it.

Erin Welsh: Yes, oh my gosh you guys. All right so should we do sources?

Erin Allmann Updyke: Yes, absolutely.

Erin Welsh: Okay. I have a few books that I read. 'Vaccines did not cause Rachel's autism' by Dr. Peter Hotez.

Erin Allmann Updyke: So good.

Erin Welsh: So good, really good. 'Between Hope and Fear' by Michael Kinch. 'Deadly Choices' by Dr. Paul Offit. And 'The Vaccine Race' by Meredith Wadman. And I have some papers as well that I'll post and I also wanted to give a shout out to some multimedia. So there's a Nova episode, I believe it's called 'Calling the Shots' and that's about vaccines today, it touches a little bit on the history but it has some great information and some great interviews with different people.

Erin Allmann Updyke

Excellent. I have more sources for this and next week's episode than I've ever had in my life. So we're gonna post all of our sources as we always do on our website thispodcastwillkillyou.com under the EPISODES tab. You can find every single source we've ever used for every episode. Yeah. So.

Erin Welsh

So thank you to Bloodmobile for providing the music for this episode and all of our episodes.

Erin Allmann Updyke

And you can find Bloodmobile's music now on-

Erin Welsh

Bandcamp.

Erin Allmann Updyke

Bandcamp!

Erin Welsh

We'll post a link on our website but I think it's [therealbloodmobile](http://therealbloodmobile.com) or something like that?

Erin Allmann Updyke

Okay, cool.

Erin Welsh

Yeah. And also thank you to you all for listening!

Erin Allmann Updyke

Thank you so much.

Erin Welsh

We love you.

Erin Allmann Updyke

This was a really fun episode and we hope that you loved it and learned a lot and we can't wait for next week's episode. It's gonna be so fun.

Erin Welsh

Okay. Wash your hands.

Erin Allmann Updyke

You filthy animals!