

Lucy

In October 2019, our family doubled in number from 3 to 6 when our triplets were born at 35 weeks gestation. We already had our 2.5 year old daughter Annie, and then we had Isabel, Lenny, and Teddy. Their weights ranged from 4.2 lbs to 4.7 lbs at birth. They were small but everyone agreed they were good sizes for triplets. because they were born early They needed some help with breathing and maintaining their own temperatures but all were discharged from NICU two weeks later. We had a lot of visits from community nurses to check on their health. They checked their weight and for any signs of infection. I was told a number of times to watch out for a virus called RSV as it was a risk this time of year, especially for very young babies and especially for those with a sibling who was attending nursery or school. I understood that we ticked a few of these risk boxes but I wasn't concerned, I thought we'd be okay.

When Lenny was 5 weeks old and not yet the weight of most newborn babies, he seemed more sniffly than usual. He was drinking his milk more slowly and he had been sick a couple of times. I thought he had a cold, I thought he would get better in a few days. One morning we woke up and I went through the usual morning routine. Lenny seemed like he was okay but he still had a cold so I left him til last so I could feed the others and spend a bit more time with him. But as I picked him up to feed him, I thought he looked pale, he seemed maybe a bit colder than usual. I felt panic. I was worried. I still couldn't drive having only had a C section weeks ago, so I phoned my husband and he came home and took us to the hospital.

By the time we got there and after only a 10 minute drive, Lenny had gotten much worse. In fact he was rushed straight through to resource and what felt like tens of staff rushed into the room to help him. He had become so sick so quickly that they thought he could have sepsis. He was tested for a number of illnesses and the swabs later came back positive for RSV. By this time Lenny had been admitted to the high dependency unit. He had been put on a CPAP machine to help with his breathing, it was later switched to BiPap and he narrowly avoided being intubated after he stabilized. He needed support with nutrition and hydration and was given a cocktail of drugs. The other two triplets were admitted to a ward overnight for observations but were discharged the next day. We were advised to keep Isabel and Teddy away from the hospital so they wouldn't pick up any infections.

It was a heartbreaking logistical nightmare caring for our three apparently well children and our critically ill baby all at once. Lenny spent 5 nights in hospital which was amazing considering how ill he was when he got there. He recovered as quickly as he had got sick and I felt so positive and thankful to take him home. Little did I know that we were only mid nightmare at this point. Less than a week later Isabel seemed to not be drinking her milk very well. After what had happened with Lenny, we had learned to watch out for signs the babies were struggling to breathe and Isabel was exhibiting a number of red flags. She was sucking in a little around her ribs so that we could see the slight outline of her rib cage and there was a little recession in the front of her neck too, it suggested she was struggling to breathe.

I took her to hospital. I was concerned but not really worried as she seemed nowhere near as sick as Lenny had been. But while she was being examined she had an apnea and it was clear that she was starting to struggle significantly with her breathing. She was admitted to the high dependency unit where Lenny had been given oxygen support all night long. The machines beeped endlessly and the nurse would rush over to do what she could. The following day Isabel deteriorated. Her tiny body struggled to breathe so much that now her entire rib cage would be visible at points. Despite all the support, her oxygen levels were too low and she went from CPAP to BiPap and then was moved to PICU and intubated. The procedure was a struggle because she was so small and she was left with a bloody nose and a collapsed lung.

She was so sick that I asked the doctors as much as I could bear to if I was going to lose her and no one could give me the reassurance I wanted. Slowly she became stable on the ventilator but she didn't improve. As the days passed, we sat beside her bedside and the nurses took so many samples of blood from her feet to check her blood gasses that her feet looked like pin cushions. Cannula after cannula came out and it became harder for the doctors to find places to fit new ones. Her body convulsed as it couldn't expel the mucus from her lungs and the nurses would rush to suction it through the endotracheal tube. It hadn't made sense to me why Isabel was so much sicker than Lenny but it transpired that Isabel had had RSV and she developed bronchiolitis like her brother but she developed a complication pneumonia.

Thanks to the amazing care she received at the Royal Manchester Children's Hospital, Isabel recovered and she came home in time for Christmas with her brothers and her big sister. On our last day in PICU I remember a doctor telling me to be careful for the rest of the winter and for next winter too. And she was right. Isabel was admitted to hospital with bronchiolitis the following winter but as a much stronger one year old and it was not so scary this time around. She needed some help with breathing and nutrition but she was okay. As she started to feel better she even began to enjoy all the attention from the lovely staff as they came into her room. Each one who came in looked right at her and said hello. And after she was discharged, I was putting her to bed one night and she stood up and she looked at me and she said her first word, hello. I will be forever thankful to the incredible medical and nursing staff who saved my babies.

TPWKY

(TPWKY intro theme)

Erin Welsh

Oh my gosh. What a horrifying, terrifying experience.

Erin Allmann Updyke

I know. Thank you so much Lucy for sharing your experience with us and our listeners. It's terrifying.

Erin Welsh

It is. I'm so glad that everyone is now doing well.

Erin Allmann Updyke

Me too.

Erin Welsh

Hi, I'm Erin Welsh.

Erin Allmann Updyke

And I'm Erin Allmann Updyke.

Erin Welsh

And this is This Podcast Will kill You.

Erin Allmann Updyke

Welcome to Season 6.

Erin Welsh

Season 6.

Erin Allmann Updyke

Whoever would have thought that we could make it this far?

Erin Welsh

You and I certainly did not think that. But it's funny, when we first started out we thought oh, we've got like two seasons maximum, we laid out all of the topics. And then over the years especially thanks to listeners who have reached out and suggested things-

Erin Allmann Updyke

Yeah.

Erin Welsh: That list just keeps getting longer and longer and longer.

Erin Allmann Updyke: Yep.

Erin Welsh: And now it's like we don't see an end in sight. Which is scary because it's like there are a lot of things that can kill you. But it's also really great because we get to talk about them all.

Erin Allmann Updyke: Yeah. And we love getting to make this podcast. So thank you all again for listening.

Erin Welsh: Yeah.

Erin Allmann Updyke: And sticking with us for our sixth season. It's going to be a good one.

Erin Welsh: It is. We've got a lot of very interesting topics planned for this next season. So you'll just have to stay tuned to see what we're going to be talking about.

Erin Allmann Updyke: Right. And who knows what global pandemics will be thrown at us next that will change our order of topics, etc.

Erin Welsh: Erin.

Erin Allmann Updyke: I'm sorry.

Erin Welsh: Please no.

Erin Allmann Updyke: Too soon?

Erin Welsh: Yes. Yes.

Erin Allmann Updyke: I know.

Erin Welsh: We'll always speak too soon. But we're kicking things off with a very hot topic, very timely topic, and that is RSV.

Erin Allmann Updyke: RSV. It's huge.

Erin Welsh: It is. And Erin, I hope you're going to tell me how to pronounce syncytial.

Erin Allmann Updyke: Syncytial.

Erin Welsh: Syncytial.

Erin Allmann Updyke: Yep, you got it. Respiratory syncytial virus. But yeah, it's going to be a good episode. I'm excited.

Erin Welsh: Yeah. There's definitely a lot that I want to know about this virus so I'm excited to dig in.

Erin Allmann Updyke: Yeah.

Erin Welsh: But first-

Erin Allmann Updyke: But first-

Erin Welsh: It's quarantini time.

Erin Allmann Updyke: It's quarantini time! How exciting.

Erin Welsh: What are we drinking this week?

Erin Allmann Updyke: We're drinking Hold Your Breath. Because it's a respiratory virus. We'll get into it all.

Erin Welsh: Yeah, yeah, we'll get there.

Erin Allmann Updyke: And what's in Hold Your Breath, Erin?

Erin Welsh: Spiced cranberry syrup, orange juice, and bourbon.

Erin Allmann Updyke: Yum.

Erin Welsh: It's really tasty.

Erin Allmann Updyke: Yum.

Erin Welsh: Yeah.

Erin Allmann Updyke: We'll post the full recipe for that quarantini as well as our nonalcoholic placeborita on our website thispodcastwillkillyou.com and of course all of our social media channels.

Erin Welsh: We certainly will. On our website, I guess I do have to do the spiel because this is the beginning of the season. I don't know, I feel like I need to.

Erin Allmann Updyke: Yeah. We might have new people listening. Welcome.

Erin Welsh: Welcome.

Erin Allmann Updyke: We have spiels that we do.

Erin Welsh: Yeah. Welcome to your first website spiel. If you go to thispodcastwillkillyou.com you can find all sorts of great resources including the resources that we mention in every one of our episodes, including transcripts, including our bookshop.org affiliate account, our Goodreads list, links to merch, our Patreon. Just so much stuff that you can find. So check it out.

Erin Allmann Updyke: Also shout out, our merch got recently revamped in the last couple of months. Shout out to our incredible artist Abigail Ervin-Penner who did all of this incredible artwork and the merch is clutch. If you haven't got your hands on it yet, you can.

Erin Welsh: Okay. Do we have any other business?

Erin Allmann Updyke

I don't think so. Let's get into it.

Erin Welsh

Let's do it right after this break.

TPWKY

(transition theme)

Erin Allmann Updyke

I'm excited that we're starting out this season with RSV especially because we ended last season with influenza.

Erin Welsh

Yeah.

Erin Allmann Updyke

It feels very full circle in a weird way.

Erin Welsh

Yeah.

Erin Allmann Updyke

So RSV or as it's properly called respiratory syncytial virus, it's one of the other really big name respiratory viruses that hospitals and hospital systems and many parents especially know all too well. We're recording this and this will be released smack dab in the middle of what is typical RSV season here in the northern hemisphere, which usually goes from about November-ish until the end of February. Spoiler alerts, this year we saw a really early start to the RSV season and I will not be surprised if it ends up having a pretty long tail as well. So we might end up seeing cases well into the spring. But we'll get into all of that later. First, what the heck is RSV?

Erin Welsh

Yeah.

Erin Allmann Updyke

Obviously it's a virus, it's in the name, but specifically it's a virus in the family Pneumoviridae which includes viruses in the genus Metapneumovirus which is another common cause of human respiratory infections like the common cold type infections. And then RSV which is in the genus Orthopneumovirus. So these are RNA viruses, they have an envelope much like influenza, they have a non segmented genome unlike our friend influenza which remember has multiple little chunks of RNA. And just really off the bat I want to emphasize how incredibly important of a virus RSV is. It is one of if not the single leading cause of acute lower respiratory tract infections and hospitalizations especially in kids under age 5 globally.

Erin Welsh

I have a question about this.

Erin Allmann Updyke

Already, I love it.

Erin Welsh

Yeah. Well maybe it's more of a rhetorical question or just an open discussion point but I feel like even though I went to get an undergrad in biology and had to take classes on diseases, did grad school and stuff like that, really the first time I started hearing about RSV was when we were doing the podcast and talking about all these different viruses and stuff. And I really feel like suddenly now it's all over the news and you can't avoid it. And I know that part of that is because we're just seeing a really unusual number of cases. But is there anything else to that? Like why do I feel like people have only started hearing about RSV now?

Erin Allmann Updyke

Yeah, it's a good question. I don't have a perfect answer for you. I can tell you based on the epidemiological data that I've seen out of the past 10 years or so, we used to greatly underestimate RSV burden.

Erin Welsh

Okay.

Erin Allmann Updyke

And a lot of that was probably because we just weren't testing for it, so we weren't distinguishing RSV from any other particular respiratory infection. So when a kid or a grown adult or an older person got infected with a respiratory virus, it was like influenza or something else and that was kind of the only distinction that was made. So part of it might just be that we're doing better diagnostics so we can understand just how important this individual virus is. I think that might be a big part of it.

Erin Welsh

Okay. That makes sense.

Erin Allmann Updyke

Yeah. But so being respiratory in nature, it's probably unsurprising to know that this is a virus transmitted mostly by respiratory droplets. So coughs, sneezes, that sort of thing. It can also survive for a really decent amount of time on surfaces especially in colder weather. And so it can be transmitted very easily by fomites, things like door handles, crib railings that kids love to suck on, even your hands, all of those kinds of things. Toys at daycare centers for example.

Erin Welsh

You know I have a question about durability. Like how long?

Erin Allmann Updyke

I know.

Erin Welsh

Yeah.

Erin Allmann Updyke

I literally wrote how long, Erin? Such a good question. So I don't know, largely because it depends so much on environmental factors.

Erin Welsh

Okay, that makes sense.

Erin Allmann Updyke

Yeah. But from the data that I have been able to gather, it's a good number of hours, like even several hours under not that great of conditions and potentially several days under good conditions for viral survival. And what those conditions are depend on if the virus stays wet vs if it dries out. And so it's really complicated.

Erin Welsh

Yikes though, several days is kind of terrifying.

Erin Allmann Updyke

I know, yeah. Maybe a couple of days, I shouldn't maybe say several makes it sound like a week. But probably at least 48 hours depending on certain conditions.

Erin Welsh

Okay, right, right.

Erin Allmann Updyke

And some of this complication and environmental durability helps explain at least in part some of the differences in seasonality that we see in different latitudes. Where in temperate regions, cold, low humidity, winter months where we're also all gathered inside and potentially spreading germs that way, tend to have much higher RSV transmission. Whereas in tropical latitudes, it tends to be the rainy season which is obviously a lot more humid that tends to see higher transmission. So the seasonality aspect is really interesting. In general the incubation period for RSV that I've seen most commonly reported is between 4-6 days, could be a little less, could be a little more. And then let's talk about the symptoms.

Erin Welsh

Yeah.

Erin Allmann Updyke

And for this I'm kind of almost going to tell another little firsthand account here. Because I remember very vividly when my kid got his first RSV infection and I remember what the doctor explained to us and I just think it was such a good explanation of the course of RSV that I'm going to tell it to you now. So when my kid got RSV, he was probably 3 months old, he was definitely under 4 months because he only had one dose of pertussis vaccine and I was convinced that it was pertussis.

Erin Welsh

Oh god, yeah.

Erin Allmann Updyke

It wasn't pertussis. I made him test for it. But anyways, I remember that he definitely had a fever but it came down with a little bit of Tylenol. He didn't seem all that miserable at first but then he was just coughing so much, just coughing, coughing, coughing his brains out. And he was so snotty, like an epic amount of snot. And intermittently I started hearing him wheeze and of course I was in med school at the time so I would listen to him with my stethoscope.

Erin Welsh

Oh god.

Erin Allmann Updyke

And I was like he's wheezing, that seems bad. At this point we should go to the doctor. What do I do? I need a real doctor. So I brought him to see his doctor and his doctor said this is almost certainly RSV. It was like November, peak here we go RSV season. At the time the doctor said he's not wheezy at this moment but I believe you that he was wheezing at home because he will probably continue to wheeze intermittently. He's been sick now for two or three days. So here's what's going to happen. Over the next two or three days, so like days 4-6 of illness, he's either going to start to get better or he's going to get worse. And if he gets worse, here's what you'll see. He'll start breathing fast, a lot faster than usual. It'll look like he's working hard to breathe. What you'll see are retractions, which mean that if you take off his clothes you'll be able to see his ribs where his belly pulls in underneath his ribs when he tries to breathe.

Erin Welsh

Oh my god.

Erin Allmann Updyke

Or in the little V of his neck right above his chest, you can see it kind of sucking in as he takes in a breath. Those are called retractions. If that starts to happen, you'll take him to the emergency room and they will care for him. And those are the two ways that this disease is going to go. And that's what the doctor told me. And it sounds terrifying.

Erin Welsh

Yeah.

Erin Allmann Updyke

And it is terrifying. But I will say that it was one of the most reassuring things to know here's what to look out for, here's the things that are going to happen, and here's the kind of two ways that it's going to go and what to do in both scenarios.

Erin Welsh

Yeah, yeah.

Erin Allmann Updyke

And it turns out that it's a really accurate description of the course of RSV. Kids especially are susceptible to RSV infections and kids especially in their first round with RSV, because this is a virus that tends to infect us over and over through the course of our lifetimes, but especially in that first year of RSV infection for a kid, they tend to get a fever. RSV is a very snotty virus so you have a lot of mucus production, you're going to have a lot of coughing because of that mucus production. And in kids, especially babies, they're not good at coughing yet. They just don't have the muscles and they don't have the reflex to get up gunk when they cough so they don't produce a lot when they're coughing. And then they either get better over time or they get worse and it's often that days 4-6 or so is when they might start to get worse. So this is a long disease that we're talking about. That's a long time to be watching a kid like a hawk and wondering kind of which way it's going to go.

Erin Welsh

Yeah, absolutely. Okay, question real quick. What are some of the factors that decide whether a kid is going to get better or going to get worse?

Erin Allmann Updyke

We will absolutely get into it.

Erin Welsh

Okay, okay.

Erin Allmann Updyke

Yeah. In as much detail as I can give you.

Erin Welsh

Okay. So I guess not a quick question then.

Erin Allmann Updyke

But it is the important question.

Erin Welsh

Yeah.

Erin Allmann Updyke

But to talk a little bit more about what the symptoms can look like in other age groups because what I just described is how the course of RSV tends to go in kids say age especially 0-6 months or a year or kids who are being exposed to RSV for the first time. In older kids it can look similar or it can look more like what RSV looks like in adults which is just the common cold, right. So cough, runny nose, sinus, congestion, sore throat, usually RSV even in adults is a pretty snotty type of cold so you might have quite a lot of congestion. In very, very little babies under 6 weeks old or very tiny babies that are very premature, they can actually have such little reserve when it comes to their respiratory system that they can present a little bit differently.

Sometimes they might just look kind of lethargic, like they just don't really look like themselves, they have no energy. Sometimes they might just have apnea which is when they just stop breathing entirely for a spell which is terrifying. Now in elderly adults over age 65 or in adults or children with underlying lung conditions like COPD or asthma, cystic fibrosis, things like that, you can also have a more severe infection that can lead to something like a pneumonia, a viral pneumonia, which we've talked a lot about on this podcast. So then the question, you asked the question of who does this happen to? And before I get to that what I want to talk about is what is actually happening in our airways. And I think once we understand that we can understand who is at highest risk for severe infection.

Erin Welsh

Okay.

Erin Allmann Updyke

So what actually happens when we get infected with this virus? As a respiratory virus, RSV is initially and primarily infecting the epithelial cells of our respiratory tract. I feel like we talk about these cells all the time.

Erin Welsh

We do. Let's do it again, I love it.

Erin Allmann Updyke

Yeah, let's. These are the cells that are lining our nose, they're lining our throat, they're lining our airways. Part of what determines how severe of an infection you're going to have with RSV is going to be whether or not it establishes an infection in the lower respiratory tract, meaning down in our lungs. RSV seems to have an easier time doing this in either an initial infection, so you've never been exposed before, you have no immunity whatsoever, that means infections in the very young, as well as in the very old or the immunocompromised. So those are the three biggest groups that we're going to see more likelihood that you'll have a severe RSV infection because it's making its way down into your lungs.

But the other part of it is that with RSV I keep saying there's a lot of snot, right, there's a lot of mucus. That's largely because we see a huge amount of immune response especially in the form of neutrophils, which are one of our white blood cells that often are the first to kind of rise up to try and fight off a virus, that tend to infiltrate into spaces with an RSV infection. So if this virus is infecting the small airways of our lungs, our bronchioles which are the kind of smallest of the branches of our lungs, then you're going to have a lot of white blood cells, these neutrophils, as well as fluid and gunk that's getting into your lungs itself. And fluid and gunk is never good in our lungs for anyone.

But for tiny babies, especially premature tiny babies, they also have tiny airways. So these tiny airways are even more susceptible to obstruction. And that obstruction is what causes the primary disorder that we see in severe RSV which is called bronchiolitis. So bronchiolitis is this obstruction, it's the plugging up of the tiny ends of our airways, the small bronchi and what are called the terminal bronchioles. This happens because of swelling, because of mucus, because our own cells are getting sloughed off, and all these immune cells are coming in. These then get plugged up and eventually collapse. And that is what also causes that wheezing sound that I mentioned that you can hear if you listen to a kid with bronchiolitis lungs. All this gunk makes it so that it's really hard to breathe out the air that makes it into our lungs. So it's obstructing the flow.

I know, it's awful. And I just want to contrast this to the other most common lower respiratory disease that we usually talk about on this podcast and that is pneumonia, right. Pneumonia is when we have a similar kind of inflammation and fluid but instead of being in the airway tubules, the bronchioles, it's down in the alveoli which are those grape cluster sacs where gas exchange actually happens. So it's like a different place within your lungs where the inflammation is happening so it leads to a different pattern of disease. In adults that end up with severe RSV, it tends to be a pneumonia. In tiny kids, those airways are so small that they get plugged up before it even makes it down to the alveoli.

Erin Welsh

That's very interesting.

Erin Allmann Updyke

I know. Yeah.

Erin Welsh

So the end result is almost the same in a way, you're simply getting not enough oxygen in.

Erin Allmann Updyke

In a way, yeah. Yeah.

Erin Welsh

Yeah. But then there are other aspects and I imagine damage to the lungs in different ways.

Erin Allmann Updyke

Exactly, yeah. So now RSV is an incredibly common infection. Nearly everyone on the planet by adulthood has been infected with RSV and probably we've been infected multiple times in our life.

Erin Welsh: I had no idea.

Erin Allmann Updyke: I know, I know. I think for so long it just gets brushed off as the common cold. I will admit too, I knew how big of a deal RSV was in kids, I did not know how big of a deal it was in older adults.

Erin Welsh: Yeah, same.

Erin Allmann Updyke: But there are certain groups like we alluded to that are at much higher risk for severe illness, this bronchiolitis especially, than others. And I mentioned that young babies are one of these primary groups. But I want to dig down a little bit deeper because on top of just young babies being infected for the first time, there's a few other risk factors that can make kids even more susceptible to severe infection. Prematurity is one of them. So being born at before 37 weeks, those kids are almost twice as likely to be hospitalized than kids who are born at term. Kids who are born premature who also have what's called chronic lung disease of prematurity or it used to be called bronchopulmonary dysplasia, it's a whole other episode, but those kids are about 14x more likely to need hospitalization with RSV infection. And for those kids with chronic lung disease, the risk is also higher throughout infancy till about age 2 instead of just the first 6 months. And kids born with congenital heart disease also have a much higher risk of being hospitalized, about 3x as high as kids with no other risk factors. And then like I mentioned, kids who have various immunodeficiencies or underlying lung conditions.

Erin Welsh: Gotcha.

Erin Allmann Updyke: But because this is such a prevalent virus, when you look at absolute numbers, the majority of kids that get hospitalized are often otherwise healthy and don't have any underlying risk factors which just goes to show you how incredibly prevalent this virus is. Like every kid is getting infected.

Erin Welsh: Erin, what is syncytia?

Erin Allmann Updyke: I don't know. Yeah, I feel like I should know.

Erin Welsh: I feel like we should know. I mean I don't know. Okay Erin, I googled it.

Erin Allmann Updyke: Okay good.

Erin Welsh: Syncytium, which is the singular, the plural is syncytia, a single cell or cytoplasmic mass containing several nuclei formed by fusion of cells or by division of nuclei.

Erin Allmann Updyke: Okay. I did know that somewhere in my brain because the reason that it's called respiratory syncytial virus is because the gunk that you see in the lungs of kids postmortem who have died from RSV bronchiolitis looks like that, it looks like a syncytium.

Erin Welsh: Okay. So I have in here why they called it respiratory syncytial virus but because it produced syncytial changes.

Erin Allmann Updyke: Yeah.

Erin Welsh: And then I was like Erin will talk about syncytia so I don't have to worry about it.

Erin Allmann Updyke

Nope. That's funny.

Erin Welsh

Okay. Well now we know.

Erin Allmann Updyke

Yep. That's actually hilarious. So what do we do to deal with this infection if kids get really sick from it? And what do we do to prevent it? I guess those are kind of two big questions. To treat it we don't have anything specific. So the treatment for RSV, if it's a mild infection, it's supportive care at home, right. If it's hospitalization, like a severe infection, then it's using very powerful suction to suck snot out of tiny kids faces and breathing assistance which usually means high flow oxygen. And if a kid is really, really sick or just really small and doesn't have the reserves to be able to keep fighting to breathe, then it's mechanical ventilation which means intubation and a breathing machine which has its whole own host of possible complications.

Erin Welsh

Yeah.

Erin Allmann Updyke

But that's really all that we have. There was an antiviral that was tried but hasn't been shown to be effective, lots of people want to think that bronchodilators like we use for asthma, so like albuterol, think albuterol inhalers, they have no real benefit in RSV bronchiolitis, same thing with steroids. So it's really all just this supportive care which is scary when you think about places that don't have access to high levels of oxygen at high flow or mechanical ventilation or hospitalization in general.

Erin Welsh

Yeah. There's a lot of places like that.

Erin Allmann Updyke

Yeah.

Erin Welsh

And so when would you test for RSV?

Erin Allmann Updyke

This is such an interesting question, Erin. It's an interesting question because there's not an easy answer on an individual level. On a public health level it's good to know what viruses people have, like what viruses are circulating, what viruses are running around and in what ratios. So from a public health perspective it makes a lot of sense to test as many people as you can that are coming into hospital systems if you have the capacity to do that. On an individual level, whether a kid has RSV bronchiolitis or bronchiolitis caused by any other respiratory virus which is possible, RSV is not the only thing that causes this same phenomenon of the plugging up of the small airways, the same way that influenza's not the only thing that causes viral pneumonia, right. So on an individual level it really doesn't change management all that much to test or to not test. And tests can be expensive, they can be hard to get. So it might not be worth it to test an individual person for RSV.

Erin Welsh

Okay.

Erin Allmann Updyke

So there's not an easy answer there but it's an interesting kind of public health vs individual health vs does it change a doctor's or someone's management of a person who comes in with these symptoms?

Erin Welsh

Right, right.

Erin Allmann Updyke

Yeah. And when we don't have any specific treatments the way that we do for say influenza, then yeah, it doesn't really change things that much. So a lot of times people aren't getting tested which means we are underestimating our RSV burden compared to other viruses.

Erin Welsh: Of course. Yeah.

Erin Allmann Updyke: Yep. We do have, not a vaccine, spoilers, and I'll talk more about that later. But we do have an interesting preventative treatment that is a monoclonal antibody called palivizumab that we can use as prophylaxis, kind of like a vaccine in a way, for kids with certain risk factors like the ones that I mentioned. Kids who are born premature, who are under a certain age like 6 months, or who maybe have congenital heart disease or chronic lung disease of prematurity. This is amazing, right?

Erin Welsh: Yeah.

Erin Allmann Updyke: This is something that has good evidence, can reduce severe disease and reduce hospitalization in these really high risk kids and babies. But, because there's always butts, it is incredibly expensive. One estimate that I saw from I believe it was the UK was like £5,000 per dose.

Erin Welsh: Oh my gosh.

Erin Allmann Updyke: I know. And I didn't see numbers on how expensive it is in the US.

Erin Welsh: More.

Erin Allmann Updyke: It's cumbersome. Yeah, more. It's cumbersome because it is an injection like a vaccine and it has to be given once a month usually.

Erin Welsh: Whoa.

Erin Allmann Updyke: Usually for 5 months during that RSV season. And it's imperfect, it doesn't prevent infection necessarily but it does reduce the risk of hospitalization. So because of all these limitations, I actually have no idea what the actual availability and access of this is not just across the globe, I imagine the access across the globe is nonexistent in a lot of places, especially if you think about not just low and middle income countries that might not have access to an expensive drug but also tropical latitudes where there isn't as well defined of a season of RSV.

Erin Welsh: Yeah.

Erin Allmann Updyke: But even in say rural parts of the US, I just don't know what access is actually like, it's hard to know. But that does exist which I think is really promising. And I'll talk a little bit more at the end about other things that we're trying to do in terms of prevention for this incredibly prevalent disease.

Erin Welsh: Yeah.

Erin Allmann Updyke: And the last thing that I just want to kind of mention because I know someone is going to want to know about it and it's really cool and interesting, even though I'm going to be like I don't know the answer, is the association between RSV and asthma.

Erin Welsh: Okay. So I was going to ask about this but I was also going to ask a more open ended question that wasn't really a question which I know is annoying. But it would be very interesting to look at in places with a clearly defined RSV season, birth month and then relationship to asthma and other later in life lung function or chronic lung diseases.

Erin Allmann Updyke

Yeah. Like if you were born where you got RSV in your first 6 months of life vs your later 6 months of life.

Erin Welsh

Exactly.

Erin Allmann Updyke

And your tendency to develop asthma. Ooh, that's super interesting. I wonder if that study has been done.

Erin Welsh

It probably has.

Erin Allmann Updyke

Yeah, I'll have to look for it because that's super interesting. But there are definitely associations between RSV infection, especially severe RSV infection in childhood being associated with the later development of asthma or what's often called reactive airway disease in younger kids because you can't diagnose asthma until 4 or 5 years old.

Erin Welsh

Okay.

Erin Allmann Updyke

But as of right now we do not have a clear sense of whether kids who are genetically predisposed to the development of asthma, something about them makes them more susceptible to RSV or severe RSV infection. Or is there something about RSV infection, severe RSV infection, that either precipitates or maybe even expedites the development in asthma in kids who are predisposed?

Erin Welsh

That's hard to disentangle.

Erin Allmann Updyke

It's very hard and it's super interesting and at this point it could kind of go either way. We know that there is an association but we don't know in which direction it might go. I think from what I could tell we have a little bit more data to suggest the former, so it's maybe kids who are genetically predisposed to asthma, like they'll probably develop asthma later in life, are more likely to get a severe RSV infection.

Erin Welsh

Okay.

Erin Allmann Updyke

Vs the other way around. But it's still a really muddy picture. So we still don't know for sure.

Erin Welsh

I have a question about the strains or subtypes or whatever they're called of RSV and the difference among them. And yeah, what we know about sort of how severity may change from year to year.

Erin Allmann Updyke

Yeah. The short answer is I don't have a ton of information for you on that. From what I found there's at least two major strains, RSV-A, RSV-B, and then there are other subtypes within that and other clinical strains that have been identified. But in general, both of these major strains circulate, A and B, at the same time A tends to be overall a little bit more prevalent and perhaps a little bit more transmissible. But from what I found we don't have great data on strain differences when it comes to disease severity or things like that and I think it's probably because of how much we've just underestimated RSV in general. I don't know how often, even if we're testing for RSV, we're testing for strains of RSV.

Erin Welsh

Speaking of transmissibility, do we have an R0 estimate for this virus?

Erin Allmann Updyke: Good question. It can vary of course. But most estimates that I saw were around 3. So for a reminder for anyone, that means that for every one person who is infected with RSV they'll go on to infect 3 people on average.

Erin Welsh: Right.

Erin Allmann Updyke: Yeah. That's RSV biology, Erin. It's a lot.

Erin Welsh: It's a lot. It's scary. I can't believe how much I didn't know about it despite how prevalent it is.

Erin Allmann Updyke: I know.

Erin Welsh: And to use I guess outdated lingo, I would say it seems like a very slept on virus.

Erin Allmann Updyke: Yeah. And I feel like I'll talk even more about that later. But first Erin, tell me what we know about where this virus came from, etc.

Erin Welsh: Okay. I'll do the best I can right after this break.

TPWKY: (transition theme)

Erin Welsh: To answer your question very briefly, we don't know exactly where RSV came from.

Erin Allmann Updyke: Of course we don't.

Erin Welsh: And you didn't ask like you usually do how we got to where we are today.

Erin Allmann Updyke: Oh yeah.

Erin Welsh: But I can say that we probably got to where we are today because RSV did what respiratory viruses do best, they spread. I don't know, that's the best answer I have. But that's not going to be all of the history section because that would be a pretty lousy podcast episode if I ended it there. So let's get into it a little bit, starting with how we first learned about this virus. In October of 1955 at the Walter Reed Army Institute of Research in Silver Spring, Maryland, a group of 20 quote unquote "normal" chimpanzees around 15-20 months old began showing signs of a respiratory disease. Runny nose, sneezing, coughing, the usual. And at first it was just a handful of the chimpanzees but within a few days nearly all of them had gotten sick. As listeners of this podcast are well aware, an outbreak of an apparently contagious disease in a population of lab animals sets off some pretty loud warning bells. And so the researchers at the institute were very eager to find what pathogen might be responsible. They took some throat swabs from the animals and ran a bunch of tests on it. I'm not going to bore you with the details but ultimately what they found was not a familiar old measles or polio or coxsackievirus but a new thing entirely, a virus they named the chimpanzee coryza agent, not RSV.

Erin Allmann Updyke: I was really expecting that to go a different way.

Erin Welsh

Yeah. The link between this virus and the observed illness in the chimpanzees was confirmed when a few other chimpanzees got sick after being intentionally infected with the virus and also when a lab worker got sick after unintentionally being infected. They all produced antibodies against the pathogen. Researchers Morris, Blount, and Savage published the account of this first observed epizootic of the chimpanzee coryza agent in 1956. And in it they didn't really hint at answering or even acknowledging the question of how scared we need to be about this new pathogen, it seems to be able to infect both chimpanzees and humans, it's clearly contagious respiratory, you know, a scary thing. But they didn't really talk about it. But in their very last sentence they did suggest that this agent may be a lot more widespread than just in chimpanzees at the Walter Reed Institute.

Erin Allmann Updyke

Uh oh.

Erin Welsh

Quote: "However, a number of human beings, particularly adolescents and young adults, have antibodies in their sera directed against the coryza agent, suggesting that these individuals have experienced infection with the new agent or one closely related to it." Very shortly after this paper was published, two more came out that showed that this virus may be a significant cause of respiratory infections especially in certain age groups. And the authors of these studies, basically what they did was they set out to test what pathogens they could potentially find or isolate from infants with severe lower respiratory illness.

Erin Allmann Updyke

Okay.

Erin Welsh

And they wanted to see okay, what's this illness being caused by? Are there any new viruses or bacterial species that we need to worry about? And so on. And it just so happens that one of the viruses they isolated from these sick infants was indistinguishable from the chimpanzee coryza agent.

Erin Allmann Updyke

Interesting.

Erin Welsh

And the more people looked, the more they found that this virus which was assumed to be new, may not be new at all and may actually be responsible for an incredible number of lower respiratory tract infections particularly among infants and young children. Although already adults were also seen to have antibodies against the virus and to get sick themselves, suggesting that reinfection was not just possible but potentially common. And these authors also suggested in these papers that given the fact that chimpanzees are not the sole host nor were likely to be the reservoir species of this virus and they actually got it from humans, perhaps chimpanzee coryza agent was not the most fitting name. With its ability to produce syncytial changes in tissue cultures, which we now know what that means, and its manifestation as a respiratory infection, maybe it should be called something along the lines of respiratory syncytial virus. Definitely not like our most, I don't know, captivating story of how something got its name but I like it.

Erin Allmann Updyke

It's not but I like it. And you know what I like about it is it's not controversial.

Erin Welsh

Yeah.

Erin Allmann Updyke

It's like let's name this virus after what it does. What a concept.

Erin Welsh

What? Wow. Yeah. And yeah, it happened pretty soon, in the late 1950s basically.

Erin Allmann Updyke

Wow. Okay.

Erin Welsh

And what followed was what we often see with the identification of a new virus. People start looking for it, they start seeing more and more of it, and then the gaps in knowledge about the virus' epidemiology, pathophysiology, symptomology, and so on all started to be slowly filled in. For instance as early as 1958-1959 or so, physicians noticed that the virus could cause illness with a huge range of severity from an apparent infection to fatal bronchiolitis. They noticed that the age group with the highest infection rates and severe symptoms was infants who also may have the highest rates of viral shedding. They noticed that even though some infections may be milder, they all still seemed to involve the lower respiratory tract, and that infections at least in North America followed this seasonal trend which is the one that you described, Erin, infections rising in November, December, peaking in January, February, and falling to low levels by April. Over the next decades into the 1970s and the 1980s, RSV became a very familiar name during the winter months. One of the usual suspects when somebody brought their infant or child into the doctor's office for acute respiratory symptoms and also a huge cause of hospitalizations for young children. For instance, studies from the 1980s reported that during that decade an estimated 100,000 children were hospitalized for RSV each year in the US, costing \$300 million dollars annually.

Erin Allmann Updyke

Whoa.

Erin Welsh

So how did this virus become so prevalent in such a short amount of time? Maybe it didn't.

Erin Allmann Updyke

Yeah.

Erin Welsh

Probably didn't. I think more likely it was there all along. I've tried to look into the evolutionary origins of RSV and earlier suspected outbreaks in human history but I didn't really have much luck. And to me honestly that makes sense, right.

Erin Allmann Updyke

Yeah.

Erin Welsh

Like in terms of its relationship with humans throughout history, RSV doesn't cause a super distinct infection. Many other viruses can cause illness that looks a lot like RSV and so it's kind of hard to look back retrospectively as we know and go was that RSV?

Erin Allmann Updyke

Right.

Erin Welsh

Was that influenza? What could that have been?

Erin Allmann Updyke

Right. It could have been any or all of the above.

Erin Welsh

Yeah, exactly.

Erin Allmann Updyke

Rhinovirus, enterovirus, adenovirus, coronavirus, influenza. The list goes on.

Erin Welsh

The list goes on. And I think the timing of its identification in those chimpanzees probably coincided with improvements in microbiological techniques that allowed researchers to distinguish among viruses which in previous decades had been fairly difficult. Whether or not there was an actual increase in the prevalence of the virus over the 1970s, 1980s, 1990s or it just looked that way because people finally had the tools to determine what was making you sick, it's unclear. I did wonder, I tried to look into this but I didn't really see anything, I wondered whether there was a connection between the rise in daycare, if there was a rise in daycare during that time, that also led to a rise in infections. But I didn't really find any papers that had investigated that. So it's just going to remain my little personal question for now.

Erin Allmann Updyke

Yeah, our own little mystery.

Erin Welsh

Yeah, yeah. Or if how that changed the timing of infection.

Erin Allmann Updyke

Right.

Erin Welsh

The first 6 months versus the first year, like when... Yeah, I don't know.

Erin Allmann Updyke

Yeah.

Erin Welsh

In any case it seems pretty likely that RSV has been around for a very long time, contributing to the rise in respiratory infections that humans have seen in colder months or in rainy months for thousands of years. On the evolutionary side of things, like I said there's not really much info that I could find about where specifically RSV came from and when it was estimated to have first infected humans. So I decided to broaden my search a bit to see if there had been any research on the evolutionary origins of the sub family that RSV is part of, Pneumoviridae, or the family Paramyxoviridae. The sub family, Pneumoviridae, contains viruses that are very similar to human RSV including murine pneumovirus, canine pneumovirus, bovine RSV, ovine RSV, and caprine RSV.

And the Paramyxoviridae has some very familiar names, measles, mumps, distemper, Newcastle disease. I found a paper from 2012 that I actually read for our mumps episode as well. I was like this sounds familiar and then I searched in my folders. And in that paper the authors tested bat and rodent species for paramyxoviruses and they found a bunch of novel viruses in bats that seemed to be relatives of RSV in humans. This doesn't mean that RSV came from bats, just that this bat RSV-like virus and human RSV and bovine RSV all share a common ancestor.

It does to me present the possibility that human RSV and other human pneumoviruses or paramyxoviruses originally spilled over from a mammal species, whether that was bat or cow or rat or something entirely different. Interestingly, just a little asterisk, human RSV is more closely related to bovine RSV than to these bat or mouse RSV-like viruses. Yeah. I wish I had more details for you and also for myself because I'm really curious to know more about the evolutionary origins of this virus. But sadly I don't have that information. If any of you out there listening has a paper or just has some info with some details, please send it our way, I'd love to read it.

Erin Allmann Updyke

And I think even more recently they've even split RSVs, the RSVs into a new family a little separate from the Paramyxoviridae. So I feel like the whole phylogeny of-

Erin Welsh

Oh, it's separate from Paramyxoviridae?

Erin Allmann Updyke

Yeah but it's new, since like 2016.

Erin Welsh

This paper was 2012, yeah.

Erin Allmann Updyke

Yeah. We'll probably see the phylogeny of RSV continue to change as we dig more down into the different strains and etc.

Erin Welsh

Yeah, especially after this RSV season.

Erin Allmann Updyke

Right. Oh my gosh.

Erin Welsh

I would imagine there to be a lot more research on the... So maybe in a couple of years we'll revisit.

Erin Allmann Updyke

Right. Just like with influenza.

Erin Welsh

Well that explains why I had a hard time finding evolutionary origins. I was like what is this thing? Okay. Okay. But regardless of how RSV got into humans or when we first started getting sick from it, very soon after it was discovered it became apparent what a huge problem this disease could be. And so naturally researchers and physicians began trying different methods to either treat or prevent RSV infections. Vaccination like you mentioned Erin, was one route that was explored early on and continues to be explored. But like you said we don't have a vaccine for RSV. And I know you're going to talk a lot more about why that is and also where we stand with some of the vaccines in development today. There's also ribavirin, a synthetic nucleoside, immunoglobulin therapy, other experimental therapies like RNA interference therapy, and so on. Which I'm sure you'll talk more about some of these potential horizons for RSV treatment.

In terms of the history of RSV specifically, that's really all that I have to offer. It was first recognized relatively recently as an important respiratory infection in young children. Its role in infecting older people and people who are immunocompromised has been observed more recently, we've learned a lot about the year to year dynamics of the virus and circulating strains. But don't worry, I'm not just going to stop here and leave you with this like super duper record short history section, especially for the season premiere. I can't do that. Instead I'm going to do a mini deep dive on a topic related to not just RSV but many other respiratory viruses and respiratory diseases. It's a life saving therapy that you hope to never need but are grateful for when it's there, a device whose history goes back further than I ever imagined, and one that frequently dominated headlines especially during the first couple months of the COVID pandemic. I'm talking about the mechanical ventilator.

Erin Allmann Updyke

I can't tell you how excited I am about this, Erin.

Erin Welsh

Well it's going to be a very cursory history. There's more details out there that I will post papers and everything. But it is going to be an exciting history. So I hope you like it.

Erin Allmann Updyke

I can't wait.

Erin Welsh

So like you said Erin, supportive care is really all we have at this time to treat RSV and when cases are severe, sometimes that includes a mechanical ventilator. So I started thinking about where this amazing technology came from and how our understanding of the risks of lung injury and how breathing works has led to improvements in artificial ventilation. Our story starts in the mid 16th century with the anatomist Andreas Vesalius whose name we may or may not have mentioned on the podcast before, I can't remember. But whose anatomical illustrations I'm pretty certain we've posted on our social media.

Erin Allmann Updyke

Got it.

Erin Welsh

At this point in history we didn't really know a whole lot about the inner workings of respiration. Basically the writings of Galen from the 2nd century CE describing breathing as necessary to maintain circulation and keep your heart beating. That's more or less as far as humanity had gotten in describing the purpose and mechanics of ventilation. So Vesalius had a pretty open playing field then when it came to making advances in understanding form and function, especially respiration. In his 1543 anatomy treatise 'De Humani Corporis', Vesalius described what we would today recognize as positive pressure ventilation. Quote: "But that life may be restored to the animal and opening must be attempted in the trunk of the trachea into which a tube of reed or cane should be put. You will then blow into this so that the lung may rise again and take air."

Erin Allmann Updyke

How interesting.

Erin Welsh

Isn't that fascinating to think about?

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah. Of course this wasn't Vesalius just hypothesizing about how you could perform artificial respiration, he actually experimented on animals to show this.

Erin Allmann Updyke

Of course he did, yeah. He's doing a bunch of tracheotomies it sounds like.

Erin Welsh

Of course. As did Robert Hooke, whose name you've definitely heard on the podcast. He coined the term 'cell', made incredible advances in microscopes, was also an astronomer, architect, physiologist, basically a big deal in the sciences in the 1600s. Even though he reportedly had an abrasive personality that prevented his work from being known for a while, just a bit of seasoning on that.

Erin Allmann Updyke

Don't do that.

Erin Welsh

Yeah. In one of his many scientific ventures, Hooke set his sights on testing Galen's hypothesis that the act of breathing was necessary for circulation. He took a dog, made a bunch of cuts in this poor dog's chest wall and pleura, and then used bellows, like the things you used to blow air into a fireplace-

Erin Allmann Updyke

Yeah.

Erin Welsh

To create a constant flow of air into the lungs. And observed what happened when he stopped.

Erin Allmann Updyke

Wow.

Erin Welsh

Quote: "This-" as in pumping air into the airway using bellows, "being continued for a pretty while, the dog lay still as before, his eyes beating very regularly. But upon ceasing this blast, then suffering the lungs to fall and lie still, the dog would immediately fall into dying, convulsive fits but be as soon revived again by renewing the fullness of his lungs with a constant blast of fresh air." Endquote. With this gruesome experiment, Hooke showed that it was indeed airflow into the lungs that was necessary for circulation and thus life. Another 100+ years would pass before scientists learned what oxygen was and recognized its importance and respiration which is a whole separate and cool story that I would love to tell someday.

Erin Allmann Updyke

Yeah. Wow.

Erin Welsh

But one unfortunate consequence of this discovery of oxygen was that mouth to mouth resuscitation, which had been developed by that time, it fell out of use because people believed that the air you would be exhaling into someone else's lungs during mouth to mouth would not contain oxygen, yeah. It would be depleted.

Erin Allmann Updyke

How interesting.

Erin Welsh

Yeah. The next big advancement in artificial ventilation happened about 100 years after then when scientists began playing around with negative pressure ventilation. I'm going to pause here to explain briefly how negative pressure and positive pressure ventilation works and the difference between them. When you breathe, your diaphragm contracts which expands your chest cavity and allows you to fill your lungs with air, specifically your alveoli which is where oxygen is exchanged for carbon dioxide in your blood. When you exhale, your diaphragm relaxes and you exhale out that carbon dioxide along with a mixture of other gasses including oxygen. This normal lung function can be disrupted by a number of things including respiratory infections such as RSV, as you described Erin, and in severe cases someone may need the assistance of a ventilator to make their lungs work and take in the oxygen they need.

So how do these ventilators work? There are two general strategies, at least how they're grouped historically, for artificial ventilation. There's negative pressure ventilation which was the first to be developed and widely applied starting in the early 1900s but isn't really in use anymore. And there's positive pressure ventilation which is what the ventilators we see today use. Negative pressure ventilation works like this. Basically you seal someone's body from the neck down or at the very least leaving just their mouth and nose open, into an enclosed airtight room or box. Then you suck out all the air from that space, creating negative pressure. This causes the chest cavity to expand with air, allows your lungs to draw in that air, and then you would pump air back into the room or box, so bringing the pressure back up and that would lead to exhalation. This is how an iron lung works.

Erin Allmann Updyke

I was just going to say that sounds like an iron lung.

Erin Welsh

Exactly, yeah. Positive pressure ventilation on the other hand involves using pressurized air to fill the lungs, such as with an oxygen mask over your face for instance or in more extreme circumstances doing like you said Erin, intubation, so tubing applied directly to the lungs that essentially takes over the whole breathing process from inhalation to exhalation. And this is what we see in hospitals today, these big specialized machines that were the topic of much concern and discussion during COVID peaks when hospitals began to run out of them for instance. And many places didn't have them for instance.

Erin Allmann Updyke

And importantly, much smaller devices than a negative pressure ventilator.

Erin Welsh

Yes, yeah. Definitely. All right but now let me get back into the history of the development of these types of mechanical ventilation and why we switched from mostly negative pressure to positive pressure devices. One of the first negative pressure ventilation boxes was developed by a scientist named Alfred Jones in the 1860s and this is where air pressure within the box was altered using a plunger manually. Yeah. Jones advertised his ventilator as the cure for an impressive number of conditions such as paralysis, neuralgia, asthma, bronchitis, dyspepsia, and deafness.

Erin Allmann Updyke

Deafness?

Erin Welsh

Yeah. I don't understand but it was the 1860s, anything goes.

Erin Allmann Updyke

Yeah.

Erin Welsh

An early version of what would later be known as an iron lung was developed in the 1870s with the intention of placing these along the Seine to resuscitate people who had drowned. Yeah, kind of an interesting little thought there. But the real iron lung, the one that was so integral during the first half of the 20th century during polio outbreaks, it's the iron lung that you're picturing right now in your head-

Erin Allmann Updyke

Yep.

Erin Welsh

That was developed by Philip Drinker and Louis Shaw at the Harvard School of Public Health in the late 1920s. Drinker got the idea after treating people with paralytic forms of respiratory failure, especially from polio. So he thought if only I could develop some sort of machine that would maintain ventilation support just for a little bit of time without having to tend to it, have it be automatically administered, just until their lungs heal enough so that they can breathe on their own, just until they get better. And he first tested his iron lung on cats and then found success and then he tested it on himself and then other volunteers. But the first patient to use Drinker's iron lung was an 8 year old girl who was having trouble breathing due to a polio infection. Her breathing was getting weaker and weaker, her lips were turning blue, and just at the point when her doctor thought she wouldn't be able to recover, they decided to try the iron lung. Almost immediately after being placed in the device, she recovered consciousness and asked for ice cream. Which I love, I thought that was so sweet.

Erin Allmann Updyke

That's so 8 year old, I love it. So cute.

Erin Welsh

She was able to be taken out of the iron lung after just 3.5 hours.

Erin Allmann Updyke

Wow.

Erin Welsh

Ultimately she did end up dying from pneumonia but this instance showed that the device held great potential for breathing assistance. The iron lung and other negative pressure ventilation devices were certainly a huge step forward in terms of respiratory support but they did leave a lot to be desired. If you picture one of these things, your body has to be sealed off from it and that makes it impossible for healthcare workers to tend to any other part of your body that's inside this iron lung for instance, not to mention the discomfort that you would feel not being able to move or just be trapped in this machine. And so to deal with this lack of access to the body, they thought let's just build a whole negative pressure room where you can hold multiple patients in bunk beds and you have their heads just like sticking out of the wall. And then a nurse or a doctor could go into that room and then tend to the patients' bodies.

Erin Allmann Updyke

Interesting.

Erin Welsh

Yeah. That's obviously not the most logistically sound solution.

Erin Allmann Updyke

No. Difficult.

Erin Welsh
Yeah. The need for an alternative solution to iron lungs became very apparent during the polio epidemic of the 1950s where cases were so high that hospitals ran out of iron lungs. And you can look up these photos of hospital wards with rows upon rows of the machines. When there was an iron lung shortage, some hospitals resorted to performing tracheostomies and then manually ventilating patients which was previously only something done in an emergency or while operating. I want to read you a description of the situation from a hospital in Copenhagen in 1950. Quote: "During several weeks we had 40-70 patients in our hospital requiring continuous or intermittent bag ventilation. To do this we have employed about 200 medical students daily."

Erin Allmann Updyke
Oh my gosh.

Erin Welsh
Yeah, daily. I read one paper that put the total number of students providing manual ventilation at 1500 and the total number of hours at 165,000.

Erin Allmann Updyke
Wow.

Erin Welsh
Doing continuous hand bagging ventilation.

Erin Allmann Updyke
Yeah. Yeah, it's not easy to do.

Erin Welsh
No. And it was actually because it was easier to put all of these patients needing ventilation in one area of the hospital that marked the beginnings of ICUs. Yeah.

Erin Allmann Updyke
Oh, that's a fun fact.

Erin Welsh
Isn't that? Another silver lining to this was that it became obvious that positive pressure ventilation, as in the hand bagging that had to be done, resulted in about half the mortality rate of the negative pressure ventilation.

Erin Allmann Updyke
I am so interested in the order that things have gone here because the very first accounts that you talked about with the dog and the bellows, that's positive pressure.

Erin Welsh
Yeah.

Erin Allmann Updyke
So to go from that to hey, we're going to do it in a really weird roundabout cumbersome way of negative pressure and then come back to being like oh no, actually positive pressure is a lot easier, it makes a lot more sense. That's so, so fascinating.

Erin Welsh
So there definitely were positive pressure ventilation devices that were either being designed or in limited use alongside these negative pressure ventilation machines like the iron lung. And I wonder whether it was the prevalence of polio and paralytic or partial paralysis in your respiratory system or whatever that may have been the more pressing need at times. But I don't really know.

Erin Allmann Updyke
Yeah.

Erin Welsh
Why does one idea catch on and one doesn't?

Erin Allmann Updyke
Marketing. I'm just kidding but kind of.

Erin Welsh	Yeah. But even the person who developed the iron lung also was working on a positive pressure ventilation device.
Erin Allmann Updyke	Interesting.
Erin Welsh	Yeah. Yeah, this polio epidemic during the 1950s really showed that like hey, we should maybe not do that anymore and turn towards positive pressure ventilation.
Erin Allmann Updyke	Yeah, right. Get to work on making this one more efficient as well.
Erin Welsh	Exactly, yeah. And so I think that really was this turning point, this realization of how much better outcomes were with positive pressure ventilation in polio alone.
Erin Allmann Updyke	Okay.
Erin Welsh	That lead to attention and all of the funding basically being put into positive pressure ventilation machines.
Erin Allmann Updyke	Cool.
Erin Welsh	<p>And so after this turning point of the 1950s, positive pressure ventilation machines, that's where most of the attention began to be focused. And so it really became about improving the functionality, just like making little tweaks here and there on those machines. Because they came onto the scene during a time when their main purpose was to essentially replace respiratory muscles or respiratory function. But over the next decades, especially with declining rates of polio thanks to the vaccine, they began to be used to correct the levels of oxygen that someone was getting, which was possible due to a greater understanding of the different gasses in our blood and how to measure them and monitor continuously and then make tiny adjustments here and there. And so all of this was done in sort of a gradual fashion.</p>
Erin Welsh	<p>We've come a very long way since those early ventilators, not just the iron lung but the first positive pressure ventilators that came on the scene. And we've come a long way both in terms of technological improvements in these ventilators as well as strategies of use, like full support to partial support. Because there are, like I mentioned, there are risks and negative health consequences to using these ventilators. And so that's been really crucial over the past few years. But we're still learning very, very much as the COVID pandemic has made painfully clear. The ventilators that we currently use are expensive, they require highly trained individuals, they are not as bulky as iron lungs but are still bulky and not very mobile.</p>
Erin Welsh	<p>And we really need cheaper, more transportable, and easier to use ventilators to increase access to these life saving devices. And this seems to be a pretty exciting and active area of research. I didn't do very much digging into like where we stand today because that's more of your thing. But I did come across one paper that described a soft implantable robotic ventilator which helps diaphragm function. So that could be kind of cool. Hopefully we'll see some improvements or cool new approaches to ventilation in the future. But the future is outside of my jurisdiction for this podcast, as is the present really. So I'll hand it over to you, Erin, to tell me where we stand with this virus today and just how unusual 2022-2023 was in terms of case numbers.</p>
Erin Allmann Updyke	I can't wait to tell you right after this break.
TPWKY	(transition theme)

Erin Allmann Updyke	As always on this podcast, Erin, we're going to be working with estimates here and not exact numbers.
Erin Welsh	Love it.
Erin Allmann Updyke	Especially when we look globally. But I have some pretty grim things to talk about right now.
Erin Welsh	Not surprised.
Erin Allmann Updyke	RSV, according to one of the papers that I read, is estimated to be the second leading cause of infant mortality after the neonatal period.
Erin Welsh	Wow.
Erin Allmann Updyke	And 99% of these deaths, the overwhelming majority of these deaths are happening in low and middle income countries.
Erin Welsh	Is number one diarrheal diseases?
Erin Allmann Updyke	I believe so, although the paper didn't actually specify.
Erin Welsh	Okay.
Erin Allmann Updyke	But I'm pretty sure it's diarrhea, yeah. So what does that mean in terms of actual numbers? Unfortunately a lot of this data is a little bit old, it's from about 2010, the best estimates that we have. I don't think there's been huge declines by any means in RSV infection, so we'll kind of just use these estimates as general numbers. But the estimated total annual global burden of RSV in children under age 5, because this is the group that we look at the most significantly, is almost 34 million episodes of acute lower respiratory illness. So that's not even close to everyone who's affected but these are the kids who are getting quite sick, lower respiratory tract infections.
Erin Welsh	That's so many.
Erin Allmann Updyke	This likely results in about 3.5 million hospitalizations. And again remember that when we talk about hospitalizations, in a lot of places there's not access to hospitals. So keep that in mind. And an estimated 253,000 deaths globally in kids under 5 in 2010.
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	250,000 children. And again these are probably underestimates, though these estimates and the reason that 2010 numbers are often cited is because they're thought to be a lot more accurate than previous estimates which were way lower, way lower.
Erin Welsh	Okay.
Erin Allmann Updyke	If we look at the US specifically, because I have some data from the US, it's estimated that there are over 2 million outpatient visits for RSV in kids under age 5. 2 million kids going to the doctor with RSV.

Erin Welsh: Wow.

Erin Allmann Updyke: Anywhere from about 58,000 or 60,000-80,000 hospitalizations every year. And an additional 60,000-120,000 hospitalizations for adults over age 65.

Erin Welsh: Yeah.

Erin Allmann Updyke: Which is so much higher than I realized.

Erin Welsh: Yeah.

Erin Allmann Updyke: It's estimated that between 6000-10,000 adults over age 65 die from RSV every year.

Erin Welsh: Oh my gosh.

Erin Allmann Updyke: 6000-10,000 according to the CDC. And between 100-300 deaths in kids under age 5.

Erin Welsh: Wow.

Erin Allmann Updyke: I know, it's a lot. And like we kind of alluded to a little bit earlier, while this is generally a seasonal virus in temperate regions, so in North America our winter goes from November-ish to February-ish and that tends to be when we see RSV starting to build up in November, peaking around February, and then declining thereafter. It circulates year round. But that tends to be when the peaks are and when the hospitalization tends to be the highest. The COVID-19 pandemic has changed a lot of things. We talked about that in our influenza episode at the end of last season and I'm sure we'll talk about it in future respiratory episodes as well. And the truth of it is I don't think we fully understand how much it's going to change and how lasting this change is going to be. But for the year and a half, two years where we were really quite locked down, so like 2020-2021, we saw significantly less RSV especially in young kids than we had seen previously. A lot less.

Erin Welsh: Right.

Erin Allmann Updyke: A lot less hospitalizations and just a lot less doctors visits in general for RSV and other respiratory infections. 2022 what we saw was really early RSV starting at the end of summer and reaching peaks even into October and November, what are normally peak numbers. We're recording this right now, full disclosure, in December of 2022 and this will be released at the end of January. I don't know what's going to happen. I don't have a crystal ball but I won't be surprised if this infection has either another peak or has a very, very long tail, right, where we see a lot more infections just persisting for longer, more hospitalizations for longer. Because there's a large cohort of kids who might be being exposed to RSV for the first time later in their life because this is the first time they've been around other kids.

Erin Welsh: Yeah.

Erin Allmann Updyke: Right? So it's really interesting kind of how it's all going to play out and what it's going to mean in the long term. Like what's our RSV season going to look like next year?

Erin Welsh: Right.

Erin Allmann Updyke: Or the year after? I don't think that we know.

Erin Welsh

Yeah. And it's interesting but also very stressful, seems like not a big enough word for it.

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah, definitely. Especially because as I mentioned we still don't have a vaccine.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah.

Erin Welsh

I mean when re-infections are common, how do you...

Erin Allmann Updyke

Yeah. How do you make a vaccine? So it's an interesting story, the vaccines. There have been I don't even know how many different candidate vaccines that have made it through various stages of preclinical and clinical trials, even as far as phase 3 clinical trials. But so far it's just been very difficult to develop a vaccine that has a good balance of immunogenicity, so actually stimulating enough of an immune response to be protective, especially in the kids who are the most vulnerable, right, the youngest of kids aged 0-6 months or up to a year, who are going to be infected for the first time who we know are at highest risk of severe infection. Stimulating enough of an immune response to provide protection while also being safe and not causing any adverse effects. There was a vaccine candidate back in the 1960s that was an inactivated version of an RSV virus that was inactivated with formalin that ended up causing significantly worse disease in that vulnerable population in young infants.

Erin Welsh

Yeah.

Erin Allmann Updyke

It caused what was called an enhanced respiratory disease after a first vaccination in kids who had never been exposed to RSV before. And that is terrible and horrific. And because of that it really set things back a ways because it's going to of course make people a lot more cautious when it comes to future vaccines and clinical trials, especially for that population who is so vulnerable to begin with. And longtime listeners of this podcast will know and remember from many of our episodes just how rigorous safety standards are when it comes to vaccines and their testing and implementation, which over the years, especially since the 1960s, has only become more rigorous, right.

Erin Welsh

Yeah.

Erin Allmann Updyke

Which is a good thing. But it also means that it takes a lot longer to develop these vaccines. That's kind of the long and short answer of why we still don't have one. There are dozens of vaccine candidates and what I think is really interesting is that not only are there candidates of various vaccine platforms that are under study, like everything from live attenuated vaccines to whole inactivated or killed vaccines, to component vaccines or protein vaccines, to DNA, RNA-

Erin Welsh

mRNA vaccines!

Erin Allmann Updyke

Yeah, nucleic acid-based vaccines like the COVID ones. So there's people doing research on every different vaccine type that you can imagine. But there's also different populations that people are trying to target for protection which is really interesting in the context of RSV. So first we know that older adults are also at really high risk. So there's people working on vaccines that are going to target older adults to just boost their immunity or something like that. There's also an effort to target just older kids in general because older kids, especially after 6-12 months, that's when we tend to start to use, usually at 12 months, live attenuated vaccines. But then there's these really vulnerable tiny infants and we don't have vaccines for them right now and we had really bad experience with the vaccines we tried to develop in 1960. So another potential way to protect those youngest babies who are most vulnerable is maternal vaccination, vaccination during pregnancy, the way that we do for pertussis.

Erin Welsh

Yep.

Erin Allmann Updyke

And so there's also groups that are working on developing maternal vaccines that produce enough immunity that can be passed through the placenta and potentially through breast milk as well to provide protection to these youngest of infants.

Erin Welsh

So cool.

Erin Allmann Updyke

Plus, as I mentioned, there is already a monoclonal antibody that is in use and there is work on additional monoclonal antibodies or other ways to give monoclonal antibodies that might be more cost effective, etc. And even though like you mentioned, Erin, we get re-infected with this virus all the time, right, which makes you think like how can you develop a vaccine for something that we just get re-infected with all the time?

Erin Welsh

Flu.

Erin Allmann Updyke

Right, flu, yeah. But what we know about RSV is that it's that first exposure that is often one of the most highest risk times. And we know that things like maternal antibodies or these monoclonal antibodies or previous infection where you've developed at least some antibodies provides protection against severe disease and hospitalization, which means it provides protection against death.

Erin Welsh

Right.

Erin Allmann Updyke

And so because of that there is this theoretical we should be able to develop a vaccine that's at least protective against severe disease and hospitalization.

Erin Welsh

Right. Doesn't need to be perfect for everyone at all times.

Erin Allmann Updyke

Exactly.

Erin Welsh

There are priorities.

Erin Allmann Updyke

Exactly.

Erin Welsh

That you can put into vaccine development, yeah.

Erin Allmann Updyke

Right. And so that's, yeah, there's a lot of hope and there's so many different groups that are working on all of these different aspects.

Erin Welsh: Oh my gosh, so many.

Erin Allmann Updyke: But as of now we still don't have one. Also this is a human specific virus and we don't have good animal models for RSV which makes it that much harder to develop vaccines.

Erin Welsh: Yeah, yeah.

Erin Allmann Updyke: But there's I think a lot of hope on the horizon and I think, like you mentioned Erin, this is something that we're hearing about more and more and more and the more that diseases get pressed, the more that they get funding and the more that they get funding, the faster that we get new technologies.

Erin Welsh: Yeah. Hopefully we'll see that in the future then.

Erin Allmann Updyke: Yeah, exactly. But that is RSV.

Erin Welsh: Wow. What a way to start Season 6.

Erin Allmann Updyke: Yeah, I'm pretty excited about it.

Erin Welsh: I have a bunch of papers. I want to shout out just a couple of them. So in terms of the history of RSV, that first paper by Morris et al from 1956 is actually kind of an interesting read. And then for the history of mechanical ventilation, there are several papers, one I really liked by Petty from 1990. And I also want to shout out a TED-Ed video that I watched to teach me how ventilators work because I had no idea. And I will link to that video on our website as well.

Erin Allmann Updyke: I also had quite a number of papers. One of my favorites, just very broad overview, was an older paper by Welliver from 2003 in the Journal of Pediatrics. If you want more on RSV and asthma and those details, there was a paper by Han et al from 2011. I have a number of different papers on vaccines and where we stand with vaccine candidates and vaccine research. And we'll post all of our sources from this episode and every one of our 5 other seasons worth of episodes on our website thispodcastwillkillyou.com under the EPISODES tab.

Erin Welsh: We certainly will. Thank you again so much Lucy for sharing your story with us.

Erin Allmann Updyke: Yeah.

Erin Welsh: Yeah.

Erin Allmann Updyke: Yeah, thank you. Thank you also to Lianna Squillace for our audio mixing, we are thrilled to have you on board for the first time this season!

Erin Welsh: We are. And speaking of audio, thank you to Bloodmobile who provides the music for this episode and all of our episodes.

Erin Allmann Updyke: Thank you to the Exactly Right network.

Erin Welsh: And thank you to you, listeners. Thanks for joining us again this season.

Erin Allmann Updyke

Yeah. Welcome back.

Erin Welsh

As always, send your suggestions, there is now a submit your firsthand account link on our website. And yeah, we always love hearing from you, you're the best, you make this possible.

Erin Allmann Updyke

And and extra shout out to our patrons, thank you so much for your support. Always, we love you.

Erin Welsh

We do. Well until next time, wash your hands.

Erin Allmann Updyke

You filthy animals.