

Erin Welsh

"H5N1 is an interloper, an unrefined newcomer, all fury without the seasoning of age. In human cells it has discovered a fresh target and it pursues its prey deep into the body, penetrating much farther than ordinary flu. This novel virus advances on the lungs themselves, attacking the branches of the bronchial tree and the myriad little buds on their tips called alveoli where the life sustaining task of exchanging carbon dioxide for oxygen occurs. The pathogen infects the coating of mucus that protects the membranes of the lungs. This newcomer penetrates into the tissue itself. It spreads farther, often infecting both lungs at nearly the same time. As the pathogen relentlessly erodes the cells of the deep lung, you find yourself increasingly short of breath, your cough is often bloody, and you may bleed from your nose and even gums.

The human body which has never encountered anything like it has no ready arsenal of antibodies to choke off the process. The body can still marshal its innate all purpose defenses but in doing so it mounts a counterattack so furious that some scientists believe it's more lethal than the virus itself. The body throws everything it has at the intruder without regard to the tremendous collateral damage this causes the lungs themselves. Ever more immune cells are summoned to the front and continue to blast away. The carnage mounts. The lung cavities fill with dead and damaged tissue, mutilated mucous cells, and other cellular wreckage. The lungs become rigid as the cells that make the liquid to keep the lungs flexible are annihilated. The seal between the bloodstream and the air passages ruptures. Red blood cells and plasma leaks into the lungs. The alveoli sacs are swamped with fluid and debris and are no longer able to exchange carbon dioxide for oxygen.

If you listen closely, you can hear the liquid crackling, your breathing accelerates, you desperately press all your chest muscles into helping you suck down precious oxygen. You're gasping for air, you're drowning. But the virus is not content to remain a solely respiratory disease. It invades the digestive tract, often causing diarrhea and sometimes vomiting. It can assault the liver and kidneys, it can provoke heart failure, it can attack the eyes. It can even breach the brain and spine. Yet in the end the lungs are where this microbe concentrates its energies and takes its heaviest toll. The lungs are also the means by which it casts its net for further prey. In this one regard it is much like its seasonal cousin. They both spread their sickness through contaminated droplets coughed or sneezed into the air, one of the most efficient forms of transmission known."

TPWKY

(This Podcast Will Kill You intro theme)

Erin Allmann Updyke

It is so terrifying.

Erin Welsh

Is it somehow scarier because of COVID or just scarier because we've read more about other pathogens and finally have more of a respect or appreciation for flu?

Erin Allmann Updyke

I think both. I think in large part it's probably COVID.

Erin Welsh

Yeah.

Erin Allmann Updyke

I think it's living through something that is in many ways so similar and so terrifying and knowing that it not just has happened again historically but it just happened and now we're going to talk about how it can happen again and potentially be much worse.

Erin Welsh

Yeah. And by can happen again, likely will happen again.

Erin Allmann Updyke

Yeah.

Erin Welsh: Yeah. So that firsthand account was from a book titled 'The Fatal Strain: on the trail of avian flu and the coming pandemic' and that was written by Alan Sipress and it was published in 2009.

Erin Allmann Updyke: I think I read that for our first influenza episode.

Erin Welsh: I think you did. I think it's on our sources.

Erin Allmann Updyke: Yeah.

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: And today we're revisiting our very first ever topic, influenza.

Erin Welsh: We are. It's our season finale celebration. Yeah, kind of a somber celebration. But I think that given the news about avian influenza this year and the timeliness of this, we really wanted the opportunity to kind of go back and redo, re-explore this pathogen that is so utterly terrifying. And there is so much information out there about it that it really deserves not only just a second episode but also an entire series.

Erin Allmann Updyke: Yes, one could certainly argue that.

Erin Welsh: Yeah, yeah. So that's what we're doing this episode, kind of talking about all of the different bits that we didn't cover in our first episode which is quite a lot. And I think also one of our aims is to bring us up to speed more about today with a particular focus on avian influenza.

Erin Allmann Updyke: Yeah. A lot has changed since 2017 and we've learned a lot more.

Erin Welsh: Yeah.

Erin Allmann Updyke: So it's going to be exciting to kind of bring it all back together.

Erin Welsh: Well should we start off with quarantini time?

Erin Allmann Updyke: We should, we certainly should.

Erin Welsh: What are we drinking this week?

Erin Allmann Updyke: Well we're drinking none other than H1Drink2!

Erin Welsh: I love it.

Erin Allmann Updyke: We couldn't not.

Erin Welsh: So for those of you who haven't listened to our very first influenza episode, we can't blame you first of all. Second of all-

Erin Allmann Updyke Not necessarily recommending it.

Erin Welsh Nope. But it is maybe pertinent to this part of the episode to know that our very first quarantini was called H1Drink1.

Erin Allmann Updyke So this time H1Drink2.

Erin Welsh Yeah.

Erin Allmann Updyke And what is in H1Drink2, Erin?

Erin Welsh It is kind of a play on the Corpse Reviver. So we did the Corpse Reviver #2 for our H1Drink1, our very first quarantini. And this one we're kind of just doing a variation. It includes apricot liqueur, light rum, lemon juice, and Lillet Blanc. And we will post the full recipe on our website [thispodcastwillkillyou.com](http://thispodcastwillkillyou.com) as well as on all of our social media channels. So check it out.

Erin Allmann Updyke And as a reminder this is our season finale. So do make sure that you are subscribed to whatever podcast app you're listening to this on and to our social media so that you don't miss when we drop our next season.

Erin Welsh We don't have an exact date for you yet, we're sorry.

Erin Allmann Updyke Nope.

Erin Welsh But don't be worried, it won't be too long.

Erin Allmann Updyke Yeah. Any other business, Erin?

Erin Welsh I feel like there should be but I don't think there is.

Erin Allmann Updyke Okay.

Erin Welsh So let's just get started.

Erin Allmann Updyke We've got a lot to cover. Let's take a break and get started.

TPWKY (transition theme)

Erin Allmann Updyke So today we're not going to repeat everything that you may have learned in our very first episode which covered influenza. But what I do want to do in this biology section is take what we learned in that episode and then expand on it. But also realizing that that was five years ago and so most of us have probably forgotten or maybe skipped over the first episode. So what I'm going to do in this section is talk about influenza viruses in general and then focus primarily on bird flu or highly pathogenic avian influenza strains. So it's going to be a lot of fun. And fun meaning terrifying. Okay.

Erin Welsh Yeah. As we usually mean.

Erin Allmann Updyke

But fascinating, all right? So as a perhaps recap for many of us, influenza viruses, these are RNA viruses, not retroviruses as I called them in our very first ever episode. One of the most biggest embarrassments of my life to this day.

Erin Welsh

Is it like one of those things that pops into your head as you're trying to fall asleep?

Erin Allmann Updyke

Yeah, sometimes.

Erin Welsh

You're like, 'I called influenza retrovirus!'

Erin Allmann Updyke

I called it a retrovirus on the internet forever!

Erin Welsh

It's in our transcript! I did see it in the transcript and I was like oh yeah.

Erin Allmann Updyke

It's in the transcript, I made jokes about it. I full on went hard. Okay, it's not a retrovirus but they are RNA viruses in the family Orthomyxoviridae. And RNA viruses in general, not always but is true for influenza viruses, tend to mutate much more rapidly than for example DNA viruses in large part because they lack good proofreading mechanisms. So what happens very commonly with influenza viruses is that small mutations can accumulate over time. And if these mutations happen to be in regions of the genome that encode the major surface proteins of influenza, we'll talk about those more in a second, aka the antigens, then that can make it harder for our immune system to recognize those antigens or recognize that virus. And this process is known as antigenic drift. This is one of the ways that influenza viruses are particularly adept at evading our immune system and why they're so tricky to target and interesting. But on top of that, influenza virus genomes are made up of multiple short strands of RNA rather than one big long strand.

And because as we'll talk in a lot of detail about there are so many different strains of influenza viruses, if an animal like say a bird is co-infected with multiple strains which is not at all uncommon, these segments of RNA can mix and match inside of their cells and recombine to form essentially brand new versions, brand new unrecognizable strains of influenza. This is the process of antigenic shift. And this amazing amount of variation in viral strains is why influenza remains such a challenging virus to combat in the form of vaccines, etc. But let me actually back up even further for a second because when we say influenza virus we're not talking about a single influenza virus, there's actually four major classes of influenza viruses, A, B, C, and also D. And when we talk about influenza viruses in humans, we mostly mean influenza A and to a lesser extent influenza B. Influenza C does circulate and causes disease in humans but it's more like a mild cold rather than what we think of as the flu. And influenza D is mostly in cattle.

Erin Welsh

Okay.

Erin Allmann Updyke

So influenza B has two major lineages that circulate only among humans, it's not a zoonotic virus. And while it can cause a decent amount of disease in epidemics seasonally it's not a zoonotic virus and it's not the major player in general when we think about influenza.

Erin Welsh

So I have a question about influenza B. So from my understanding the vaccines that target seasonal influenza A, the influenza A strain that's in there might change from year to year depending on what is predicted. But B doesn't really seem to change. Why doesn't it really change that much?

Erin Allmann Updyke

That's a good question. There's only two major lineages of influenza B. So I don't know as much detail because I didn't dig hardcore into influenza B but it's likely just that there simply isn't as much variation as what we see with influenza A.

Erin Welsh: Okay, so fewer opportunities for combination.

Erin Allmann Updyke: Exactly.

Erin Welsh: Okay, gotcha.

Erin Allmann Updyke: Because it's not a zoonotic virus, it's only circulating among humans.

Erin Welsh: Right, interesting.

Erin Allmann Updyke: But let us now focus for pretty much the rest of this episode on the biggest player and that is influenza A. So most people are probably familiar with classifications of influenza A viruses and those are H1N1 or H3N2. You've probably heard those circulating around every time that there's a new strain that causes an epidemic, right? So those letters, H and N, refer to two specific antigens on the influenza virus surface itself. The H antigen, hemagglutinin, and the N antigen, neuraminidase. You don't have to remember those names. You could just remember H and N. So the H proteins, you can think of these as the proteins that bind to our cells and allow influenza virus to actually enter our cells.

Remember of course that all viruses have to get into our cells in order to be able to replicate, they rely on our machinery to finish that process of replication. Influenza viruses are respiratory viruses, right, so they predominantly are infecting the cells that line our upper and lower respiratory tract. These H proteins on their surface are what allow them to bind to these cells in particular and enter those cells. Which means that these H antigens especially are the ones that in theory and in practice our immune system recognizes and if we are able to block it we can stop this virus from entering our cells entirely.

Erin Welsh: Question.

Erin Allmann Updyke: Okay.

Erin Welsh: So the difference between upper and lower respiratory tract-

Erin Allmann Updyke: Ooh Erin.

Erin Welsh: And the differences in the Hs. And are some more adept at invading both the upper and lower or just the upper or...? Yeah.

Erin Allmann Updyke: 1000% yes.

Erin Welsh: Okay. Which ones?

Erin Allmann Updyke: Okay. I can't give you an easy answer on that because it varies.

Erin Welsh: Okay.

Erin Allmann Updyke: The answer to all of these questions of detail are probably going to be it depends.

Erin Welsh: Yeah, that's classic. Yeah.

Erin Allmann Updyke

Because let me keep going and we'll see not just how much variation there is but how terrifyingly much variation there is.

Erin Welsh

Great, love it.

Erin Allmann Updyke

So we can't also forget about the N antigens. These are involved in the process of once that virus has replicated in our cells and is all packaged up and ready to burst forth to go infect more cells, the N antigens are what help influenza virus actually release from inside of our cells. That's what the N antigens are doing. So another potential target but a harder one given that it's an intracellular site of action. So it's really this H antigen that is the one that when we think of vaccines we're predominantly potentially targeting. And we'll get to all of that much later in the episode.

Erin Welsh

It's interesting to think about from an evolutionary perspective because it seems clear why there would be variation in H, in the hemagglutinins.

Erin Allmann Updyke

Right.

Erin Welsh

But the neuraminidase, what is the variation in that functionality?

Erin Allmann Updyke

Ooh, that's a really good question. Yeah, I don't know.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah. It's really interesting though. What's the benefit of having different receptors to do the binding and releasing?

Erin Welsh

Right. What is N1 vs N2? Is there a functional difference or is it just these are different enough to be called different?

Erin Allmann Updyke

Yeah, enough, there is.

Erin Welsh

Right.

Erin Allmann Updyke

Yeah, yeah. That's a good question. So there are 18 different major H antigens, 16 if you don't count the ones that are mostly only found in bats. And there are 11, or again 9 if you don't count the ones that are mostly only in bats, major N antigens. Knowing that you can combine Hs and Ns in pretty much any configuration, that alone is a huge amount of potential for recombination and change, right. 18 and 11 or even 16 and nine. That's a ton of variation. I can't do that math.

Erin Welsh

No Erin math?

Erin Allmann Updyke

No Erin math this episode. But on top of that, you asked what are the differences between the different H antigens.

Erin Welsh

Yeah.

Erin Allmann Updyke

There is not just a difference between say H1 and H2 but because of the build up of changes to these H and N antigens via that antigenic drift, via those small point mutations, what that means is that not every version of H3N2 is exactly the same. There are parts of the H antigen and parts of the N antigen that are more conserved and there are other parts that are much more variable even within say H1 or H5.

Erin Welsh

Interesting.

Erin Allmann Updyke

It's fascinating. And yes, absolutely these different H antigens are going to have different affinities for specific receptors on our epithelial cells and that is going to determine which cells they invade and how readily. So as we see with particular strains like H5N1 in our firsthand account that are able to invade lower respiratory tract very rapidly and even invade beyond our respiratory tract, that's likely something that's largely mediated by particular changes to that H or possibly N antigen, allowing it to release more readily from certain cells than others. So that's all of this variation. Let's get into more details of what we know about influenza as an illness. Okay?

Erin Welsh

Yeah.

Erin Allmann Updyke

So influenza viruses of course are respiratory viruses which means that they're transmitted by droplets or aerosols when we cough, sneeze, talk, laugh, etc. There's also a lot of indirect transmission via fomites like door handles, shared coffee cups, whatever you lick your hand and then touch. And this route of transmission in particular, fomites or more indirect transmission, seems to be and is thought to be a pretty important route of transmission. Although, because I figured you were going to ask Erin, I did not get a sense and the papers that I read actually suggested that influenza is not actually a very environmentally stable virus. And despite how much we know about influenza, we still don't know enough to be able to say like the relative contribution of this transmission rate versus that transmission route. Does that make sense?

Erin Welsh

Yeah, you know me so well.

Erin Allmann Updyke

I know.

Erin Welsh

Those were literally the two questions I was brimming, like on the top of my tongue.

Erin Allmann Updyke

I preempted you this time.

Erin Welsh

You did.

Erin Allmann Updyke

But in any case you're breathing and sneezing this stuff out because this is a virus that's primarily infecting our respiratory cells, the respiratory epithelium. And in general the incubation period for influenza is remarkably short. People are often symptomatic by day two after inoculation, sometimes by day one and almost always by day four. So very short incubation period especially compared to a lot of things we've covered recently. And people are generally infectious, that is high viral titers in their nasal epithelium, up to 24 hours before symptoms begin.

Erin Welsh

Which is where the trouble starts.

Erin Allmann Updyke

It sure is. And if you think about it too, that's incredibly rapid how quickly this virus gets into our cells, starts replicating, bursts out, and is ready to spread. In terms of who gets infected, everybody gets infected with influenza, some data suggests that it's actually children who are the most likely to become infected and the older you are, the less likely you are to become infected. But when it comes to severe infection and mortality, it's both children and older adults over age 65 that are at highest risk of severe infection and death.

Erin Welsh

It's that classic U-shaped mortality curve.

Erin Allmann Updyke

Yep. In all but the 1918 pandemic.

Erin Welsh

And a few others but yeah.

Erin Allmann Updyke

Other people who are at particularly high risk of severe infection include people who are pregnant and then a lot of other comorbidities like heart failure, pulmonary disease of various kinds, cigarette smoking, immunocompromising conditions, all of these things essentially just make it harder for our bodies to fight off this infection or easier for us to get infected with it in the first place. And I think we're all probably familiar with the symptoms of the flu, although I think a lot of people might confuse it with any of another million viruses that we just call the common cold because influenza is not the common cold.

Erin Welsh

No.

Erin Allmann Updyke

With influenza you are sick if you are symptomatic which not everyone is.

Erin Welsh

Right, okay. Question real quick.

Erin Allmann Updyke

How many?

Erin Welsh

Yeah, thank you.

Erin Allmann Updyke

I don't know, I actually didn't see that number reported very commonly.

Erin Welsh

That's so interesting because I feel like we know that so well now for things like COVID.

Erin Allmann Updyke

Yeah, we should know that and I just somehow missed it. But I didn't see it.

Erin Welsh

But presumably there's a subset of people who are asymptomatic.

Erin Allmann Updyke

Absolutely. And asymptomatic carriers can still shed for even up to 6 days which is generally how long people shed.

Erin Welsh

Okay.

Erin Allmann Updyke

But yeah, you're sick. You have a fever, you have muscle aches, full body, like your entire body is aching, your throat is sore and it's red, your nose is probably runny, you're coughing, you're possibly coughing so hard that you're hurting your ribs, you feel like you're coughing your brains out. And this is if you have a mild infection. In this case symptoms last 7-10 days. so it's not just a few days that you're feeling cruddy, you're feeling bad for a long time.



Erin Welsh

Yeah.

Erin Allmann Updyke

And if or when this virus makes its way into your lower respiratory tract, it can then cause a viral pneumonia, it can progress to an acute respiratory distress which can then progress to shock and potentially death. One of the primary drivers that determines if someone is going to have a severe infection vs a less severe infection besides just what strain of the virus is it is how far down into that respiratory tract did the virus invade. And this is probably determined by a whole number of factors like our individual immune response largely? How well did we tolerate vs resist that virus in the upper respiratory tract before it tried to travel down? What strategies did our immune system employ and how effective were they? But then also likely some degree of infectious dose, like how much of the virus were we exposed to, how big of a load did we have to fight off? And then of course the strain of the virus itself, like how variant is it, how big of an affinity does it have for those lower cells versus our upper cells? And on top of that because this virus and our immune response to it can cause so much damage to our lungs, influenza virus, especially viral pneumonia can put people at significantly higher risk of a superimposed bacterial pneumonia especially from a Staph aureus or a Streptococcus pneumonia.

Erin Welsh

Right. Okay, question about the nomenclature I guess of influenza A viruses. So we know the Hs, we know the Ns, but then there are variations within a particular H and N pairing. So how does that work and how do we refer to those?

Erin Allmann Updyke

Yeah, there's not good ways to refer to them. The ones I've seen it's usually like H3N2 strain B3.4.5.222 or something like that.

Erin Welsh

Okay.

Erin Allmann Updyke

So there are specific strains and sometimes too they're still named by the first place that they were discovered or the year that they were discovered.

Erin Welsh

Right.

Erin Allmann Updyke

So there's a lot when we have particular strains that have say become epidemics or have caused really big outbreaks in birds or spilled over into humans a particular number of times or something like that, then they do tend to get more specific names but they're not nice friendly names.

Erin Welsh

Yeah, yeah.

Erin Allmann Updyke

They're very viral names if that makes sense.

Erin Welsh

Unfriendly names, yes.

Erin Allmann Updyke

Yeah. But so this is where I want to kind of shift focus and talk more specifically about the bird flu or highly pathogenic avian influenza strains. So it turns out that when you hear talk about avian influenza, in some respects we're kind of talking about nearly all influenza A strains.

Erin Welsh

Oh yeah.

Erin Allmann Updyke

Yeah. The primary natural reservoirs for influenza A viruses are birds, especially aquatic birds like ducks and geese and swans and gulls and those cute little sandpiper things on the beach. Lots of cute little water birds. With the exception of a few strains that are found predominantly in bats and not really other places, the vast majority of influenza A strains have birds as their natural reservoir. These strains, the vast majority of them, in both wild and domestic birds are what we call low pathogenicity strains or LPAI. So in the birds they infect they don't cause a lot of disease, they might not cause any disease but they can circulate very readily.

However some strains especially those of the H7 and H5 and I think H9 varieties have emerged as being highly pathogenic, aka HPAI. And it's very likely that these strains emerged by a number of mechanisms but antigenic shift and antigenic drift that I talked about earlier play a really big role, especially reassortment leading to antigenic shift. And this can happen in a couple different ways. In wild birds, many of the aquatic bird species that I mentioned like ducks and geese and gulls tend to roost in really large numbers. And because many of these influenza virus strains are low pathogenicity it's easy for a lot of these different strains to circulate in a particular population.

But one thing that can happen is that these low pathogenicity duck strains for example can pop over into our lovely food system, aka poultry farms which are also extremely dense, generally quite unsanitary, beautiful mixing grounds for viruses. In both of these scenarios, both in large roosts of wild birds and in poultry farms, it's very easy for these different strains to mix in a single animal, recombine, and potentially gain traits that lend themselves to higher pathogenicity or virulence in the process. And what we can see then happen when these highly pathogenic avian influenza strains emerge is kind of three major things, all of which are terrifying. Number one, it can result in outbreaks in wild birds which can result in massive die offs of wild birds which is not good for the environment or the birds.

Number two, we can see outbreaks in poultry, in domestic poultry either directly from spillover events or because these highly pathogenic strains emerged in the domestic birds themselves, which can cause massive die offs that also can result in the culling of flocks which means people might lose substantial income. This can also result in spillback into wild bird populations, so you then have both domestic and wild bird deaths. And then of course there's the thing that makes public health professionals so worried and that is number three, these highly pathogenic avian influenza strains can spillover into human populations and potentially cause very severe disease. And this has happened.

Erin Welsh

Oh it happens and it's scary.

Erin Allmann Updyke

Oh yeah.

Erin Welsh

And I think that we've definitely touched on this topic several times, the evolution of virulence and why not all viruses or not all pathogens will just become nicer to us over time.

Erin Allmann Updyke

Yeah.

Erin Welsh

They may evolve to become more virulent and poultry farms are a great example of this, right. When you have a ton of birds crowding in one space and it's really dirty and there's no escaping.

Erin Allmann Updyke

Dense.

Erin Welsh: Yeah. Then it makes more sense to ramp up, as a virus it makes more sense to ramp up your replication and just cause widespread infection and there aren't many drivers for decreased virulence necessarily.

Erin Allmann Updyke: Right. Because that virus is going to be able to spread so easily and quickly through a population, it doesn't matter if it kills its host really rapidly, it's still going to have time to spread especially in the case of an influenza virus which is replicating so rapidly to begin with.

Erin Welsh: Exactly. And there have been different estimates of the mutation rate or the rate of evolution of influenza viruses based on different hosts and certainly domestic poultry is top.

Erin Allmann Updyke: That's terrifying.

Erin Welsh: It is.

Erin Allmann Updyke: And what's even more terrifying is like we said this has happened. One strain in particular, though several HPAI strains have spilled over into humans, one strain in particular, H5N1, has spilled over handfuls of times dozens of times into human populations either usually from domestic or wild birds. And when this strain has spilled over into humans, it has caused severe infections with mortality rates of 50%-60%. In general so far these outbreaks have shown relatively limited human to human transmission which is good for now. But the real worry is how many additional mutations would it take in a human or even in the bird before it makes it into humans for one of these highly pathogenic avian strains to maintain that same level of virulence but with more efficient human to human transmission. That would be something devastating. And then there's really interesting questions as to why do these particular strains cause such severe disease in humans. And part of it as we actually heard in our firsthand account is that in the case of H5N1 we have evidence that this strain in particular causes extrapulmonary infection a lot more readily than most other influenza viruses. So it's not only infecting the respiratory tract, it's infecting other tissue types as well.

Erin Welsh: How is it doing that?

Erin Allmann Updyke: We don't know necessarily.

Erin Welsh: Okay.

Erin Allmann Updyke: There's a relatively limited number of human cases that have happened so far and so there's not a ton of data on in vivo anything when it comes to H5N1.

Erin Welsh: Right. Okay.

Erin Allmann Updyke: So we still don't know also how much of the damage of this virus and this strain is due to direct viral cytopathic effects vs what a huge amount of immune system response it stimulates. But in either case the mortality rate is terrifying.

Erin Welsh: Yeah.

Erin Allmann Updyke: And we'll talk a lot more later on about how much these viruses continue to circulate and spread among domestic fowl populations in particular. So it's really something that worries a lot of public health professionals.

Erin Welsh: Oh yeah. When we talk about species barriers and why some influenza viruses that infect birds don't infect humans, what is that barrier specifically? What is it about that H or that N or whatever that prevents that virus from infecting humans?

Erin Allmann Updyke: Yeah. A lot of it is likely the H factor and just what particular residues on say duck respiratory or GI epithelial cells because in birds influenza viruses infect both the respiratory and the GI tract often. So it's probably just that we don't have as many of those same receptors or we don't have receptors in places that are as easy for that virus to get to. And that would be the biggest barrier, it would be the receptors and being able to actually get into our cells in general.

Erin Welsh: Okay.

Erin Allmann Updyke: There could be others.

Erin Welsh: Interesting.

Erin Allmann Updyke: Yeah. So that is the biology of influenza and influenza A. Erin?

Erin Welsh: Terrifying.

Erin Allmann Updyke: Terrifying. You want to tell me where this sucker came from and...

Erin Welsh: All the rest.

Erin Allmann Updyke: All the rest?

Erin Welsh: I will do my best right after this break.

TPWKY: (transition theme)

Erin Welsh: Before getting too deep into the research for what I wanted to cover this influenza go around, I figured I should first check back through the transcript from our first influenza episode, our very first episode ever.

Erin Allmann Updyke: Yeah. And then you immediately regretted it just like I did.

Erin Welsh: 100%. How can anyone make any sense of this? Yeah. But I also wanted to see what I covered if anything so that I didn't talk about it again. Like you said, turns out I didn't have to worry all that much about it because it was just kind of disorganized mess everywhere. But it was really interesting to skim through to see what I didn't cover, like what questions I still had about the history of the influenza virus, especially in terms of its evolutionary history and avian influenza. And then that is sort of what I based this part of the episode on. And it was also really interesting to read it through the lens of today after we've been in a pandemic for 2 plus years. That episode came out in October 2017.

Erin Allmann Updyke: Wow.

Erin Welsh: We're recording this in October 2022.

Erin Allmann Updyke: Wow.

Erin Welsh  
Which is amazing. Yeah, 5 years later. And at the time of that first recording, we were horrified by the choices that people made during the 1918 pandemic like the parade in Philadelphia for instance. We seemed shocked at the idea of everyone wearing masks and we talked about the very real and very scary possibility that the next pandemic that we could see would be caused by an influenza virus, in particular H5N1.

Erin Allmann Updyke  
Oh my gosh.

Erin Welsh  
And although we were wrong about the causative agent of the next pandemic, we were right to be scared, to still be scared frankly.

Erin Allmann Updyke  
Yeah.

Erin Welsh  
My intention today is not to scare you, I don't think our intention is to scare you but to present what we know about the evolutionary history of influenza viruses, take a brief jaunt through the history of past influenza pandemics, pandemics multiple because there were many of them, and then turn towards the highly pathogenic avian influenza virus H5N1 and how its epidemiology has changed over the past decades. And it's in this last part that I want to draw attention to the parallels between the emergence of this H5N1 virus and the emergence of other pathogens of pandemic potential, things like the 1918 influenza virus, SARS-CoV-1, and of course SARS-CoV-2. Because those stories from initial appearance to sweeping the globe, public health responses and political commentary, they're disturbingly similar.

Erin Allmann Updyke  
I know.

Erin Welsh  
And I say disturbing because even though we know how these pandemics happen, applying that knowledge to prevention seems almost impossible. But before I fall further into this pit of pessimism, fatalism, let's start back at the evolutionary roots of influenza viruses, specifically influenza A. Like most other pathogens we talk about on this podcast, coming up with a timeline for the origins and evolution of influenza viruses, that's pretty difficult.

Erin Allmann Updyke  
I can imagine.

Erin Welsh  
Despite the fact that to quote Wille and Holmes 2020, quote: "From an evolutionary perspective more is known and more sequence data have been generated about influenza viruses than arguably any other group of pathogens." Endquote.

Erin Allmann Updyke  
I'm not surprised by that.

Erin Welsh  
Yeah. What does seem likely is that influenza viruses have been around for hundreds of millions of years, hundreds of millions of years, and that they have infected their natural reservoirs, these water birds, specifically the orders Anseriformes which are ducks and Charadriiformes which are shore birds and gulls, I hope I'm pronouncing that right.

Erin Allmann Updyke  
I didn't say those orders because I knew I couldn't pronounce the second one. So I was like you know gulls and cute little pipes.

Erin Welsh  
Yeah, that's actually probably what I should have done. Regretting it now.

Erin Allmann Updyke  
I think you did a great job.

Erin Welsh: Thank you, thank you. Anyway these influenza viruses have been infecting those birds for thousands and thousands of years. And of course birds aren't the only animals where influenza viruses can be found. Pigs, bats, amphibians, fish, even hagfish, and more. I know, your face.

Erin Allmann Updyke: Hagfish?

Erin Welsh: I know. And more are likely to be discovered the more we look of course. And the patterns in the relatedness of these influenza viruses suggests that co-evolution between influenza viruses and their hosts has been going on as long as vertebrates have been vertebrates.

Erin Allmann Updyke: Wow.

Erin Welsh: I know.

Erin Allmann Updyke: That's kind of nice. Kinda fun.

Erin Welsh: It's pretty cool.

Erin Allmann Updyke: Yeah.

Erin Welsh: But a paper from 2014 concluded that all of the influenza A viruses that we see today in mammals, minus bats, and birds descended from a common ancestor dating back to the late 1800s.

Erin Allmann Updyke: Interesting.

Erin Welsh: Yeah. All of the existing diversity which is high in influenza viruses that we see today in mammals, minus bats, and birds came from a lineage branching off in the late 1800s. Okay but what does this mean? Why does this matter? It matters because it highlights a very important characteristic of influenza virus evolution, their tendency to undergo selective sweeps. Basically what happens is that a new advantageous mutation emerges in one strain that leads to all other strains being outcompeted, eliminated, so that all future lineages come from this one mutant branch.

Erin Allmann Updyke: Oh my gosh, I love this so much.

Erin Welsh: And also we have a present day example or a present day illustration of this. Think about COVID-19.

Erin Allmann Updyke: Right.

Erin Welsh: And how the dominant variant of SARS-CoV-2 is constantly changing.

Erin Allmann Updyke: Right.

Erin Welsh: We don't really see COVID infections caused by delta anymore, delta was displaced by omicron and even the original omicron lineage has been displaced by a later one.

Erin Allmann Updyke: Yeah, yeah.

Erin Welsh

And this will keep happening, this is just how it's going to go. The one that is the most transmissible and causes the most infections, that's going to outcompete the rest and then that's the only lineage that will survive and on and on and on.

Erin Allmann Updyke

Okay, love this.

Erin Welsh

I know, right? And selective sweeps are interesting in light of how we look at existing diversity and evolutionary relationships or the evolutionary history with different influenza viruses. But they're also important from a public health standpoint. Viruses succeed when there are susceptible individuals to infect and the more novel a mutation makes a strain or variant compared to previous ones, the more susceptibility there is going to be in the population. And that holds for humans or birds or pigs or what have you. What determines the level of susceptibility in a population is not just how different the virus is from previous variants but also how many people were exposed to those previous ones, how novel the virus is to them.

Erin Allmann Updyke

Right.

Erin Welsh

And that's what separates seasonal flu from pandemic flu. With the circulating seasonal influenza viruses, they usually only undergo small changes from year to year. And so most of our immune systems have seen them or have seen similar strains before, either through vaccination or infection. So we don't get infected with this new slightly different strain or if we do we just experience a mild infection. But let's say a new influenza virus strain is introduced, maybe spilled over from pigs or birds and none of our immune systems have seen it before. That's when you have the potential for a pandemic. The four influenza pandemics that we've seen since 1918 demonstrate this. In 1918, that usual U-shaped mortality curve that we talked about was flipped upside down, hitting the younger and middle-aged generations the hardest which suggested to some that the older generation had encountered an influenza virus similar to the 1918 strain. The 1957, 1968, and 2009 influenza pandemics were caused by viruses that had undergone reassortment from previously circulating viruses. And reassortment by the way is just when influenza viruses swap bits of their genome and create new strains.

Erin Allmann Updyke

Like antigenic shift.

Erin Welsh

Exactly. People hadn't encountered these new reassorted viruses and so boom, pandemic. This is a source of grave concern for highly pathogenic avian influenza H5N1, that it will swap genes maybe with a human influenza strain, gaining high human to human transmissibility and retaining its highly pathogenic nature. The influenza pandemics of 1957 and 1968 were caused by viruses that had undergone reassortment between previously circulating avian and human influenza viruses. So it can happen. And let's not also discount the role of the humble pig as a little mixing bowl for influenza viruses.

Erin Allmann Updyke

The humble pig.

Erin Welsh

The Humble Pig, that's going to be the name of my bar whenever I make it. But let me rope those fears of H5N1 in a bit and instead take us briefly through the history of influenza as I didn't really do in our first episode. Although influenza viruses are as old as time, it's unclear when humans were first exposed but it's certainly plausible that a passing interaction with ducks or with pigs during domestication could have led to small outbreaks growing in size as settlements got larger. And while some researchers have pointed towards the Hippocratic texts as having the first description of an influenza pandemic, specifically the cough of Perinthus in 412 BCE, the symptoms don't really match up all that well and diphtheria has also been proposed as a more likely explanation.

Other possible but debated influenza epidemic descriptions can be found throughout the hundreds of years that followed. In 1173-1174 CE, in 1510, and in 1557 which some argue was a pandemic. But the agreed upon date for the first clear influenza pandemic is 1580. The disease broke out initially in Asia and then spread to Africa and then Europe before being brought to the Americas. And in all places infection rates were reported as being incredibly high with a sizable mortality rate, 8000 deaths in Rome alone, and some Spanish cities were described as being decimated.

Erin Allmann Updyke

Whoa.

Erin Welsh

Two quick asides here. The first has to do with assessing historical influenza epidemics. Influenza has some fairly general symptoms, so how can you tell whether a pandemic is caused by influenza in historical accounts when you can't do molecular testing? Of course you can't be certain but you can look for clues that are suggestive of influenza. One is that it occurs in the winter months. Another is its pattern of spread which has tended to be though not always from somewhere in Asia to move on then west to Africa and Europe and then the Americas, that it explodes rapidly with a high infection rate and often high mortality rate at least compared to seasonal flu, and of course the symptoms have to match. If you've got all that, influenza seems likely. But those characteristics are not unique to influenza alone and more recently some researchers are re-examining these past influenza pandemics and asking whether they could have actually been caused by a different respiratory virus, say perhaps a type of coronavirus. Okay, aside number one over, aside number two, here we are. The etymology of influenza which I didn't talk about I'm pretty sure.

Erin Allmann Updyke

I don't think you did either.

Erin Welsh

Okay, well I'm talking about it now. Surprisingly difficult to track down. It seems like there should be an easy explanation.

Erin Allmann Updyke

Yeah.

Erin Welsh

And generally speaking people do seem to agree that it comes from Italian, ultimately derived from the Latin word 'influentia' meaning either to flow into or influence, both suggesting that the influence of the stars or the influence of the fluid from the stars would flow into you to make you sick.

Erin Allmann Updyke

Weird.

Erin Welsh

Yeah. Something to that effect.

Erin Allmann Updyke

Okay.

Erin Welsh

But when it was first used seems up for debate. So I've read that it was first used in 1357 from an epidemic in Florence, Italy, sometime in the 15th century, 1743 during an epidemic in Rome, or my favorite, quote "way, way, way back in the day." Endquote.

Erin Allmann Updyke

That sounds like my answer.

Erin Welsh

I know, right?

Erin Allmann Updyke

It was way back in the day.



Erin Welsh: I mean that could be any one of those dates.

Erin Allmann Updyke: So they're not wrong.

Erin Welsh: They're not, it's true.

Erin Allmann Updyke: It's the most correct answer.

Erin Welsh: Technically right is the best way to be right. The precise year that it was first used may not really matter all that much but I do think it would be helpful to understand how well known or distinguishable this disease was.

Erin Allmann Updyke: Yeah, yeah.

Erin Welsh: Okay but back to pandemics. The next influenza pandemic occurred in 1729, starting in Russia before covering the entirety of Europe within six months and the rest of the world within three years.

Erin Allmann Updyke: It's also so impressive to think of these influenza pandemics so long ago when travel was not as easy given how rapidly this virus spreads. And that the vast majority of people are not infectious for that long after they start to show symptoms.

Erin Welsh: But if it is that infectious of a virus or that transmissible, then anyone you come into contact with-

Erin Allmann Updyke: Right. I know, it's just still so impressive that you can make it from Russia to anywhere else in the 1700s.

Erin Welsh: I know. Impressive and scary.

Erin Allmann Updyke: Terrifying, yeah.

Erin Welsh: I guess it's just if it did it then, does air travel really make that much of a dent?

Erin Allmann Updyke: We've all seen Contagion. Anyways.

Erin Welsh: Yep. Have not watched that since COVID. But yeah, interestingly this pandemic, the one starting in 1729 which had high mortality also had recognizable waves of infection with increasing severity. 40 years later the next pandemic occurred in 1781-1782 beginning in China, spreading to Russia within a few months, and then on to Europe and the rest of the world within 8 months. As is characteristic of influenza pandemics, attack rate was super high especially among young adults notably with 2/3 of the population of Rome falling ill, 3/4 of the population of Britain, and at its peak 30,000 got sick each day in St. Petersburg.

Erin Allmann Updyke: Wow.

Erin Welsh: Yeah. Also I just thought of something about what you brought up and global travel and how long it would have taken to get from Russia to Europe for instance.

Erin Allmann Updyke: Place to place.

Erin Welsh

We may not be dealing with the same influenza viruses that we see today. So you could have potentially been infectious longer.

Erin Allmann Updyke

That's a really good point. Yeah, yeah, yeah.

Erin Welsh

Or shedding, yeah. But anyway. Okay, so going back to pandemics. So the next pandemic happened about 50 years after that one in 1781, so this was in 1830-1833. This one originated in China and spread south to Indonesia and the Philippines and then West India, Russia, and on to Europe and the Americas. This pandemic reportedly had infection rates comparable to those in the 1918 influenza pandemic with 20%-25% of the population becoming infected, again in waves, though not with the super high mortality rate. 60 years went by before the next pandemic in 1889-1890. And this was the first since the rise of germ theory and the enormous shifts in medicine and medical training that had occurred in the 19th century.

And this marks the first influenza pandemic for which we have detailed records, statistics, timing, and a better sense of the pathology for this disease. The virus reached Europe from Russia and spread across the Atlantic to the Americas then onto Australia and New Zealand, Southeast and Southern Asia, and Africa all within about a year which is again pretty fast. Infection rates were high but the case fatality rate was low. Despite this the scale of death was enormous, one million people in a global population of 1.5 billion.

Erin Allmann Updyke

Wow.

Erin Welsh

The world wouldn't have to wait another 50 or 60 years for the next influenza pandemic though because a short 28 years later the deadliest influenza pandemic the world had seen would result in 500 million infections and 50-100 million deaths worldwide. Although I'm tempted to redo the coverage of the 1918 influenza pandemic from our first episode, I want to make sure that I get to what I really want to talk about today which is the emergence of highly pathogenic avian influenza. And so I'm just gonna glance over it essentially. So the 1918 influenza pandemic left the world reeling. And if you want to read more about it there are countless resources, I'll post them.

And although many researchers tried to isolate the causative agent of the 1918 pandemic while it was happening, the technology just wasn't there yet. And it was only in 1933 that the influenza virus was finally isolated. Almost immediately afterwards, research on a possible vaccine began with a live attenuated vaccine first being produced and used in factory workers in the USSR in 1936. 4 years later, the inactivated bivalent vaccine containing H1N1 and influenza B was developed and deployed, likely contributing to reduced influenza morbidity and mortality during WWII. The history of influenza viruses could genuinely be an entire episode all of its own.

Erin Allmann Updyke

Oh I bet.

Erin Welsh

And I'm definitely not doing it justice here. But essentially it was a good thing that influenza vaccines were around for the 1957 and 1968 influenza pandemics which had 1-4 million deaths and 1 million deaths respectively. And 40 years would pass before the most recent influenza pandemic which was in 2009, resulting in 800 million to 1.4 billion infections and 120-203,000 deaths, although I've seen higher estimates as well.

Erin Allmann Updyke

I do not think that I realized how large those numbers were for swine flu.

Erin Welsh

I didn't either. There's a paper I'll post that sort of modeled these estimates.

Erin Allmann Updyke Okay.

Erin Welsh Yeah.

Erin Allmann Updyke Because yeah, I mean you always hear like it wasn't as bad as we expected.

Erin Welsh Right.

Erin Allmann Updyke Right?

Erin Welsh Those are likely not confirmed cases but estimated and modeled.

Erin Allmann Updyke Right. Interesting though.

Erin Welsh Yeah.

Erin Allmann Updyke That's a lot.

Erin Welsh It is. I didn't read too much about the 2009 pandemic because there were just way too many rabbit holes to fall down into in this entire episode. But I did come across something very interesting that I don't remember if we've ever mentioned and I think that we did and that is the apparent increase in narcolepsy onset following the pandemic.

Erin Allmann Updyke I don't remember ever talking about that.

Erin Welsh Okay. Well that of course brought to mind the encephalitis lethargica episode and that whole thing. And so it made me really, really want to do a narcolepsy episode next season.

Erin Allmann Updyke Definitely. And maybe we did talk about it a little bit in encephalitis lethargica.

Erin Welsh I wonder. We must have.

Erin Allmann Updyke We must have.

Erin Welsh We must have.

Erin Allmann Updyke I think we talked about influenza 1918.

Erin Welsh Yeah.

Erin Allmann Updyke Okay, all right. Yeah. Narcolepsy, okay.

Erin Welsh Yeah. All right, back to pandemics. Maybe it's just been a while since we've covered a really pandemic pathogen but I was struck by just how many pandemics that influenza viruses have caused. And it made me wonder whether we could draw any patterns at all and what those patterns might be from these pandemics.

Erin Allmann Updyke Yeah.

Erin Welsh

So some researchers have suggested that there's a set interval between flu pandemics ranging from 10-50 years and that we are due for the next one in X number of years, that travel and increased population size hasn't significantly impacted this interval so it must be something intrinsic to the virus itself. Yeah, your face and my face. I'm also inclined to disagree. I don't believe that pandemics happen on a schedule or that influenza virus evolution is anywhere near predictable enough to know when the next pandemic strain might emerge.

Erin Allmann Updyke

Yeah.

Erin Welsh

But to borrow a quote from a paper by Potter from 2001, quote: "It is self evident from the history of pandemics that each year that passes brings the next pandemic one year closer."

Erin Allmann Updyke

That I would agree with.

Erin Welsh

100%.

Erin Allmann Updyke

Yeah.

Erin Welsh

Speaking of which, let's now turn to highly pathogenic avian influenza. It may be futile to seek to predict exactly when the next pandemic influenza will occur but we already know some of the likely circumstances under which the next pandemic virus could emerge, namely humans interacting with domestic fowl. Most papers put the first recognition of avian influenza in 1878 when Perroncito described a deadly disease sweeping through chickens and other poultry in Italy. It's really unlikely that this is the first actual instance of avian influenza but as often happens this publication and the nickname 'fowl plague', isn't that great?

Erin Allmann Updyke

Yeah.

Erin Welsh

Led to additional reports of the disease which was distinguished from other well known avian infections like fowl cholera. The pathogen responsible for causing fowl plague was found to be a filterable, transmissible agent in 1901 and isolated as a virus in 1934. Of course the more people looked the more fowl plague viruses they found which were recognized as influenza viruses but not demonstrated to share internal antigens with influenza A viruses infecting mammals until the 1950s. So it took awhile to make the connection between oh, these are all closely related to one another.

Erin Allmann Updyke

The same.

Erin Welsh

Highly pathogenic avian influenza viruses were found in domestic poultry like H5N1 which was isolated from a small and self-limiting but extremely deadly outbreak on a chicken farm on the east coast of Scotland in 1959. And these viruses were also found in wild birds, particularly migratory birds. The more viruses that researchers found and the more birds they found these viruses in, the more they realized they had to worry about especially with the evidence suggesting the 1968 H3N2 pandemic virus had gotten a couple new genes from an influenza virus found in ducks.

Erin Allmann Updyke

Uh oh.

Erin Welsh

Surveillance studies conducted from 1973-1986 involving over 20,000 birds revealed a prevalence of avian influenza of about 10% with ducks and geese most infected. Another study found that 26% of 4800 ducks about to migrate were infected and with even higher rates 60% in juveniles. The high prevalence, incredible diversity, and extreme virulence of some influenza viruses in domestic and wild birds did ring alarm bells for many public health researchers. But that ringing was kind of faint for a while because there had been no apparent instances of these deadly viruses being transmitted directly from birds to humans. But that ringing would grow a whole lot louder in 1997. In the spring of that year in Hong Kong, three year old Lam Hoi-ka became increasingly sick with what seemed like a severe respiratory infection. Fever, cough, sore throat, and the infection wasn't getting any better. Although doctors tried everything they could, he got worse and worse. His lungs, liver, and kidneys failing and a week after he was admitted to the hospital he died.

Samples had been taken from Hoi-ka while he was still alive and sent to the lab where they were expected to confirm that his illness was caused by seasonal influenza which is generally mild but can cause severe infection in some cases of course. But nothing was a match. The virus was definitely influenza A but it didn't seem to be any of the subtypes they were testing against. The chief of the virology lab at the Queen Mary Hospital sent off the samples to other researchers around the world to see if someone else could solve the puzzle. Two months later one of those researchers showed up in person to reveal what they had found. It wasn't an H1 or a weird H3, it was an H5, specifically H5N1, a virus that had up to that point only been known to cause infections and deadly ones in birds. It turned out that earlier that year a horrifically deadly disease had swept through some poultry farms northwest of Hong Kong, killing most if not all of the chickens at these farms. That virus turned out to be H5N1. But this news didn't really register as public health news, after all this strain had never been known to infect humans.

Could this poultry outbreak have been the source of infection for Lam Hoi-ka? The connection wasn't immediately obvious. The family lived in an apartment building 15 miles away from the farms, so how could he have been exposed? It turned out that a few weeks before he had gotten sick, the teachers at his nursery school brought in baby chicks and ducklings into the classroom to keep his class pets. They didn't last long, over a couple of weeks both ducklings and two of the three chicks had died. The remaining chick was long gone by the time epidemiologists arrived on the scene to test for H5N1 but that classroom exposure seems the likeliest source for Lam Hoi-ka. An epidemiologist would have more opportunities that year to track down cases of H5N1 spillover from domestic poultry to humans because over the course of that year 18 people became infected with the virus, 6 of whom died. And this outbreak, even though it seems really small in size, only 18 people, it sent the world into high alert and for good reason. Could this be the start of the next influenza pandemic?

In response 1.2 million chickens in Hong Kong were culled to try to stop the spread which was a controversial and unpopular decision for many people because of the tremendous economic impact. It was your livelihood gone. But it turned out that 1/5 of those chickens had been infected with the virus and once the culling had ended the human deaths and infections also seemed to stop. But the worry remained. This outbreak turned what we thought we knew about avian influenza on its head. We thought that a species barrier prevented avian influenza from infecting humans and human influenza from infecting birds. Not so. The other assumption that spillover could happen but human to human transmission of an avian influenza virus was unlikely, that was also about to be challenged. Even though the culling of those 1.2 million chickens in Hong Kong arrested the spread of H5N1 to humans, there was no eliminating it from bird populations.

Highly pathogenic avian influenza viruses popped up in the early 2000s again in domestic poultry after causing huge outbreaks, some of which were successfully controlled by culling. But the cat was long out of the bag. H5N1 was detected in wild birds in Asia in 2003 and over the next few years the virus had spread to poultry in Africa, the Middle East, and Europe, causing deadly outbreaks in birds as well as spilling over to humans where instances of human to human transmission seemed to occur although in very limited chains up to this point. It's somewhat debated what led to the spread of H5N1 which is now globally distributed but it seems likely that it was migratory birds. Outbreaks on domestic poultry farms seem to follow the timing and location of where migratory birds are flying over, as do some human cases. And Erin, I'll leave it to you to give us the final numbers on how many cases of H5N1 have occurred in humans but I know it's been in the hundreds, maybe 800 or so, with that staggeringly high mortality rate you quoted, 50%-60%.

In the age of COVID, 1000 or so infections may seem like nothing at all, just a day in your county. But it's truly not, especially when the mortality rate is so high. Some people take comfort in the fact that H5N1 hasn't yet evolved to be more transmissible human to human, while others feel it's just a matter of time. Complacency is not acceptable. COVID showed us just how unprepared we were and I worry still are for a pandemic. Public health isn't just about control and containment, it's also about prevention. It's the Centers for Disease Control and Prevention although people often forget to include that last part, including us, we often leave it off. Some viruses are extremely difficult to control or contain once they emerge, especially if they're infectious before causing symptoms which makes them great pandemic viruses as we saw with SARS-CoV-2, 1918 influenza virus, and many other pandemic viruses.

And so our best shot lies in preventing them from emerging in the first place. The good news is that we know the circumstances under which these viruses are most likely to emerge and the places where viral evolution and spillover is most likely to happen. The bad news is that these circumstances, the breeding grounds for pandemic pathogens not only still exist but are likely increasing in size and number, making spillover more likely and monitoring for these pathogens more difficult. That combined with globalization? Well we know the rest. Massive unregulated farms where poultry or pigs or cows all crowd together, wet markets where viruses can co mingle freely before spilling over to humans, overuse of antivirals or antibiotics in poultry leading to resistant strains, fear of stigma or economic impact leading to the suppression of disease reports.

What's shocking to me is not that avian influenza has spilled over into humans but that there hasn't yet been a pandemic. Reading about highly pathogenic avian influenza filled me with such a creeping dread because it's the same thing that we've seen time and time again. It's what we saw with SARS, it's what we saw with COVID, and it's what we're going to see with the next influenza pandemic. From the book I read that was published in 2009, quote: "The moral of SARS is clear, the flu virus must be controlled in birds. Whatever it takes, the microbial agent must be extinguished before a readily transmissible flu strain jumps to people. Because once it does, global spread is inevitable, there won't be any way to stop it." Endquote. I think the biggest question that remains is what exactly will it take to prevent the next influenza pandemic. And are we equipped to do those things? Are we equipped to do more than just react? I don't know.

Erin Allmann Updyke

I don't have the answer to that either so I hope you're not hoping I can answer that.

Erin Welsh

I'm not. I don't if anyone has the answer. I hope people do. I won't ask you to answer but I will hand it over to you at this point to fill me in on where we stand with influenza today.

Erin Allmann Updyke

Oh my gosh, I will try and do my best right after this break.

TPWKY

(transition theme)

Erin Allmann Updyke

We'll talk briefly because I think it's still deserving about epidemic flu and then get into the details on the status of highly pathogenic avian influenza. And I will try to not end on the most of downers but no guarantees.

Erin Welsh

Sorry.

Erin Allmann Updyke

Every year World Health Organization estimates that anywhere from 3-5 million people worldwide become severely ill from influenza. So I'm not just talking global numbers, I'm talking sick enough to matter to things like hospital systems and work systems, etc. 3 to 5 million people globally just from epidemic every year, seasonal influenza. And it's estimated that anywhere between 290,000-650,000 people die worldwide from the flu every year. These are not small numbers.

Erin Welsh

No, they're not.

Erin Allmann Updyke

In the US it's estimated that between 3%-11% depending on the year of the US population is symptomatic from the flu. So not necessarily severely ill but at least symptomatic.

Erin Welsh

Okay.

Erin Allmann Updyke

And the estimated economic burden in the US alone is between \$6 billion to \$25 billion a year from both direct medical costs as well as indirect time missed from work etc type costs.

Erin Welsh

Dang.

Erin Allmann Updyke

So I hope that we can all be on the same page that even apart from the terror that is highly pathogenic avian influenza, even apart from novel strains and pandemic potential, annual flu epidemics are a big deal and they're incredibly costly in terms of lives and dollars. So that's flu. It matters. But then of course there is highly pathogenic avian influenza and there is like you described Erin, massive pandemic potential. And we all probably not just from your terrifying descriptions-

Erin Welsh

Sorry.

Erin Allmann Updyke

But also from currently living through a global respiratory viral pandemic, I think we have a renewed appreciation for just how serious and real this threat really is. So there is a group of organizations, the World Health Global influenza program developed a tool that's called the Tool for Influenza Pandemic Risk Assessment which basically joins together the World Health Organization, the World Organization for Animal Health, WOA, their acronym used to be called the OIE, as well as the Food and Agricultural Organization or the FAO. And these groups together and I would say predominantly the WOA attempt to monitor and assess the risk of pandemic influenza from a one health perspective. We love to see it, right?

Erin Welsh

One health is great.

Erin Allmann Updyke

One health is great. But I will say as much as I did find data on the WOA page, I was a little bit disappointed that the World Health Organization page on avian influenza hasn't been updated since 2018. And the most recent maps that you can find of HPAI from them at least are actually dated all the way back to 2014. So it's a little bit difficult at least if you're just going directly to the World Health Organization to try and access the more current data.

Erin Welsh

That's disappointing.

Erin Allmann Updyke

It's a little disappointing. Let's move on. When we look at human infections, as of a paper that was published in 2020, so these numbers are likely from 2019 and maybe early 2020, there have been 883 officially reported highly pathogenic avian influenza cases in humans. 860 of those have been caused by H5N1 and 23 of them from H5N6. And these numbers are only slightly higher than what I actually reported back in 2017 in our very first episode. However it is also still true that of those, over 450 have died as a result of their infection which is an over 50% mortality rate. And that's terrifying.

Erin Welsh

Yeah.

Erin Allmann Updyke

But where it gets way more terrifying is just if we look at what's happening in birds. So if we look just at the US alone because it was easy to get really good numbers in the US, as of October 13, 2022, 2 PM EST, there have been 47,392,498 cases of highly pathogenic avian influenza in domestic birds since January of this year. 47 million across 42 states in 528 different reported outbreaks since January in the United States.

Erin Welsh

Okay.

Erin Allmann Updyke

And 2930 in wild birds in 583 separate outbreaks across 46 states.

Erin Welsh

So some pretty terrible numbers there.

Erin Allmann Updyke

So far only one human case has been reported in the US in someone who was working directly with culling infected birds back in April in Colorado. Shout out, Erin!

Erin Welsh

Shout out.

Erin Allmann Updyke

Yep. They survived and had a relatively mild infection. But this is continuing to spread including among wild birds, many of which have now begun their migrations south and therefore this is not the end. If we look globally this is not something that this year is just happening in the US. According to the WOAHA, the World Organization on Animal Health, there have been outbreaks either singular or more commonly plural that are ongoing in Mexico, Canada, the US of course. In Europe outbreaks have been reported in Bulgaria, Hungary, the UK, Germany, Netherlands, Russia, Moldova, Spain, France, and Poland. In Africa outbreaks have been reported in Nigeria. In Asia they've been reported in Japan, Korea, Taipei, and the Philippines so far in 2022. And to be completely honest that might not actually be all of them because the way that the WOAHA reports things out is monthly or sometimes every couple of months but they report out current outbreaks that have new cases and new outbreaks but not necessarily if there were outbreaks that don't have new cases reported. And I couldn't find nice cumulative summary reports from 2022 so far.

Erin Welsh

Okay.

Erin Allmann Updyke

So there may be countries that had outbreaks earlier in the year that I missed. But in short, in this year alone, 2022, we are looking at hundreds if not thousands of individual outbreaks accounting for millions of cases in both wild and domestic birds in dozens of countries across the globe.

Erin Welsh

I mean how many more times this episode can we say it's terrifying?



Erin Allmann Updyke

Well we can say it one more time after this because right now it's October and September tends to be the lull of cases and then it often picks back up in October with peaks in February. And what's been really scary about this season in particular is that what we saw throughout all of these outbreaks is that they didn't go away in the summer, even in places like the US where usually you would see really low, almost no numbers of avian influenza across the summer months. We didn't see complete elimination during those months like we usually have in the past.

Erin Welsh

Why?

Erin Allmann Updyke

They just have continued to spread. Why? They've made it into particular bird populations that have allowed it. Why? Why? And like you said Erin, prevention is incredibly difficult. Of course there are recommendations, things like separating wild and domestic birds to reduce contact between these populations, ensuring good hygienics in poultry facilities but we know that's very difficult, it doesn't always happen. Vaccination of birds can be helpful to some extent but it doesn't do anything for wild bird populations. And the same limitations on vaccines for birds exist as those for humans which I'll talk more about in just a minute. But our vaccines are not perfect. And rapid containment once we've identified outbreaks is really important but like you mentioned Erin, this usually involves culling which is a difficult thing to ask of people because that's a huge financial stressor and not everywhere, not every government financially compensates people for the loss of their flocks.

Erin Welsh

Yeah.

Erin Allmann Updyke

On top of that, just to make it a little bit worse.

Erin Welsh

Just pile it on, yeah.

Erin Allmann Updyke

You want to pile it? Urbanization and habitat loss for wild birds, especially waterfowl, means that both humans and our domestic animals are naturally put into closer and closer contact with these birds on a regular basis. And so it's just so much easier for transmission to cross species.

Erin Welsh

Yep, yep.

Erin Allmann Updyke

So none of that was good news. But that is the truth of where we stand with highly pathogenic avian influenza. 2022 has been a particularly bad year, especially in the US, we haven't seen an outbreak like this since 2015 when we had an outbreak of 50 million birds and we're almost there and it's October. So let's see if we can find any good news, any silver linings.

Erin Welsh

Vaccines!

Erin Allmann Updyke

Yeah. I guess I wouldn't say silver linings but just things to look forward to.

Erin Welsh

Things to have to cling to hope.

Erin Allmann Updyke

There we go, hope clingers.

Erin Welsh

Yeah.

Erin Allmann Updyke

Vaccines. You're right, Erin. So everyone knows that every year we have to get a new flu shot, every year your doctor is like did you get your flu shot? And every year at the end of flu season we find out how effective or not so effective that year's vaccine was. The reason that we have these different shots every year is because of how much variety there is in the genome of influenza viruses because of that antigenic drift, especially those small mutations that are happening every year. And so every year the vaccine aims to cover the most likely circulating strains. But the current vaccines that we have are far from perfect. A) We don't always get the strains right, sometimes they continue to mutate and we get them wrong. B) The vaccines themselves are not the most immunogenic and so we don't actually mount that incredible of an immune response to them. And C) because of the way that we currently produce influenza vaccines which is using eggs as incubators, sometimes these viral strains actually mutate in the eggs to become less effective during the process of replication.

Erin Welsh

Fantastic.

Erin Allmann Updyke

Yeah. So that's why effectiveness can vary anywhere from 10%-60% year to year. Now I will say that even a less effective flu vaccine tends to still provide good protection against severe disease and death and hospitalization, even though it may not protect as well against infection itself. So don't think that I'm saying don't get your flu shot, it is imperfect but for right now it's the best that we have and something is a lot better than nothing. But the real question is and has been for a long time, can we do better? And especially can we develop a universal flu vaccine, something that protects against a wider variety of strains and does so more effectively? A vaccine that could in theory even protect against these pandemic potential strains that we don't even know about yet.

And the answer is there's a lot of people who think we can and so they've dedicated their lives to working towards it. We still don't have one that I can say in the next X number of months or years we're going to have a universal flu vaccine. There are I think two that I found in the last couple of years that have made it either to or through Phase 1 clinical trials that have a lot of potential. One of them is from a paper that was published in 2020 and I tried to get a sense of where it stands today but I couldn't quite but I'll post the paper so that you can read it. It's a really interesting vaccine that is made of chimeric H antigens.

Erin Welsh

Beautiful.

Erin Allmann Updyke

So what they did is that they linked those conserved portions of the H antigen which are similar across a whole bunch of different strains, H1 and 2 and 3, etc, but usually isn't the part that our immune system responds to and makes antibodies against because it's usually the head, the different part of the H antigen that is the most immunogenic, so that we are making the most antibodies towards.

Erin Welsh

Right.

Erin Allmann Updyke

So this vaccine, it makes specific Hs that have a less immunogenic head but a very immunogenic stock that is conserved across all of these different strains. So it allows for you to mount a really good amount of immune response against that stock.

Erin Welsh

Interesting, I love it.

Erin Allmann Updyke

Yeah. And so in Phase 1 trials it did really well, people mounted a really great immune response. But what we don't know yet because we need more trials is to know how does that play out in actual flu infections? How well does that protect you against actual infection?

Erin Welsh: Right.

Erin Allmann Updyke: But it's exciting. The other vaccine that actually started Phase 1 trials with NIH this year is a whole virus vaccine that is made of low pathogenicity avian influenza viruses. And the hope, at least this is what happened in mice, is that these mice mounted very robust immune responses that then actually were protective against a wide variety of strains including those not included in the vaccine which is fascinating.

Erin Welsh: Ooh, that's cool.

Erin Allmann Updyke: Yeah. And so that vaccine is currently undergoing Phase 1 trials right now, 2022. So we'll see what comes of it. But it's hopeful. That's where we stand.

Erin Welsh: I feel like that's pretty good.

Erin Allmann Updyke: Yeah.

Erin Welsh: I feel like I was a little bit down on humanity and that might be from COVID, living through the COVID pandemic.

Erin Allmann Updyke: Yeah. And I think it's reasonable. I think that the idea of in the paper or the book that you cited of we must eliminate this microbe, that's not realistic.

Erin Welsh: No.

Erin Allmann Updyke: I don't think that's a thing that is possible given how widespread influenza is, given how rapidly it mutates, it's just not possible. I do think that creating a vaccine that does a really good job at preventing severe illness, at preventing death, I do think that's possible. And so I have hope.

Erin Welsh: I think that's possible. I think that raises the issue of access and equitability across different countries.

Erin Allmann Updyke: Always.

Erin Welsh: And so you're right in that it's in the birds, it's not going to leave the birds, it's going to keep evolving and mutating in the birds and spreading and so on and so forth and more spillovers. And I think that the most important thing to target is those opportunities for spillover and the opportunities for mixing and reassortment of different viruses.

Erin Allmann Updyke: 100%.

Erin Welsh: And that's difficult to do. There are a lot of different drivers. It's not just about okay, we'll just stop this.

Erin Allmann Updyke: Right. No, it's complicated.

Erin Welsh: Yeah.

Erin Allmann Updyke: Yeah.

Erin Welsh Application always is.

Erin Allmann Updyke Well that was a lot.

Erin Welsh That was a lot.

Erin Allmann Updyke That was a lot of influenza talk.

Erin Welsh I have one more question.

Erin Allmann Updyke Okay.

Erin Welsh How scared do we need to be?

Erin Allmann Updyke Oh Erin.

Erin Welsh I'm just kidding because right now I have open on my computer screen the transcript from our influenza episode from 2017.

Erin Allmann Updyke Yeah?

Erin Welsh To quote you.

Erin Allmann Updyke Okay, what did I say?

Erin Welsh Go ahead and get your seasonal flu shot, wash your hands, and just be a little afraid I guess. Oh and then you add "don't hang around birds."

Erin Allmann Updyke Yeah. Love that.

Erin Welsh Love it. Do you echo those sentiments today?

Erin Allmann Updyke I would say way to go, 2017 Erin. You knew it.

Erin Welsh Yeah.

Erin Allmann Updyke Yeah.

Erin Welsh Yep.

Erin Allmann Updyke Well.

Erin Welsh Sources?

Erin Allmann Updyke Yeah.

Erin Welsh I have unlike our 2017 episode a ton of sources for this episode.

Erin Allmann Updyke Oh my god. It's so embarrassing how few sources we had. Like what?

Erin Welsh We hadn't hit our stride.

Erin Allmann Updyke Yeah.

Erin Welsh I will shout out again the book 'The Fatal Strain' by Alan Sipress and I have a ton of papers that I will post on our website post for this episode.

Erin Allmann Updyke I also had quite a number of papers for this episode. One that I did really like was actually from 2021 and it was called 'Influenza virus and SARS-CoV-2: pathogenesis and host response in the respiratory tract.' Super interesting because it compared influenza virus and SARS-CoV-2. So that might be of interest to a lot of people. Had a number of other papers on the specific pathogenicity and a few if anyone wants to deep dive especially on the transmission aspects of influenza viruses. And then of course a number of other papers on the current status as well as where we stand with universal flu vaccines. So we will post all of our sources from this episode and every one of our 5 entire seasons on our website [thispodcastwillkillyou.com](http://thispodcastwillkillyou.com).

Erin Welsh Thanks to Bloodmobile for providing 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.

Erin Allmann Updyke Yeah.

Erin Welsh We really couldn't do this without you.

Erin Allmann Updyke Nope.

Erin Welsh We wouldn't do this without you.

Erin Allmann Updyke Nope. I hope that you all enjoyed this season and we're really looking forward to next season, it's going to be great.

Erin Welsh If you have any suggestions that you would just absolutely have to hear about or if you have a firsthand account that you would like to share, please reach out to us at [thispodcastwillkillyou@gmail.com](mailto:thispodcastwillkillyou@gmail.com) or on the CONTACT US link on our website.

Erin Allmann Updyke And as always, a special thank you to our patrons. Your support means more than we can possibly say. Thank you.

Erin Welsh It means the world. It means the world. Well until next season, so weird, wash your hands.

Erin Allmann Updyke You filthy animals!