

TPWKY

This is Exactly Right.

Patrick

My name is Patrick and I live in Orlando, Florida. In June of 2020 both of my parents were hospitalized with COVID. It started with my mother. My mother was 72, active, and in good health. She ran her own cosmetics franchise and practiced yoga on a regular basis. Her only underlying condition was asthma which was not severe. On June 25th she walked into the hospital complaining of shortness of breath, a persistent cough, and a fever. She was admitted and began aggressive treatment with high-flow oxygen. Due to COVID precautions, we were not allowed into the hospital and had to communicate with her through the phone.

As the days progressed her condition worsened. When she would cough, she would gasp for air as if she was drowning. We kept our phone calls with her short so she could conserve her oxygen. Eventually we told her only to use text messages. The hospital gave her convalescent plasma but the treatment course was limited and it didn't seem to help. On July 4th she was intubated. With my mother on the ventilator, any updates regarding her condition and prognosis were dependent upon the nurse or doctor on the other end of the phone. The information regarding my mother's condition would change based on the person observing it. We closely watched her ventilator settings and our hopes and emotions would rise and fall with the daily reports. However there was no true guidepost with which to evaluate her progress. We were frequently surprised by new conditions such as her being septic, a persistent pneumothorax, and the development of Afib.

On August 6th, after 32 days on a ventilator, the hospital transitioned her to compassionate care and removed her from the ventilator. 34 minutes later, my mother died. Before she died, we saw the X-rays of her lungs. Instead of the shadowy outline of two healthy lungs, it looked as if a family of spiders created an impenetrable web that showed as white lines crisscrossed throughout the X-ray.

My father was admitted to the hospital two days after my mother. My father has been disabled since 2001 after suffering a stroke which permanently compromised his balance and range of motion. He also suffers from heart disease and has frequent bouts of Afib. Despite his medical history, my father's only COVID symptoms were a fever, diarrhea, and extreme exhaustion. After five days in the hospital he was discharged because he did not need oxygen. However he was still testing positive for COVID. The convergence of his mobility issues and exhaustion meant that he could not even sit up in bed and could not care for himself. We struggled to take care of him while wearing PPE to avoid exposure to ourselves. The same day my mother was intubated, we had to have my father readmitted to the hospital because the level of care he needed exceeded our capabilities. My father spent two more weeks in the hospital and survived. January 2021 would have marked my parents' 50th wedding anniversary.

Throughout this process, we struggled to obtain reliable and accurate information regarding my parents' conditions. Before my mother died, we were given the opportunity to come into the ICU and see her. The images from that day in the ICU have stuck with me more than those of my mother herself. The entire ICU was COVID patients. Each patient was on a ventilator and confined to their room. Outside of the door to each room was the IV pole with no fewer than six IV bags and pumps. The atmosphere was eerily silent. The only sound we heard were a faint beeping in the distance and the stifled sniffing of nurses who took turns sitting at the nurses station quietly crying with their heads buried in their hands. It was clear to us that the doctors and nurses were trying to care for all of their patients but they were continuously confronted by the dim, silent reality that most every person in the ICU would not go home.

Rachel

Kia ora. My name's Rachel, I'm from Aotearoa, New Zealand and my husband and I both work in education in Auckland and we have two young kids. I wanted to share the experience that I have at the moment living in a country which is essentially post-COVID. We currently have no community cases of COVID and only 55 cases in the country as of the 8th of December, which are all quarantined at the border and are as a result of people coming back into the country.

We went into lockdown with the rest of the world in March and the lockdown level 4 lasted for five weeks and during that time we had very strict conditions. Only hospitals, pharmacies, petrol stations, and supermarkets were open and we were only allowed out of the house for one local walk a day or for our designated shopper to go get groceries from the local supermarket. The idea was that we didn't put ourselves at risk, anything that we did that might increase our chance of interacting those outside our bubble we just didn't do.

And then we went to level 3 where online shopping and takeaways were allowed for another few weeks. And then by May schools were open, businesses were pretty much back to normal. Our Prime Minister took the scientific advice that she received really seriously and we were rallied as a team of 5 million to protect each other and unite against COVID-19.

Ashley Bloomfield was the Director-General of Health and he did a press conference at 1pm everyday to update everyone on new cases and which clusters had new cases. And even though not everyone agreed with lockdown, we had very few cases of people breaking it. People received government support and most people got paid at least 80% of their wage over lockdown. And our borders are still closed except for returning citizens and permanent residents and they have to undergo two weeks isolation in a government-funded facility, which is a 5 star hotel, until they can return three negative tests.

So after that first lockdown we had 100 days with no new cases and to be honest, it really felt like that was it. But then we had one relapse just in Auckland, the Auckland region went back into lockdown for three weeks when one family tested positive in the community. And they were able to find out that that as somebody from quarantine who had delayed incubation period, so they came up positive once they were back in the community. And so contact tracing is a huge part of New Zealand's response and they now trace all cases genomically to help link the clusters.

So COVID is this weird thing right now. We know it's out there, we did the work to eliminate it from the community, and there's sort peripheral awareness of it because we wear masks on public transport in case another case comes through quarantine. We hear stories from overseas and it's by no means completely rosy, like it's hard for people with loved ones overseas and you can't fly into the country unless you have a space booked at the managed isolation. So there are people that are missing out on coming home for Christmas but we also go to concerts and have plans to travel within New Zealand over summer and have big family Christmas celebrations.

And we see what's going on but we're not really part of the global narrative of quarantine, the ever present fear of infection or death for us here in New Zealand. And instead because of how swiftly the government acts if there is a community case we're sort of on edge. But it's very easy to forget in the day-to-day that it's out there because our lives are back to normal, so to speak, our kids are at school, we're at work, and apart from not being able to travel overseas there's not a huge difference to how we live now compared to in February. But we do have that feeling of how lucky we are to be in this situation.

So basically all that to say there's a light at the end of the tunnel, New Zealand is proof that testing, contact tracing, quarantine, and science and collective action can prevail and hopefully will across the rest of the world as well.

TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Thank you so, so much for sharing your stories with us and thank you also to everyone else who has written in to share your firsthand account of how COVID-19 has impacted you. We absolutely love hearing from you and we feel like telling your stories is such an important reminder of how far-reaching the effects of this pandemic have been
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	Yeah, welcome to our 14th! I can't believe we've made it this far.
Erin Welsh	Oh my gosh, I know.
Erin Allmann Updyke	Installment of our Anatomy of a Pandemic series on COVID-19. Today we are revisiting the virus itself, SARS-CoV-2, which we visited first many, many months ago.
Erin Welsh	Many, many, months.
Erin Allmann Updyke	So today we'll refresh you on what exactly this virus is, what new things we've learned about its transmission, we'll touch on some of the new strains or rather variants that you've probably been hearing about, and we'll talk about the different tests for COVID-19 and how those actually work. And honestly so much more.
Erin Welsh	Yeah, there is a lot of great information in this episode, so get excited.
Erin Allmann Updyke	I'm excited.
Erin Welsh	But first, are you also excited that it is quarantini time?
Erin Allmann Updyke	I'm always excited for quarantini time!
Erin Welsh	Absolutely! What are we drinking this week?
Erin Allmann Updyke	We're drinking Quarantini 14!
Erin Welsh	Woo! What a surprise.
Erin Allmann Updyke	And in Quarantini 14 we have lime juice, lemon juice, rum, and maraschino liqueur. And we'll post the full version of this quarantini as well as our nonalcoholic placeborita on our website thispodcastwillkillyou.com and all of our social media channels, so make sure you follow us there.

Erin Welsh
Absolutely. Okay, let's see. We've got a little bit more business to cover. So we are still soliciting firsthand accounts for this COVID-19 series and if you would like to submit your firsthand account, head to our website thispodcastwillkillyou.com and click on the COVID-19 FIRSTHAND tab at the top of the page and that will send you over to a Google Form where you can fill out some of the information for your firsthand account. And once again, thank you so much to everyone who has submitted their firsthand account so far.

Erin Allmann Updyke
Yeah. We also are in the process of getting transcripts made! Yay!

Erin Welsh
Woohoo!

Erin Allmann Updyke
For all of our episodes. This is long overdue and we're very excited, they will be available under the TRANSCRIPTS tab on our website thispodcastwillkillyou.com. So check back there or follow us on social media to know when they're all being released.

Erin Welsh
Mm-hmm. And then there's just the usual business stuff. So we have a Goodreads list, we have a Bookshop affiliate account if you want to read more about any of the subjects that we mentioned that there happens to be a book about, and we also have tons of incredible, amazing, beautiful, super cool TPWKY merch.

Erin Allmann Updyke
Yeah we do.

Erin Welsh
And you can find links to all of those things on our website thispodcastwillkillyou.com.

Erin Allmann Updyke
How many times can we say the name of our website in this episode? (laughs)

Erin Welsh
Oh my gosh. oh my gosh.

Erin Allmann Updyke
Anyways, let's get into today.

Erin Welsh
Let's get into today, yes. So our guest today is someone that you are likely familiar with because we talked with her all the way back in March for our first virology episode. Also she's been all over, amazing, you know, our first and tons of other podcasts.

Erin Allmann Updyke
Yeah she's basically super famous at this point.

Erin Welsh
She's supes famous. And we think she's great, we thought she was great way back in the day, we still think she's great, so we wanted to ask her once again all about the virus and what we've learned.

Erin Allmann Updyke
Yeah.

Erin Welsh
We recorded this interview on December 30th 2020, last year.

Erin Allmann Updyke
Last year, a whole year ago.

Erin Welsh
(laughs) And so here she is, we are so thrilled to have back on virologist Dr. Angie Rasmussen, affiliate at the Georgetown Center for Global Health Science and Security. And she is going to answer all of our questions about SARS-CoV-2, the virus that causes COVID-19. And we will let her introduce herself right after this break.

TPWKY

(transition theme)

Angela Rasmussen

I'm Angela Rasmussen, or Angie, I am an affiliate and a virologist at the Georgetown Center for Global Health Science and Security, soon I will be a research scientist at VIDO-InterVac which is a vaccine research institute at the University of Saskatchewan.

Erin Allmann Updyke

Excellent. Thank you so much for coming on again, we're thrilled to speak with you. If you could kind of just help refresh our knowledge and tell us a bit about SARS-CoV-2, the virus that causes COVID-19, like what kind of virus it is, maybe other viruses it's related to, and what that tells us about the virus and the disease it causes?

Angela Rasmussen

Absolutely. So SARS coronavirus 2, as the name implies, is a coronavirus, it is a beta coronavirus. So the coronavirus family is divided up into three major branches: the alphacoronaviruses, the betacoronaviruses, and the gammacoronaviruses. SARS coronavirus 2, like SARS classic, is a beta coronavirus and it's also what's called a sarbecovirus, the SARS-like betacoronaviruses which is a subgroup of that particular genus. So it's most similar to SARS coronavirus classic, it's also related to MERS coronavirus which is another betacoronavirus as well as to two of the common cold coronaviruses which are also beta coronaviruses. And the other two common cold coronaviruses that circulate in humans are alphacoronaviruses.

So it's part of this larger family called coronaviruses and what all coronaviruses have in common is they have a single stranded RNA genome, so their genome, their genetic material is encoded on one single piece of RNA, a single strand. So unlike our genomes which are double stranded DNA, it's just one strand of RNA and it's what we call positive sense, meaning that if it gets into a cell it can be directly translated into protein by the ribosomes which are the organelles inside your cell that basically make proteins from RNA, that's their normal function.

So that's what coronaviruses have in common with each other, they all evolved at some point from a common ancestor coronavirus back in ancient times and now they're a very diverse family. We probably only know a handful of the coronaviruses that are out there and only a subset of those actually infect people. So what people should keep in mind, not to scare anybody, but SARS coronavirus 2 is a sarbecovirus as I mentioned and there are quite a few of those that have been found circulating in wild bat species. And not all of them can probably infect humans but some of them may be able to. So there may be other coronaviruses out there floating around in the wild that maybe potentially human pathogens but we really don't know that much about that. We, I think, really need to know more about that to prevent future pandemics from happening.

Erin Welsh

Mm-hmm. Yeah. So now let's talk what has been all over the news lately and that has been strains. So in our earlier episode back in I think March where we talked with you about the virology of SARS-CoV-2, we asked a bit about a couple of the different strains that seem to have emerged, at the time calling the L and S strain, and we talked about what that might mean in terms of disease outcomes.

And lately we have a lot more information about just overall strains of SARS-CoV-2 in general and in particular there's been a lot of coverage about the one U.K. strain, as it has been called in the news, that seems to have now popped up in the U.S. for instance and popped up all over different countries. And there's some indication that it might be more contagious.

Could you just sort walk us through what this U.K. variant is, whether this appears to be a new strain, how different it is, and whether there are any clinical outcomes that we are seeing in regards to this strain?

Angela Rasmussen

Absolutely. So before I get started I'll say that even the big use of the word 'strain' is somewhat confusing for people sometimes because it can be used in a variety of different ways. So I tend to call the variant a 'variant' because it's not really that different from all the other variants of SARS coronavirus 2 that are floating around out there. It has, I think, 23 different nucleotide substitutions or deletions, there are 23 changes basically to the genome overall that make up this new variant. And that basically means that it's genetically different but we expect all these variants to be circulating around anyways because the one thing about RNA viruses that you can count on is they mutate every time they replicate.

So this is a normal and expected thing, to have different variants with different properties emerge. Whether they're strains or not is a matter of debate because sometimes when people say 'strain' they mean something that's radically different either genetically meaning that a large part of its genome is substantially different from the parent virus, or that it might be different immunologically meaning that your immune system will mount fundamentally different responses, make different antibodies to it. And we don't have any evidence that that's happening for this.

So the L and S strains that we talked about, which feels like a million years ago, didn't turn out to be L and S. I think that the L and S stood for, I think, low disease or lethal, I can't remember what they stood for. But one was mild and one was more severe and that didn't turn out to be true, that was probably just an artifact of the population sizes they sampled.

But this variant in the U.K. which has the extremely catchy name of B117 does appear to be more transmissible and that's really based on a couple different lines of evidence. One is that it became very prevalent very, very, quickly in the southeastern United Kingdom. And I should note that it didn't really necessarily emerge in the U.K. but that's where it was first detected because their genomic surveillance program where they're actually sequencing about 10% of the viruses that they identify in terms of new cases, that made it very easy for them to track the sort of rapid takeover, if you will, of this particular variant. And it just became... It out-competed, essentially, all the other variants that were circulating in that population in about a couple of months.

So that's really fast for a single variant to take over so there was that evidence. They also observed that people who were infected with this particular variant had higher viral loads at the time of diagnosis. And that's a little trickier because people aren't usually being sampled everyday and tested, and you know during the course of a viral infection your viral load will change as the virus is replicating and then as it starts to be cleared. So it's hard to say if that's the mechanism by which it's more transmissible, meaning that people who are infected with it are shedding more virus, but that's what this preliminary data seems to suggest.

And then yesterday I saw that they had released some data, some epidemiologic data about the secondary attack rate and that basically showed that people who were infected with this were more likely to transmit the virus to others in their households or in their workplaces. So it does appear to be more transmissible, you know, we've now found it in the U.S. in Colorado, it's probably elsewhere in the U.S., it's been found in I think 25, 26 other countries so far. So this variant has been emerging and has been spreading globally for a while now, we just hadn't picked up on it until the week before Christmas.

Erin Welsh

Mm-hmm, gotcha. And so if the mechanism by which it is more transmissible is the higher viral load or shedding more virus, does that have any sort of clinical outcomes as well? Like do we see more severe disease in people infected with this variant compared to other variants?

Angela Rasmussen

So that hasn't been observed yet and it doesn't appear that this variant results in increased pathogenicity or increased disease severity. You know, we don't know the mechanism by which it's more transmissible, that viral load data is suggestive that that might be the case but other people have shown that one of the mutations in the spike protein which is in the receptor-binding domain binds ACE2, the receptor for the virus, more tightly. It could have something to do with that, it could have something to do with increased fitness which basically means that the virus is about to replicate to higher titers, we don't know.

But the good news is it doesn't appear to be associated, at least observationally, with more severe clinical disease. And there is a mutation that inserts a stop code on into the ORF8 protein. And previously with both SARS coronavirus 2 and SARS classic, deletions in ORF8 have been associated with attenuation or making the virus less virulent. So it may be that this stop code on in ORF8 has something to do with that, might not, but people are investigating this now. But the good news and the bottom line is that it doesn't look like this variant is more pathogenic.

Erin Allmann Updyke

That is good news. I guess, you mentioned that there are other variants kind of floating around and I know that that's something that a lot of people have expressed questions or concerns about. Do we have any evidence of any other variants that do seem to cause more severe disease or even potentially affect different populations differentially than more common variants?

Angela Rasmussen

So not really. Initially this U.K. variant, it was said that it's infecting children more and today some data came out in a preprint that showed that maybe not. So it's really hard to say but to my knowledge, there haven't been any variants described that are more virulent than others apart from that L and S paper way back when. That doesn't mean that they're not out there, but right now, at least in the U.S. and in most countries besides the U.K., we just aren't doing enough genomic surveillance overall. So it's really difficult to associate particular variants with particular disease severities if you're not actually sequencing a big portion of the variants that you're seeing.

I mean in the U.S. if somebody goes in and gets a COVID test, you know, if they're very sick they'll go to the hospital but that doesn't necessarily mean that somebody's going to be doing the sequencing that's required to say, 'Okay this person's infected with this variant vs. that one.' So it's not to say that there aren't variants out there that are associated with more severe disease but to my knowledge, we haven't found any yet.

There are other variants that have been said to be more transmissible. There's one currently that was reported right around the same time as the U.K. variant in South Africa that also may be more transmissible. They've said that it might also have some impact on virulence but right now there's not a lot of data about that, or at least I haven't seen any to indicate whether or not that's the case. So the take-home message for me with this is we would maybe have more information about this is we did more genomic surveillance, so we should really think about finding ways to do that.

Erin Allmann Updyke

Mm-hmm.

Erin Welsh

Yeah. And so in a general sense, where do all of these new variants come from?

Angela Rasmussen

They don't come out of thin air, they come from the place where all viral variants come from and that is evolution. When RNA viruses like coronaviruses replicate their genomes, they usually make mistakes and that's because the enzyme that replicates or copies their genomes essentially makes typos, it's called the RNA-dependent RNA polymerase or RdRP. Coronaviruses actually have an advantage, probably not from an evolutionary standpoint but it's good for us, they have a lower mutation rate than many other RNA viruses because even though their RdRPs are still very error-prone, they have another enzyme that is an exonuclease that basically can do partial spell checking, essentially. So it can correct some of the errors that the RdRP makes when it copies the genome. But nonetheless, mutation does occur and some of those mutants, which occur randomly, will be in a place that results in some sort of competitive advantage to the virus. Either it makes it replicate better, it allows it to enter cells more easily, it allows it to evade the immune system more easily.

There's a lot of different ways that a mutation could have that sort of impact on a virus. But if it does give the virus some sort of advantage, it's said to be under positive selection. So these new variants are the result of basically these mutations being acquired, providing some kind of advantage to the virus, and then getting passed on because they are under that positive evolutionary selection.

People ask me a lot, 'How do we stop the virus from mutating? How do we prevent these variants from emerging?' The best way to do that is to keep the virus from replicating and the best way to do that is to keep it from finding new hosts to replicate in. It all comes back, basically, to masks and social distancing and staying home and washing your hands and avoiding getting infected in the first place.

Erin Welsh

Mm-hmm. I have a quick question about, going back to B117 and about the mechanism of transmissibility. How much do you think behavior could play a role in that? So for instance, if that variant is less virulent than the other circulating more common variants and that means that potentially more people who are infected with it are still walking around, maybe shedding virus asymptotically and don't know. So could that be one of the major drivers of this apparently increased transmissibility?

Angela Rasmussen

It could. And I don't think we have enough data to answer that directly but I'm gonna try to speculate a little on how behavior might be involved. It could be because people are more commonly asymptomatic and infecting people when they don't know that they're sick but that happens for normal variants of SARS 2 as well. It could just be because it's more transmissible. The U.K. also relaxed some of their restrictions in preparation for the holidays which I think is kind of a dumb idea (laughs) because if Christmas is coming up, the virus doesn't care. It doesn't take the holidays off. So if you relax your restrictions, people think that okay, it's safe, I can get together with my family, I can go to work, I can go have dinner at a restaurant or a bar, something like that. You're in a situation that's going to be more conducive to transmission anyways and if you have a variant that's more transmissible, then you're going to see transmission in those riskier circumstances increase. And I think that that could explain it just as well as anything else.

We already know that there's a presymptomatic transmission and a lot of the literature doesn't really distinguish asymptomatic from presymptomatic. So there are people who are asymptomatic completely through the entire course of their infection and then there are people who are diagnosed while they are asymptomatic but they later become symptomatic. Those people already drive a fair amount of transmission, so if people are in a situation where they're more relaxed, they're not being as vigilant about these non-pharmaceutical interventions intended to reduce exposure risk, and you have a more transmissible variant added into the equation, whether there are more asymptomatics or not is probably not as relevant as just the fact that a situation which you would've maybe had five people get infected now is resulting in ten people getting infected.

Erin Allmann Updyke

Yeah, that makes sense. So I think one of the big questions that a lot of people are concerned about with all this talk of new variants is what do these new variants mean for the effectiveness of all these new vaccines that have been developed? So could you kind of explain whether these new vaccines will work against these new variants and how.

ANgela Rasmussen

Yeah, so that's really the million dollar question. The short answer to that right now is that we don't know, but those experiments are in progress. And it's actually fairly easy to assess this. Basically what you do is you take plasma or serum, the liquid component of blood which has antibodies in it, from somebody who was either vaccinated or has recovered from being infected, we call that 'convalescent plasma' or 'convalescent serum'. And you take that and you incubate it with the variants or with another virus that has the spike protein from the variants on top of it, that's called a pseudovirus. You take those antibodies and then you take the virus and you incubate them together and see if the antibodies can still neutralize that virus.

So this variant from the U.K. has, I believe, 7 nucleotide changes specifically and 2 deletions in the spike protein, and that could change the virus' ability to bind antibodies that were produced from the vaccine. It also might not. And one thing that's important for people to keep in mind is that it's very unlikely that just a couple of mutations are going to completely evade the overall immune response. Because what the vaccines are made with, they direct antibody responses to the full-length prefusion spike protein which is the protein that is on the surface of the virus particle. That protein is obviously pretty small to us but it's pretty large to your immune system and different antibodies will bind all over the surface of that spike protein. It's thought that the antibodies that bind to this specific part of the spike protein that binds the receptor which is called the receptor-binding domain are the most neutralizing, meaning that they will be best able to render the virus noninfectious, but not always. Virus proteins can undergo conformational changes, changes in their shape and structure that occur when an antibody binds to a different part of the protein. So it's unlikely that, you know, unless the mutations themselves are producing sort of radical structural changes to the entire protein, that a few mutations are going to completely avoid the entire broad repertoire of antibodies that are going to be raised against it by your immune system.

However, ultimately we won't know until we do the experiments to actually find out. To a certain degree, a lot of these mutations that distinguish different variants are just kind of like a fingerprint. They're just mutations that were acquired, they don't necessarily offer any time of advantage to the virus but because they're incorporated and then they get replicated, they're preserved. So you can use them sort of as genetic fingerprints to see how a particular variant has evolved if you're doing enough sequencing but they're not always functionally important.

The other thing people should really keep in mind about this is even if the vaccines are less effective against these variants, these vaccines are synthetic and they're easy to change. You could make new mRNA vaccines very quickly and I think that it would be very easy to adjust these to accommodate for new emergent variants.

And over the long term, people have asked me, 'Are we gonna have to keep getting COVID shots over and over again because it's like the flu?' Well, SARS-coronavirus-2 is not like influenza fortunately. And there are other reasons why we need to get different flu shots every year, first and foremost because there are a lot of different influenza viruses including strains and multiple subtypes that are circulating and they can all reassort with each other which makes things even more complicated. But we are aware that we need to make new flu shots every year because of this exact issue. So if we can do that annually with an inactivated influenza vaccine, we can certainly do that probably less than annually to accommodate for evolving SARS-coronavirus-2.

Erin Allmann Updyke

Mm-hmm.

Erin Welsh

Yeah. So speaking of the spike protein, what additional things have we learned about the structure or surface proteins of SARS-CoV-2 that maybe have given us some more insight into how it causes disease or some of the widespread effects that it has on the body?

Angela Rasmussen

Well that's a good question and the short answer is not that much. (laughs)

Erin Welsh

(laughs)

Erin Allmann Updyke

(laughs)

Angela Rasmussen

This is still a very active area of research. But one thing I thought was interesting is that people who have more severe disease have been seen to have more antibodies to the N protein, which is also another viral protein that's not spike, but it might suggest that maybe they're sort of developing different immune responses than people who are able to successfully control the infection, in which case many of those antibodies are neutralizing antibodies that are specific for the spike protein. And it's not really clear why that is, I mean it could be for a variety of reasons. It could be because the antibodies targeting N just aren't as effective at neutralizing the virus and so people have more widespread infections or it takes them longer to clear the infection. It could be because that's inducing immune responses that are associated with more disease severity rather than with the virus clearance.

So T cells in your body can be polarized, they call it, to act in a few different ways. Th1 polarization is thought to be antiviral, so that's basically your T cells saying, 'Alright, we're gonna start telling the B cells to crank out a bunch of neutralizing antibodies. We're gonna tell the CD8 T cells to go out and start killing infected cells. We're gonna tell the CD4 cells to start thinking about antiviral immunological memory. We're gonna control inflammation.' There are other responses that are associated, typically they're supposed to be for clearing your body of parasites like worms and things like that, Th2 responses that are very heavy on antibodies and these other types of specialized immune cells called granulocytes including eosinophils and mast cells. And it's thought that airway hyper-reactivity can often be the result of an inappropriate Th2 response to a virus.

And that's a very simplified way of putting a really complicated process but that's just one example of how sometimes the wrong type of immune response can lead to more disease severity rather than the immune system doing what it's supposed to do and clear out the virus. So those anti-N antibodies have been a hot topic of discussion for that reason, just because it's not clear if that's even important but it is an observation that's been made and it maybe explains why some people go on to develop ARDS or acute respiratory distress syndrome that's associated with severe COVID-19 and why some people have very mild infections that they can control and clear and don't have any problems with.

And then there's the whole issue which we still really don't know very much about at all along COVID, which is not due to a persistent infection most likely but due to sort of a reprogramming of inflammatory responses. We don't really know much about what causes that, why some people get that and some people don't, why some people get that when they have pretty mild disease. So there's a lot that we need to do here to look at the types of immune responses. And I realize this doesn't have a lot to do with your original question which was what do we know about antibodies to other viral proteins. But it may be that responses to other viral proteins by your immune system or interactions with the virus can determine outcome.

Erin Allmann Updyke

Fascinating. So in terms of kind of transmission, I think there's a lot of discussion about transmission of SARS-CoV-2. At this point is there indication that the virus is truly airborne in terms of transmission? Do we have any evidence, I know early on there was talk of like fecal-oral transmission with the diarrhea. Do any of these routes seem to be playing a role?

Angela Rasmussen

So by inhalation, definitely. Short-range transmission by droplets and aerosols is clearly an important route of transmission that really drives transmission. This has been an incredibly frustrating conversation to have in the public domain because the term 'airborne' itself I think can be really confusing for people. In the strictest sense it means that the virus is borne by the air and we get it from breathing it. To some people that might mean that, oh god it's gonna get into the HVAC system and people are gonna be breathing it from long distances away, and is it safe anywhere because we all need to breathe... And the reality is like yes, it's in shared air. So if you're in a room with a bunch of people like say, I don't know, you got together with your extended family for the holidays and you're all having dinner in your poorly ventilated dining room, then yeah that's gonna be a huge risk of transmission by inhalation.

I don't like calling it airborne though just because a lot of people hear that and they think like that scene in Outbreak where Dustin Hoffman is like, 'It's gone airborne!' and looks up at the vent in the hospital.

Erin Welsh

(laughs)

Erin Allmann Updyke

(laughs) Uh huh.

Angela Rasmussen

And it's not transmitted that way. There have been a couple reports of people in stacked apartment buildings that share plumbing lines having infections. They can't rule out infection from congregating, for example, in shared spaces in those buildings. But I think that if that were happening all the time, we would have a lot more people infected especially in New York. Having lived in New York in some terrible apartments, I can guarantee that we would have seen COVID spreading like wildfire in New York City in apartment buildings that are sharing sewage lines and I'm sure are not perfectly sealed. We would've been seeing a lot more of that.

So I think that this is opportunistic airborne in that in certain circumstances it's very easy to transmit this by inhalation and that really is thinking about shared air. So any time you're in an enclosed space with people who are breathing and putting out respiratory droplets and aerosols into the environment and you can breathe them, particularly cumulatively over a period of time, that's going to really increase that risk. And that risk of course can be mitigated by doing things like wearing masks as source control to prevent you from emitting particles yourself into the environment when you breath or speak, it can be mitigated by increasing ventilation in those enclosed spaces by avoiding them altogether, it can be mitigated by taking it outside where there's obviously no enclosures anymore. It cannot be mitigated by like taking it to a temporary plastic tent that's fully enclosed, that's not outside. (laughs)

Erin Allmann Updyke

(laughs)

Erin Welsh

(laughs)

Angela Rasmussen

But it definitely transmitted by inhalation. I just think the term 'airborne' is not really helping the discussion. COVID is transmitted through shared air without a doubt and that's a major mode of transmission, much more than fomites or contaminated surfaces.

Erin Welsh

Mm-hmm, yeah. So now shifting a bit to talk about testing for SARS-CoV-2. Can you walk us through what these various test experiences are like?

Angela Rasmussen

The testing that we've had since the beginning of the pandemic, the sort of gold standard for diagnostic testing is PCR. And this is basically a technique where you take, you essentially are photocopying part of the virus biochemically to see if you have it, and if you have it then you'll amplify that through the PCR reaction. If you have a lot of it to start out with then you will develop the signal on that PCR test sooner than later and that's what, if you've heard people talking about the CT or the cycle threshold value, that's what that refers to. So a lower CT, meaning the sooner you got to identifying a positive signal with the PCR test, the more virus you had to start out with.

So that's the gold standard and that's a very specific test, so there's not a lot of false positives contrary to popular belief. Now the problem with the PCR test is that it's quite sensitive but it's not perfectly sensitive, so if you don't have very much virus, if you just were infected you won't necessarily detect that. It'll be a false negative essentially. If you just got over having COVID, you might be shedding viral RNA, which is what the PCR test detects, for a long period of time and that I think is what some people have referred to as a false positive. It's not actually a false positive cause you are detecting a real signal from viral RNA, it's just that the PCR test can't test for infectious virus. And so it's really important in that regard to have an understanding of when you were actually infected because a positive test in somebody who's recovered doesn't mean that you're actually still infectious over a long period of time and that's been shown by multiple streams of experimental evidence and epidemiological evidence.

So that's the PCR test. There are PCR tests that you get by the nasopharyngeal swab which is the big long Qtip. Some people are now doing those tests with the anterior nares which are the nostrils basically only. And some people have also developed PCR tests that use saliva, which are actually more sensitive than the nasopharyngeal swabs and certainly I think probably a more pleasant experience to give a select sample than to stick a giant Qtip up your nose.

So those are all the PCR tests, the so-called high complexity molecular diagnostics. Now you probably have also heard about the rapid tests, or sometimes they're called antigen tests and these are tests that are looking for the viral proteins, what are called antigens. So the antigen tests detect the viral proteins, there are a couple different ways that they can do that. There are some other rapid tests in development too. LAMP, which is a rapid nucleic acid amplification method that looks at RNA, it just doesn't go through the whole PCR cycling process. Some people have developed a test that has not been authorized yet that uses CRISPR technology to look for viral genetic material. But the main tests that are available now are the PCR test and then these rapid tests that look for antigen in a very short period of time.

The main disadvantages to the rapid tests is that they are, for diagnostics anyways, they're less sensitive than the PCR tests and they're also less specific. They are more likely to give you a false positive. There's been some controversy about this because some people have proposed using rapid antigen testing daily so that people can monitor their own status. And I think that there is a place for that, I mean this is where we're getting into just my opinion, but I don't think it replaces molecular diagnostics or PCR testing. I think people should have the ability to test themselves but I they should also have clear guidance for what to do, and that is they should call their doctor, make sure that their case can be reported, and then make sure that they have all the information and support that they need to actually isolate themselves and put contact tracers in contact with people that they have been in close physical proximity with recently to make sure that those people can quarantine and get access to testing as well.

Erin Welsh

Mm-hmm. Yeah. So our last question is pretty general and that is, so what do you think this pandemic has taught us about virology? Whether that's virologists working together or communication about virology or anything specific related to SARS-CoV-2. What do you think this pandemic has taught us about the field of virology?

Angela Rasmussen

Oh god. (laughs) Well, it's taught me that there's a lot of people who are not virologists who think that they are.

Erin Allmann Updyke

(laughs)

Erin Welsh

(laughs)

Angela Rasmussen

It's also taught me that people, including very educated people including some of my colleagues... I mean, it's really been telling, it's brought out in some people, I think, the worst in people and it's brought out in others the best in people. And it's really taught me that in general scientists and our society, human beings, keep making the same mistakes over and over again. And I've seen that in so many ways. Like I keep having to explain the same concepts to people, I keep having to debunk the same misinformation. And I think that's because to some degree people don't actually want to learn.

We live in a world right now where people, they want facts, they want them immediately, and if those facts aren't there - which in science is usually the case, we as scientists are trained to say, 'This is very uncertain, we don't know, it may be this, it may be that.' In general people have very little patience for that now and it can be very, very difficult to communicate that we don't know this right now, here's some of the possibilities, we're looking into it, we'll let you know as soon as we find out. But people want things now and it's been very surprising to me to see how that vacuum has been filled.

For me, it's certainly taught me that the way that I was trained to do virology through analyzing data, (laughs) developing hypotheses and testing them and then if they're wrong, revising my hypotheses and testing those new ones is still the correct way to do that. But I've learned that I really have a long way to go, as do most of my colleagues, in communicating that uncertainty to people.

It's taken me a lot of experimentation and I still haven't gotten it right in terms of how I communicate. You know, like we don't know if antibodies are gonna work against these new variants that are emerging, for example. I can tell ya how we'll go about looking into that, I can teach you all about the spike protein and antibody binding and how the immune system works. Although still, the immune system is like the most complicated thing in the world so I think we've all learned that even though we already knew it. But you know it's really, really hard for me to communicate to people that there's still probably going to be a lot of knowledge gaps even after we do this one critical experiment, even after this one paper comes out in this big elite journal.

There's still gonna be a lot of things that we don't know and I think the real challenge that all of us have faced from an individual like me all the way to like the New England Journal of Medicine is that sometimes getting an answer fast is not the same and it's not good; that maybe we should figure out a way to communicate to people like we should slow down, we should take our time with this because it's too important to get wrong. It kinda does matter if that answer is the right one (laughs) or if it's based in evidence. But for me anyways, the most important thing I've learned I think is that we were not only unprepared, grossly unprepared to deal with a generational pandemic even though we knew it was coming, but we were also grossly unprepared to engage the public in fighting it. And that's something that absolutely has to change and that's something that I'm probably going to be thinking about for the entire rest of my career, if not the rest of my life.

TPWKY

(transition theme)

Erin Allmann Updyke

Thank you so, so much Angie, Dr. Rasmussen, for coming on and talking with us again. I learned so much from this episode.

Erin Welsh

Yeah.

Erin Allmann Updyke

So as always in this series, we want to go back and cover the top five things that we learned. Erin?

Erin Welsh

Yes, we'll start with number one. All viruses mutate.

Erin Allmann Updyke

Mm-hmm.

Erin Welsh

Basically, random mutations can happen every time a virus replicates and those mutations are what can lead to new strains, or rather new variants. And so it's completely normal and expected that a virus, and especially a RNA virus, will have multiple variants. It's something that we were all expecting. And in the case of coronaviruses like SARS-CoV-2, the mutation rate actually isn't as high as we see in some other RNA viruses like influenza. And that's a good thing. It means that it doesn't change as quickly or as dramatically. And so while we have seen a number of different variants pop up and spread across the globe, these variants represent very small changes in the virus genome and they aren't drastically different viruses. Many of these mutations, in fact, mean nothing at all really biologically and have no biological implications.

We have, however, seen that at least one variant, the so-called B117 which is the one currently making headlines, does seem to be more transmissible than other variants. But we still don't know the precise mechanism for this apparent increased transmissibility and at least some of its rise in prevalence could be due to the lowering of restrictions on things like public gathering and indoor dining and so on that led to just a whole lot more transmission in general. And fortunately this B117 variant, and actually other variants so far observed, don't appear to be associated with more severe disease.

But the bottom line is that we also probably aren't doing enough surveillance overall to know for sure exactly how many variants there are or whether some are more virulent than others, meaning more likely to cause severe disease. So the big question is how do we stop this process of mutation; of new variants emerging? And we can't stop it but we can slow it down. We can slow it down by reducing transmission. Fewer new hosts for the virus means less replication and thus fewer opportunities for new variants to arise and spread.

Erin Allmann Updyke

Exactly. Number two. The question of will these new variants affect how effective the vaccines that we have will be? And the truth is we don't 100% know. However it is highly unlikely that the small changes in these new variants will mean that the vaccines that we have are not effective. So we learned in our vaccines episode that the mRNA vaccines produced by Pfizer and Moderna as well as the viral vector vaccine that's produced by AstraZeneca all encode the entirety of that spike protein, that's the protein that SARS-CoV-2 uses to actually enter our cells. So when you get vaccinated and your body starts producing this spike protein, you then start making antibodies against it, a whole bunch of them which target multiple parts of that protein. And the spike protein, it turns out, is a pretty large protein, it's like over 1200 amino acids long, and the changes that we're seeing in these viral variants are super small. In the case of B117, we're talking 23 nucleic acids out of their whole genome. Not all of those 23 changes are in that particular spike protein. So while it is possible that small changes can affect vaccine effectiveness, it is overall unlikely.

But that's probably not super reassuring to a lot of people. So we do have two other better pieces of news that we learned. People are doing the research to answer this exact question of vaccine effectiveness as we speak. So that's awesome. And now that we have this vaccine technology, it's not going to be difficult in the future to make small changes as necessary to these vaccines going forward to make them effective against new variants. In fact, in the case of mRNA vaccines, it's actually a lot easier to produce new proteins or new mRNA than it would be to produce a new, entire, whole killed viral vaccine like we already do every year for influenza, for example.

Erin Welsh

Yeah, that's really important and pretty reassuring, I feel.

Erin Allmann Updyke

Very reassuring, yeah. (laughs)

Erin Welsh

Number three. We learned that the term 'airborne' gets confusing and it's probably not the best term to use in general. But what we do know is that for SARS-CoV-2, inhalation of viral particles is still the driving factor behind transmission. And that means that any place where you are sharing air with other people, like in a restaurant or a bar, on a plane or at your Aunt Judy's house, you have a risk of transmission. And ways to mitigate this risk, I mean we've covered them over and over again. But just to reiterate, it includes wearing a mask, increasing ventilation, being outside, being further apart. But if you are in shared air, whether inside a building or inside a plastic tent outside at a restaurant, distance alone does not cut it because you are still sharing air.

Overall, other forms of transmission like from surfaces or fomites or fecal-oral transmission don't seem to be big drivers of virus transmission, which is great news. But that doesn't mean that if you rub your nose and then shake someone else's hand and then they touch their nose that they can't get infected through that route. So that's why we still have to wash our hands and not touch our faces when we can help it. It's the Swiss cheese approach all over the again. The more layers of protection you have, both literally and figuratively, the lower the risk of transmission.

Erin Allmann Updyke

Yeah. Also does anyone shake hands anymore? I feel like we're never gonna shake hands again.

Erin Welsh

Yeah and I'm okay with that, I think.

Erin Allmann Updyke

I'm okay with it.

Erin Welsh

Yeah.

Erin Allmann Updyke

I'm a fan of the elbow bump, I don't know.

Erin Welsh

Yeah. I like just the wave.

Erin Allmann Updyke

Yeah. Number four. So we learned a lot about the difference between PCR-based tests, which are looking for viral RNA and then the rapid tests which are detecting antigen and are overall less sensitive and specific than the PCR-based tests. We also learned that these at-home tests that have recently been approved are these antigen-based tests and while they are excellent in a number of ways, we do need to make sure that there's really good communication and guidance around what to do with the information that these tests provide. Right now that guidance is severely lacking and without it, wide implementation of at-home testing with rapid tests could really backfire. False negatives and false positives are possible but a positive test really needs to be followed up in some way and we need to have guidance or some sort of protocol as to exactly how to follow up if we're gonna be using these tests at home.

Erin Welsh: Mm-hmm, yeah. And number five, our last point. And this point seems to be a highly recurring theme in the COVID-19 episodes.

Erin Allmann Updyke: The number one theme of these episodes. (laughs)

Erin Welsh: Yep. I think it's been in every episode so far but that just underlines how important this particular theme is and that is communication. Communication during a pandemic is hard but it's also essential. In this country especially, in the U.S. but truly around the globe, we need to be able to communicate truthfully and directly among scientists, public health professionals, healthcare workers, and communities. And one of the biggest challenges we've faced in this pandemic is how we communicate uncertainty. So much of this last year has been uncertain. And the scientific process works to wade through uncertainty to find answers but it takes time and this pandemic is one of the first times that a lot of people have gotten a front row seat as to how slowly and incrementally knowledge can grow and how rarely things in science seem black and white.

We don't know all of the answers when we start the process and jumping to conclusions, either discarding or disseminating information early without evidence, just makes everything more confusing in the long run. It's hopefully something we can learn from moving forward. How to better communicate this process and the uncertainty surrounding it to the wider public.

Erin Allmann Updyke: Yeah. Big time.

Erin Welsh: Yeah, yeah.

Erin Allmann Updyke: We're learning as we go.

Erin Welsh: Oh yes. Thank you again so much Dr. Rasmussen, Angie. Like we're all friends now, right? We're best friends? We can call you Angie?

Erin Allmann Updyke: We're friends. We're BFFs. We're gonna go to a zoom happy hour eventually.

Erin Welsh: Yeah. (laughs) Yes, thanks again for taking time out of your busy schedule, we loved chatting with you and your explanations are so great and like easily understandable, it's fantastic.

Erin Allmann Updyke: Yeah. Also if you want even more detail about the variants of SARS-CoV-2 that have been all over the news, Angie wrote a really awesome article in The Guardian that we will link to in our show notes and on the website that explains these variants in a lot of detail and also talks about why things like travel bans aren't effective in stopping the spread of new variants. It's definitely worth the read.

Erin Welsh: Yeah, absolutely. Thank you to Bloodmobile for providing the music for this episode and all of our episodes.

Erin Allmann Updyke: And thank you to Exactly Right network of whom we are proud to be a member.

Erin Welsh: Yes. And thank you to you, listeners, for listening. We appreciate it.

Erin Allmann Updyke: Yay!

Erin Welsh

Send us your COVID questions, whatever. We'll keep these things going.

Erin Allmann Updyke

Yeah. We really have a lot more in the works, in the pipeline.

Erin Welsh

We do, we do. (laughs) All right well until next time, wash your hands.

Erin Allmann Updyke

You filthy animals!