

Beth Mole:

Good afternoon. Welcome to today's live virtual discussion, Evolving Virology: How the COVID-19 pandemic is shaping research, a part of our Road to Ars Frontier series. I'm Beth Mole, senior health reporter here for Ars Technica. We have with us today Dr. Angela Rasmussen, a virologist at the Vaccine and Infectious Disease Organization at the University of Saskatchewan and an affiliate at Georgetown University Center for Global Health Science and Security. Welcome, Dr. Rasmussen.

Angela Rasmussen:

Thank you so much for having me.

Beth Mole:

Before we get started, a quick reminder, we should have some time at the end of the conversation for few of your questions. To ask a question, just tweet it us at @arstechnica, using the hashtag #arsfrontiers.

So we're about two and a half years into a devastating global pandemic. Over 518 million people have been infected worldwide, and over 6 million have reportedly died. The World Health Organization last week released a report that the true global toll of the pandemic, the excess deaths, might be nearly 15 million. This is a pandemic that has touched and changed almost every aspect of our lives, and that certainly includes virology. The global spread of a novel virus has raised countless new questions, spurred the collection of a daunting amount of data, and definitely shifted research priorities.

So I wanted to talk with you, Dr. Rasmussen, about how virology is evolving in this context and particularly how that evolution might help us prevent the next pandemic, and also how it might help us deal with the aftermath of this one and another outbreak of an emergent virus, which will inevitably happen. With so many COVID-19 patients, what are we learning about treating and preventing the wide spectrum of outcomes from a viral infection, including long-term conditions like long COVID? So basically, we'll be talking about the sort of book ends of the pandemic, and there's a lot to cover.

So starting with the pandemic preparedness, this virus is causing the pandemic. The coronavirus SARS-CoV-2 is a zoonotic virus. It jumped from animals to humans, likely starting in bats. And such cross-species spillover events are exactly the scenarios that we worry about in terms of things that can spark a pandemic, and they maybe happen a lot more than we know and are going to keep happening maybe more and more.

I was struck by a paper published in Nature last month about how climate change will drive more of these spillover events, forcing animals to shift to new places, bringing them more in contact with people, and they're going to bring their pathogens and their parasites with them. In the paper, they focused on, which included your colleagues at Georgetown, they forecasted that there might be at least 15,000 new cross-species viral transmissions by 2070. That's pretty scary. We're in a pandemic now. We have this huge risk of more ahead. So this feels very much like a wake-up call. What can we, as a society and virologists specifically, be doing right now to get ahead of this next spillover virus with pandemic potential, and are we doing it?

Angela Rasmussen:

Yeah. Well, this is a great question, and it's probably one that I could talk about for much longer than the time we have, so I'll try to be succinct. But that paper, which is an excellent paper, is really not news to virologists. Most of us have been thinking about this and understanding that, even in the past 20 years, we've seen a number of different viruses emerge or reemerge. We've seen a huge uptick in the

number of Ebola outbreaks that are occurring on both West and Central Africa. We've seen other viruses that are related to that emerging.

We've seen a lot of viruses that most regular people on the street haven't heard of emerging. I don't know how many of you have heard of Crimean-Congo hemorrhagic fever, but cases of that are up. Cases of Rift Valley fever are up. We've seen two novel coronaviruses prior to the pandemic emerged, SARS classic, as well as MERS coronavirus. We've seen Zika emerge. We've seen dengue expand its range. We've seen many, many new novel viruses and many viruses that are not novel, but that are really expanding their foothold.

And the reason for this is in part due to climate change. It's also due to human behavior that drives climate change, so increased mobility, changes in the way that we're using and developing land, and climate change itself, which is providing disrupting ecosystems and it's causing different animals and people to change really the ways in which they interact with each other and encounter each other. And all of those things together are what has led to this increase in viral spillover, but it's not just the spillover events. It's not just the cross-species transfer. It's also the fact that human behavior, again, plays a big part of this. So in order to have an outbreak be sustained in a human population, you also have to have conditions be right in that human population. You have to have people living in close proximity to each other. You have to have those dense populations to support that human-to-human transmission after the original spillover.

So the good news is that all of these spillovers that are going to occur will not always result in an outbreak, an epidemic or a pandemic, but as we've seen with SARS coronavirus 2, when all of the stars align and the conditions are just right, they can obviously have a devastating effect. And really in many ways, we actually got a little bit lucky with SARS 2, because the case fatality rate for SARS 2 is much lower than some of the other potential pandemic pathogens that have been on our radar. This would've been even more of a disaster if this had a much higher case fatality rate, and it was also a respiratory virus that was very easily transmitted.

So I really do think that we thought we were pretty well-prepared before this. The US in particular was ranked the most pandemic-prepared country in the world. We had all this investment in research. We were doing all this investment in virus discovery. We were doing some things right, but it's quite clear that we weren't doing everything right, and there's both prevention and a response component, and in that regard, I think we failed.

And one of the biggest reasons that I think we failed is that a lot of the pandemic responses have really been nationalized. This is a global problem that is facing all of us, and if we really want to be prepared and more capable of responding to the next one, we need to be looking for global solutions, not just what are we going to do in the US to make sure that the US is shoring up its pandemic defenses. We really do need to be thinking of this as a threat to all of humanity. We need to be focusing on solutions that rely on global cooperation, that rely on surveillance programs, that transcend national borders, and that provide a fair and equitable exchange of scientific knowledge and collaboration across borders, particularly in the global south and in low- and middle-income countries that are likely going to be more profoundly affected should an epidemic or pandemic occur.

Beth Mole:

Okay. So do you feel like we're starting to get building those now? Do you think that's something that you're seeing some shifts towards more of those sort of global collaborations and sort of frameworks?

Angela Rasmussen:

Yes and no. I think that the World Health Assembly and the World Health Organization has been shouting about this really since the beginning of the pandemic, and people are listening. Certainly, scientists appreciate that this is really important. Will there be funding for it? Unfortunately, that's where I think we're still falling short. Now, historically, and the other two emergent highly pathogenic coronaviruses are great examples, when SARS classic emerged in 2003, there was, all of a sudden, a huge bolus of funding available for doing research into everything from basic science to vaccines, to antiviral drugs. And that was sustained for a little while, but then SARS didn't become a pandemic. It was a near miss, as many people have said. And so guess what, when those grants came up for renewal, a lot of them were not renewed because that was no longer considered an important investment.

The same thing happened for MERS where again, oh, no, bad coronavirus, high mortality rate, potentially transmitted by the aerosol route, potentially a real danger to everybody, didn't result in a pandemic as it turns out MERS is not transmissible from human to human, and so again, all of that funding went away. And this boom and bust cycle of funding really impacts these international relationships profoundly, as well as the fact that there's not nearly enough emphasis of doing equitable collaborations. There's still quite a bit of what we would call parachute science, people kind of going in to low- and middle-income countries, demanding samples and access, and then really not helping to build out the infrastructure, not helping to support the scientists in those countries to continue that work.

So I think that where we're falling short is we really do need to have sustainable investment, both in terms of collaborating and developing these international collaborations, as well as funding researchers who are already working on this. And boy, everybody who works on any virus now has turned into at least a part-time coronavirologist. So there's a lot of really worthy research that does need to be continued and expanded, particularly in terms of building this more global collaborative infrastructure.

Beth Mole:

Right. So kind of moving to sort of the one piece of pandemic preparedness and is the sort of surveillance of viruses. And I kind of wanted to sort of touch on it in regards to your sort of boom and bust comments and sort of thinking about the future with that. So we've seen, during this pandemic, a lot of quick scale-up of surveillance and monitoring global genetics, genetic sequences being shared globally. We've kind of kept pretty strong, I would say, and you can tell me if I'm I'm wrong, close eye on the evolution of this virus as it's spread around the world.

But then right now, we're kind of in this low of the pandemic. People are tired, tired of it. We've just kind of seen testing and sequencing and that monitoring, that surveillance kind of pull back. Do you worry that's kind of another sign of that sort of boom-bust cycle? And yeah, does it worry you not just for sort of maintaining a good close eye on the variants that are still to come of this virus, but for the next threat?

Angela Rasmussen:

Yeah. I mean, it does worry me quite a bit because I think that we're not getting rid of SARS coronavirus 2 anytime soon. It can infect a number of different animal species, as we've been discussing. It can certainly persistently infect immunocompromised people. We've seen examples of both of that. That's how new variants essentially emerge, from those, as well as from transmission in largely unvaccinated populations. And those unvaccinated populations are becoming fewer and far between not because necessarily the vaccine rollout has gone well globally. It actually hasn't. But there is a lot of infection. And so the global population is slowly getting some residual population immunity.

So what we need to be thinking about now are these other potential sources of emerging variants, and we just simply won't be able to track those without robust genomic surveillance system. And that has to be a global system. I mean, this is a great example of how we can stand up some new technologies and put things in place very quickly, and that's great, but we haven't been able to do that actually in a way that is even across the entire world. We're relying on some countries that disproportionately do a really good job at this. South Africa, the UK, the US has certainly gotten better, and we have resources, like I said, where people are contributing sequences from all over the world.

But again, if people don't have money, if they don't have sequencers, if they don't have the expertise, if they don't have the computational power to be producing this data, if they don't have the ability to go out and support these surveillance efforts, that data is going to dry up. Sequences don't just materialize out of the ether for free.

And as the virus continues to spread within these other reservoirs, potentially becoming able to spill back into the human population and evade vaccines, potentially becoming more pathogenic, we're going to be playing sort of variant whack-a-mole, and we're not going to be able to address these problems as soon as we could, if we don't have robust, continued genomic surveillance. And if we are truly moving into an era where containment and control of this virus means updating our vaccines regularly, the only way that we're able to do that for influenza is because there is ongoing sustained influenza surveillance. We need to have a similar surveillance system set up for SARS 2. And in the course of setting up such a surveillance system, we would have these global network of places that could sequence not just SARS 2, not just flu, but any potential novel virus and try to figure out what it is more quickly.

I would say that I just remind people that one of the reasons we were able to develop vaccines so quickly, relatively speaking, was because this virus's sequence was shared relatively early after the rest of the world knew about this pandemic. So we all found out about it on December 30th. December 31st, the sequence was released by some of my colleagues, as well as some very courageous scientists in China, on January 10th. So that sequence became available, and vaccine development could be in immediately. We need to have that early warning system in place, not just for SARS 2 and tracking its trajectory now, but for new pathogens that might emerge in the future.

Beth Mole:

So you are working on a Coronavirus Variants Rapid Response Network. So that sounds like it could be helping with some of that surveillance. Could you tell me, tell us a little bit about that network?

Angela Rasmussen:

Absolutely. So this is a program that's funded by the government of Canada to really be a nationwide network, to respond to the emerging variants. And the whole network itself covers everything from basic science all the way to knowledge mobilization, indigenous outreach policy, really kind of the entire gamut. My role in this network, along with five really extraordinary colleagues, is to look at both the impact of host responses on different outcomes, as well as assess the likelihood of different North American animal species to be infected with SARS coronavirus 2, and potentially give that back to humans, so zoonothroponotic transmission risk.

We are approaching this in several different ways, including developing collaborations with people doing wildlife surveillance, as well as in my lab, doing experiments in the lab to actually see which animals are susceptible. And we already know that there are some that are indeed susceptible and have actually become reservoirs, such as white-tailed deer, but what we really want to know and

what I think that deer really showed us is that this is something that people aren't really spending enough time looking at, and if we want to stay on top of this, we really do need to have a better understanding of which species we need to be monitoring and where our surveillance efforts would be best directed.

Beth Mole:

Right. So there's always more to learn as we see more variance, as we do more sequencing and surveillance, and we've kind of talked about sort of the pullback of that surveillance, but we have seen a lot of surveillance in the earlier stages of the pandemic and maybe more so than in any outbreak in the past, or as much as we've had. And has it given us a chance to really watch this virus evolve? Have we learned anything from being able to keep track of this as closely as we have, have we learned anything about how coronaviruses evolve that are surprising and lessons that might carry over to other potentially pandemic viruses or emerging viruses?

Angela Rasmussen:

Well, we've certainly learned a lot about this virus. Probably, we've learned much more quickly than any other virus probably in history because of being able to really watch it evolve in real time. And certainly about this virus in particular, we've learned a lot about some of the features that allow it to, for example, evade vaccine-induced immune responses or infection-induced immune responses. We've learned a lot more about the biology itself of the virus. We've learned more about which parts of the virus are likely to continue being sort of hotspots for mutation.

But there's still so much that we don't know. For example, we actually don't know that much about some of the proteins in the mutations outside of the spike protein. We don't know entirely what all their functions are, and this is true for viruses that have been studied for decades. I think a lot of people don't really understand that there are still a lot of unanswered questions about things like poliovirus that people have been studying for a really long time. So it's completely reasonable that we haven't discovered all of this stuff for this virus that we've known about for a little over two years.

I do think we've learned some new things about coronaviruses, specifically about their diversity in nature, about some of the features that make them pathogenic and transmissible. Again, though, we're still learning a lot about that, and with the new variants that keep emerging, some of them are different from one another. They have different properties and phenotypes, and that's something that I think we're going to be studying for years to come.

I definitely think we've learned a lot about some of the things that we need to have in place so that we can do this type of functional characterization work, which is really crucial for developing therapies, for developing counter measures, as well as for understanding different approaches that we could use to contain it. I think that we really need to be thinking about how we can be standing up these interventions and these methods of studying new emerging viruses going forward.

And again, this comes back to we need sustained investment in pandemic prevention and response. It's really hard to develop countermeasures while you're trying to figure out how the new virus works. It's really good if you have some of those things in place already so that you can just start getting to work as soon as you know that there's a new pathogen, and in order to do that, you have to have the systems in place to do that type of research. But obviously, yes, of course, we've learned a lot about this virus, and we've probably learned more about it more quickly than any other virus in history. That said, though, there's still a lot to learn.

Beth Mole:

Right. So that might be a good point to sort of switch over to the other side of a pandemic and sort of talk about the aftermath and what we've learned after this one. So I think right now, right from the start of the pandemic, one striking thing, I think, that might have surprised some people was just how diverse the outcomes of a SARS-CoV-2 infection can be. We saw right from the start that some people were having asymptomatic infections and other people were having severe disease and having neurological symptoms, multiple organs involved. Some die, of course, sadly. And there's a lot of people in between.

And now, two and a half years later, it's become very clear that some people develop long-term problems, long COVID, which itself has a constellation of symptoms and is kind of not very clearly defined yet, but they can include things like lingering fatigue, brain fog, heart palpitations. Is any of this having studied host responses to viral infections? This is huge range. Was this surprising to you? And-

Angela Rasmussen:

Not at all.

Beth Mole:

Okay.

Angela Rasmussen:

And the reason for that, and this is true for COVID, as well as most other complex diseases, is that really the host response is a major determinant, if not the most major determinant of disease outcome. And I don't just mean... I mean, of course, you have to be infected in order to get COVID, but a lot of the outcome, like how severe your disease is, which organ systems is it going to affect, are you going to get long COVID, probably a lot of that is actually determined by how the host responds to the infection.

And this makes it extremely complicated to try to figure out, and the reason for this is that every person is different. Every person is genetically distinct. With lab mice, it's easy because then you can just look at the genetic differences. With people, there's epigenetic differences. There are differences in terms of comorbidities that they have. There are differences in terms of their diet, where they live, how they behave, how they interact with people that all result in really different levels of risk, and that's really very difficult to parse out.

The other thing is when you have enough people that are infected with any virus, you start to see a more diverse presentation of different clinical illnesses, simply because so many people have been infected that even rare outcomes or post-responses that lead to rare outcomes seem like a lot of people. So that's why we do see different manifestations of acute COVID-19. That's also why we probably see many different manifestations of long COVID, which we still actually don't even really have a good handle on, I think, in terms of how many people get it, how profoundly it affects their lives, how long it lasts, and how we should be treating it. And I think that these are questions that we're really going to be struggling with for some time to come because clearly, long COVID is something that's now affecting millions and millions of people. It potentially is a mass disabling event, or it is a mass disabling event, and I don't think we have a very good understanding of its pathogenesis at all.

Beth Mole:

Okay. Do you feel hopeful that we'll have with so many people, that we'll be able to sort of unravel some of those nebulous reasons about why there are these rare outcomes?

Angela Rasmussen:

I do. And the reason for that is that is one area where I think a lot of people are working on it. They're enrolling patients. They're doing the right kinds of clinical studies. Unfortunately, it just takes a lot of time to do that, but I do think that people are really focusing on that because I think at least in the scientific community, people have really realized what a significant problem it is. It is going to be even after the sort of acute phase of the pandemic has ended.

Beth Mole:

Right. And then one other thing is that that seems to be kind of unique, maybe, you can tell me, is that SARS-CoV-2 tends to be pretty mild for children. That was also something that was very noticeable at the beginning of the pandemic and is kind of mostly relatively mild compared to older adults. That's been sort of throughout the pandemic. Is that surprising to you? And do you feel like we're going to have the opportunity or getting closer to understanding why that's the case?

Angela Rasmussen:

I mean, that's a really challenging question. I'm not sure that we're closer. I think we will get closer because it is something also that's being studied. But I would say that it's not terribly surprising. I mean, there's definitely respiratory viruses, respiratory infections especially, that have different impacts in people of different ages, and for other viral pathogens as well. So it's not terribly surprising that there are age-dependent differences. Also, SARS coronavirus 1 also disproportionately affected older people. This is something that has been well understood at least for the sarbecoviruses or the SARS-related coronaviruses.

So it's not terribly surprising, but I think at the same time, you have this rare outcome issue where most children have relatively mild disease, but the children who have severe disease, they may not die from it, but oftentimes, if a child is put on a ventilator, it causes them terrible problems going forward. And there are, unfortunately, children that have died from SARS 2. So I think that, again, it comes down to if you have enough infection, and children are without questions susceptible, as susceptible as adults to infection, you are going to unfortunately have a certain number of people who have a really severe outcome or possibly even die. And I think it's cold comfort for parents who have one of those kids that does get really sick that most kids don't get sick, that sick.

So I think it's a really difficult question, and it's obviously also something that people are really looking into, especially because the kids who do get very sick with COVID, or they get MIS-C, have really, really severe outcomes that can potentially affect them for years down the road. So it's certainly something that people need to study and look into. It's very important.

Beth Mole:

Right. Well, I think we are coming up on our time. Thank you again, Dr. Rasmussen, for speaking with me today. This is very informative, wonderful conversation. For those tuned in, join us again tomorrow for our final virtual conversation in our Road to Ars Frontier series. My colleague, senior products expert Sharon Harding will be joined by iFixit co-founder and CEO Kyle Wiens for a discussion on the fight for the right to repair. And for more information about our live event in Washington, DC this Thursday, visit frontiers.arstechnica.com for more information. Thank you again, and have a great day, everyone.