Arnab Chatterjee: What we know about H5N1 bird flu

Lauren (00:08):

This is science Changing Life, and I'm your host Lauren Fish. If you're listening into this episode, you've probably been reading about H5N1 bird flu, an influenza virus that's recently started circulating in other species, including dairy cows. How likely is this virus to reach pandemic potential and what actions can we take to help limited spread? To answer these questions, we sit down with RN Chatterjee, the vice President of Medicinal Chemistry at Caliber's gags, which is the drug discovery and development arm of Scripps Research. He breaks down the likelihood of H5N1 transmitting between humans and the steps we can take now to better prepare ourselves in the future. Thank you so much for being here. Sure, of course. So first I was hoping you could just provide kind of an overview. What is H5N1, how it likely is it for humans to contract this virus?

Arnab (00:54):

Right. So H5N1 is really a novel strain of influenza virus. It basically, the flu virus uses two proteins in the way that it gets into cells and how it's comprised. And so it can switch kind of the ability to, one component is called H, one component is called N. And so each of those numbers represent a different format. So seasonal flu typically has a very conserved H protein and N protein, but they do change, which is why our seasonal flu vaccine every year is slightly different because there are modifications, but this is considered a much bigger change. And so it's likely that it could cause a disease that is significantly worse than seasonal flu, simply because we as humans don't have immunity to that particular strain.

Lauren (01:43):

Right. We haven't been exposed like we are to seasonal flu.

Arnab (01:45):

Exactly, exactly. We don't have vaccines that we've had over time and build natural immunity and also immunity that comes from vaccination.

Lauren (01:53):

Right, exactly. So at this point, how likely is it for H5N1 to spread to humans? Where is it circulating

Arnab (01:59):

Right now? Right now it's primarily in animals. It's in many different animal species, and there is animal to human transmission, which means that for people who are around infected animals, for example, our cattle supply in the us, people are seeing those workers are seeing a lot of influenza virus. And it's also not clear how one would necessarily be able to avoid that if that's the sort of work that they do, because it's impossible to completely protect yourself from the transmission event. What has not happened yet, and what I think we as scientists are hoping will take longer is human to human transmission. And so that is really the point by which there will be another likely change in the proteins of the influenza virus itself. And that is, I think what causes us great concern because that then means that that would be a big enough change, which would stop seasonal flu vaccines and even antibodies, vaccines people are making to the current H5N1 construct will likely be much less

Lauren (03:04):

Effective. Right. Because it'll be that much more different.

Arnab (03:07):

It'll be that much more different. And then once that happens, then the probability that we can use vaccination of existing vaccines or antibodies of current circulating strains will simply not be very effective. And we saw that with COVID-19. We saw that the first monoclonal antibodies that were generated both here at Scripps and throughout the world, pharmaceutical industry took a massive undertaking to build monoclonal antibodies that as COVID-19 changed, those antibodies essentially became ineffective and got pulled.

Lauren (03:38):

Right. Yeah. Just completely evolved past

Arnab (03:40):

Them. Exactly.

Lauren (03:41):

So what are some of the current efforts that people are working on to help mitigate the spread of H5N1 before it gets to that kind of pandemic potential?

Arnab (03:50):

So I mean, I think there's a lot of questions around what surveillance looks like. So as we know from work, not only at Scripps but also at other institutions and public health authorities that looking for the virus, be it in water supplies or in other animal transmission events and whatnot, that has been the primary tool that we've used the challenge with influenza viruses, that it is exceptionally widespread now. Right. It's so pervasive. It is likely in many animal species that we simply don't track at all. And when that starts happening, then the likelihood of another mutation leading to transmission between humans becomes more likely. We saw that in the context of COVID-19, but certainly in flu it's already exceptionally well, unprecedented. Exactly. Previous

pandemic flu viruses underwent a similar sort of pattern where it spread very widely amongst animals, and then it took sometimes a time, but I think it's important time that we have.

(04:50):

So right now, surveillance is a big part of it. The other part that's a big part of it is trying to build vaccines that can be used against multiple H proteins and multiple n proteins. And so that is early stage and people are looking at various different approaches. The NIH is doing a lot of work less so within the private sector, but the majority of it's within academic institutes and the government. But finding pandemic flu vaccines has been a big challenge and we don't have anything right now that is available. So what we would be left with is the ability to generate a vaccine once there is a well-characterized strain, which we saw similarly to SARS Cov to two and CVID 19. And that will take some time. And I think that's that first few months, let's just say optimistically though, for COVID-19, it did take six months until we identified the virus and we had the first vaccines available for larger

Lauren (05:48):

Populations. Right. No, that makes sense. So what were some of the other key learnings from COVID-19 that have prepared us for this? I mean, obviously you touched on, which I'm sure a lot of that infrastructure in place now is hopefully able to be used. I understand that it's a much more pervasive virus, so it's harder to track. But what are some of those key learnings we have from Covid that can be applied

Arnab (06:11):

Hopefully? Yeah, certainly all of the mitigation strategies to protect vulnerable populations, everything from being able to limit contact or to at least have proper protective equipment, certainly in the hospitalized setting is critical. But I think one thing that we didn't learn from COVID-19 that unfortunately will be much more pervasive with the pandemic flu virus based on what we know from previous pandemic flu strains, is protecting young people and protecting children. We were able to get away with COVID-19 in many ways, opening schools earlier and being able to have adult to children and children to children contact that did not allow COVID-19 to spread. So I think that is going to be likely the biggest impact. I think vulnerable populations, those who are immune suppressed, those who are elderly have comorbidities. Those folks are certainly going to be challenged with flu like they were with COVID-19. And we see that with seasonal flu, but what we have not seen is a pandemic flu virus and the effect that can affect children. True. So I think that that is one area where a lot of the mitigation strategies that we had that got by for Covid Ovid 19 apply simply not be simply not be enough for a pandemic flu virus.

Lauren (07:25):

Yeah, that makes sense. Yeah. That I guess was one of the bright sides of the Covid pandemic was that it didn't affect children the way that past seasonal flu pandemics have.

Arnab (07:35):

Exactly. Yeah. So pandemic flu viruses, Spanish flu virus, many, many young children were affected and a high mortality rate. So within that context, I think the development of the other thing that I wanted to mention too, we have learned a lot about how to develop drugs for influenza. And I think that those sort of learnings are now starting to make their way. NIH has become much more accepted. WHO. Other authorities around the world are starting to recognize that we need more drugs to deal with the flu virus

Lauren (08:09):

More of like an arsenal

Arnab (08:10):

Behind. Exactly. Exactly. And those things are beyond what seasonal flu kind of does and can lead us to pandemic flu preparedness, but it's still in its infancy. I think if we look at the history of COVID-19 drug development, the drugs were really not there. Svir was for other purposes, VIR was for other purposes. So we had to kind of do bottom up drug development. I think we're in a much better situation now for another coronavirus. I think we have many more tools, but unfortunately our tools, influenza, which is a very different virus, it does not encode similar proteins as coronaviruses. The only thing that is in common is that it spread via respiration. And so those parts are, we're under prepared for

Lauren (08:57):

That. Okay. What are some of the things in that arsenal that are helpful? You mentioned drugs, I assume antivirals. Why are antivirals also necessary if people are developing vaccines in tandem?

Arnab (09:12):

Right. The reason why antivirals are important is because they affect the proteins themselves that the virus encodes. So a virus encodes only a handful of genes versus many, many genes that mammals and even eary outs generally do. So what we've learned is that when we use those, when we have those limited targets, we really don't have as many different ways to treat someone who has an influenza virus, but there are proteins that the virus needs to be able to replicate. So when we're talking about how do we block the virus from getting in, we have those antibodies and we have the vaccines. But these challenges is that over time, the virus, like it did with SARS cov to two and COVID-19, will evade those mechanisms and come up with new mechanisms to be able to get inside of a cell. The advantage of once of antivirals is, and especially direct acting antivirals, so ones that affect the actual replication of the virus, certainly there are drug targets that one can use to stop the virus from getting in.

(10:15):

And some of those are actually conserved mechanisms. So you would be able to hopefully be able to avoid resistance and avoid mutations quickly. It would last for longer Exactly. But once it gets inside the cell, then it has to use those proteins. And if

we come up with effective combinations of drugs, that stops the virus from mutating against one of those targets, we also have been exceptionally fortunate with COVID-19 in that respect, paxlovid, rem, desi vir, they don't appear to cause mutations. The virus does not appear to want to mutate away from those. Unfortunately, for flu, we already know for seasonal flu, the drugs that have been developed for seasonal flu, that there's quick evolution in rapid mutation of the flu virus towards those drugs. So we need to come up with interesting strategies of how to combine drugs together so we can limit that. And we know from HIV and from hepatitis C that the combination of drugs has a profound effect on improving efficacy, but also profoundly improves the ability for the virus not to mutate away from those drugs. And so I think that's kind of the call to

Lauren (11:20):

Action, more of that cocktail approach. So it can't really circumvent anything.

Arnab (11:24):

And we didn't have to do that for COVID-19, and we joked about it a lot that there was no scientific need for Pfizer and Merck to work together to combine Paxlovid and Lopinavir for Gilead to work with Pfizer and Merck. I think for flu, we will need to have either people working together to do it and in a world where they don't, will need to have the nonprofit and academic world to be able to move forward in drug combinations. And I think that's a critical

Lauren (11:50):

Aspect. And this larger collaboration component, all of these sweet spots, academia, smaller biotech, larger pharma, all have their role to play. Right. In making sure that we can actually develop these quickly, effectively, and share as many resources as we

Arnab (12:04):

Can. Exactly. Exactly. And I think for flu especially, we will need to be mobilized. And so now we have some hints of what we can start doing today. So I think that's really critical to get that process started now.

Lauren (12:15):

Right. So what is Scripps Research doing to combat H5N1?

Arnab (12:19):

Yeah, so obviously I mentioned the universal flu vaccine approach. So there's multiple groups here at Scripps who are working on universal flu vaccines. Really exciting work because I think that that's really going to be a critical element in this. And then what technology do we use to manufacture those? So that's one component of it, understanding the structural biology of those proteins that the virus uses to get inside the cell. Many tremendous amount of expertise here to be able to understand at an atomic level what those proteins are, how we know seasonal flu, for example. Ian Wilson's group does that. And understanding how the seasonal flu changes and how we can on a molecular basis, design better vaccines, better antibodies. And then at caliber,

working together with several folks, faculty members at strips working on combining and coming up with new antivirals. So those would be ones that we can produce now, we can stockpile today.

(13:14):

We know that they will be effective if used appropriately. There's been a larger interest in anti-infectives of what's called anti-infective stewardship. And really a lot of this comes from clinical practice. How do we effectively use drugs in a hospital setting and even in an outpatient setting to be able to limit drug resistance? And I think that has actually been quite successful just in the last few decades of how physicians actually prescribe and maintain the safety of drugs and the efficacy of drugs as long as possible. But I think we need to start coming up with drug combinations for influenza. We're doing that at Caliber. And what's really exciting about that work is that that's something that can be cheaply made today. It can be stockpiled, it can be made available as soon as there is any examples of human to human transmission. And even in the context of COVID-19, even though we didn't have those tools, people now say that if there were those sort of tools available that one could give to high risk individuals, for example, people who could succumb to the disease, but also to healthcare workers and other folks who were involved, that would've dramatically impacted the spread and allowed the vaccines and the antibodies and all the other things that needed to be developed only once the pathogen was actually sequenced and understood, could we actually start having a much bigger impact and limit the amount of casualties.

Lauren (14:42):

Yeah, absolutely. You mentioned healthcare workers, people that are on the front lines and just so exposed to these viruses. So yeah, it would've just been so amazing, especially in those early days, to have something stockpiled, as you mentioned, that would be easily accessible.

Arnab (14:56):

And I think that a lot of it also needs to come from the ability for us, and something we've been very mindful of is how can we make these drugs cheaply? How can we have a lot less drug that we need to make? How can we maximize the number of doses that can be given to people, not only to if they have infection, to not succumb to the illness, which just to remind everyone, it's 60% is the historical average of pandemic influenza virus. So it is not the single digits that we know happened with SARS COV to two and COVID-19. So in that world, we need effective treatments that can be taken early, and we also need ways to be able to protect people who likely are going to see a lot of virus. And so both of those things really come from the same set of tools. So the one nice thing about direct acting antivirals is that they can be used not only for the treatment of the disease, but also to protect people from getting the disease. And we know that exceptionally well from our work and HIV and other unrelated viruses, but similar transmission.

Lauren (15:59):

Right, exactly. Where you're having to. Yeah, like we mentioned more of this arsenal cocktail combination approach. Exactly. I also want to talk about reframe as well, because that was a huge assistance in the COVID-19 pandemic and identifying potential drugs that could be helpful. So can you explain what Reframe is and how's being used in

Arnab (16:18):

This case? Yeah. So reframe is essentially every small molecule drug that again, can be produced cheaply, made available, stockpiled, and make them available to the entire community to test. And so that actually is a pretty large number of molecules. It's about 14,000

Lauren (16:34):

Molecules.

Arnab (16:35):

It's crazy. And what's really amazing is that if you went and asked the question, how many of these molecules can I buy and test, it's only half. It's actually slightly less than half. Oh, wow. And so we actually, with the Gates Foundation undertook a massive campaign to make all of the molecules that you can't buy and make them available in quantities such that we can do many, many screens both in vitro and in some cases in vivo, interestingly enough, to be able to provide those to the scientific community to test free of charge. All the only requirements is that they need to publish the data so that people can review it, develop an open access. Exactly. And so we did that in January of 2020 with SARS-CoV-2, we found a lot of molecules like rem, Desi severe and other things that were effective. We found many things that people claimed were effective that at least did not work well in our hands and didn't work well in our hands, meaning it didn't work in enough systems for us to actually say this could potentially be useful for treatment of COVID-19. And so we've made that tool available. We've also used it and tested it against flu, and we found interesting molecules that one would need to develop further to be able to get to an interesting molecule to use for H five N

Lauren (17:50):

One that could actually be effective in humans.

Arnab (17:52):

Exactly. And so that's the work we're doing in the lab right now. Certainly we've learned many things about it for COVID-19. We've used it against other viral infections. We've used it in other respiratory diseases like tuberculosis, things that aren't even antibody viruses. And the beauty of it is that it allows the community to access it. It allows a platform on reframe db.org for people to compare their data to other data that's been generated in similar systems. So you could start getting a confluence of data that's suggests that one molecule may be more important to follow up and actually look at in more detail. And so that's what we've done with flu, especially over the last two years, to really come up with things that not only could be useful against seasonal flu, but also

against pandemic flu viruses. Again, accessing and hitting those targets that are conserved between the different types of influenza viruses. And so that's what we're doing in the lab right now. It's an amazing opportunity to provide those molecules. I'll say we have a lot of work left to do on that front. There's still about 2000 molecules in reframe that are not commercially available that we have not made yet. And so I think that's an opportunity for even in a more meaningful way, increasing the amount of data that we have to make sure we're not missing anything.

Lauren (19:10):

We're covering your bases. If we already have all of this information, we need to make sure we're utilizing it.

Arnab (19:15):

Exactly. And I think that's the real challenge, is that as a scientific community, we need to be able to do these things proactively and be able to make the data available and allow people to critique the data for people to come up with other ways to test. And so that's been really exciting to be part of. And I think that will only have greater and greater traction. Absolutely. And for people to be able to,

Lauren (19:40):

Especially as more and more people use it. Right. Yeah. Just kind of the exponential growth of

Arnab (19:44):

That. Exactly. Exactly. We're constantly talking about, I think in a world now where we're talking about how to integrate in together large amounts of data and how do we use that, how we use that in appropriate models for us to think about how can we actually design and come up with new hypotheses and new things to test in the lab. I think it's a real shame that we have half of the number of compounds that have been safely put into humans that we actually have very little data on. And certainly the people who develop those drugs have a fair amount of data, but what's in the public domain is actually quite

Lauren (20:14):

Small. It's very limited.

Arnab (20:17):

And so to really be able to build out that data set and to enable that in the caliber strips ecosystem

Lauren (20:23):

Is fantastic. Amazing. I think that's an incredible caveat where you can access this of course, but you have to freely publish whatever it is that Yeah, it's incredible. So for

everyone listening, what is your call to action to the community to help mitigate the spread of H5N1? Or what can people do now regardless of who they are?

Arnab (20:44):

Yeah, I mean, there's a lot of things to do. I think what do we from COVID-19 is that it touches everyone's life in a profound way. And I think in many ways we can understand that there are some things that we can do personal protective equipment, limiting interactions, but we know that over time that has a significant impact on society. It has a significant impact on our mental health. It has significant impact in our economic health. It has a significant impact in people's ability to live their lives. And so from my perspective, I really think the call to action is be aware of what's going on in terms of public health. I think our public health infrastructure more and more needs the support and recognition from everyday citizens around how is something spreading and not necessarily in a doomsday panicky sort of situation. With COVID-19, we were kind of left in that situation.

(21:41):

And so now it's really about, okay, we do know a lot about seasonal flu. We have learned a fair bit about pandemic flu. So it's not as this an insurmountable challenge for us to be able to come up with an appropriate pandemic preparedness response, but we need to be aware of what's going on. And I think part of that also involves educating those who may not be aware of those things. Exactly. I think COVID-19 unfortunately has polarized people in terms of how they think about mitigating it, but I don't think anyone would argue, at least thoughtfully argue that it didn't have a huge impact on us. Absolutely. And there was not a single country in the world, no matter what their strategy was to deal with the virus or mitigated that was not affected in a profound way. So I think that's an essential thing we need to understand.

(22:24):

I think for me, it really does come down to being able to invest in the best science, to be able to make sure that we're better prepared for pandemic flu than we were for SARS Cov to two. And I think that does come down to us being able to say it's an important investment. It is an insurance policy against society functioning properly, and there's a lot of need for us to be able to get the best minds, but also get the best resources to be able to have that impact. When you're talking about a 60% mortality rate, you're talking about a disease that when it affects someone, we need to act very quickly. Absolutely. And so what we've learned in the context of Tamiflu or seasonal flu is that drugs work, okay. They're not given necessarily early enough. We don't always necessarily have the right means to apply it, but those drugs do work and they do stop many people from succumbing to the disease.

(23:20):

And so we need to be able to understand that onset of an illness, especially in vulnerable populations, requires immediate action. And I think we need to, as a society, do a much better job of educating people, but also be able to train them and then most importantly, allow them to act to be able to come up with interesting antivirals, interesting vaccine designs. And for me, I think you need both. Because those first a

hundred days, there'll be a lot of panic and there will be a lot of people wondering, how is this going to affect people? Exactly. And we can't ahead of time predict all of those aspects. But if we have the right tools in place, understanding where the disease is, being able to treat and prevent people from the disease and then accelerate manufacturing of vaccines and other things that will have even a greater impact to protect people from the disease, I think is essential.

Lauren (24:12):

Right. Okay. I don't have any other questions. And is there anything else that you think would be important to cover that we haven't talked about?

Arnab (24:20):

One of the things that comes up in my mind often is the need for collaboration. And I think that no one organization can do this effectively. Reframe is just one such example of that. But I think working together with the federal government, working with people who are very good at drug manufacturing, and being able to say, okay, we have something very interesting here. How do we scale this? How do we make it available to enough people around the world in centers where we think that there is a greater impact of the disease? I think that's a critical element of it. So my hope is that, and obviously we do a lot of that with the Gates Foundation. We do a lot of that in the us. We do that with WHO. We do that with a lot of the work that we do in other parts of the world. But organizing all of that in a collaborative way and having the right platforms to actually share data and share information and act quickly is something that I think we can continue to strive for. And I think in COVID-19, we got a little siloed at the end. People were developing drugs and developing vaccines, but they weren't necessarily sharing data and communicating. And I think we'll need to certainly do that in this case because I think this will be one where there is a lot of foundational knowledge around influenza. The world of Coronavirus

Lauren (25:33):

Folks, it was grand new, but in this case,

Arnab (25:35):

We have this. It was a very, very small number of people. And in flu, we luckily have many, many people who've done really great work in flu, both in the private and in the public sector. Bringing those folks together I think is going to be essential. And so I think that's one of the things we're excited about is being able to do that. And certainly there's actors like the Gates Foundation, NIH and others, but I think as an institute that's doing science in the lab, training the next generation of scientists and then making these impactful drugs to put into clinical trials, I think the collaborative environment is really

Lauren (26:06):

Critical. It's absolutely key. I mean, I can imagine it must be so challenging here. The organizational structure of all of these different entities is so different. And so to be able

to communicate, share things collaboratively I can imagine would just seem insurmountable in certain cases.

Arnab (26:21):

And I think we can start that now. I think that's something that we can do now. And we've had a lot of great discussions on how to generally deal not only with pandemic flu, but with other viral and non-viral pathogens that are communicable and are ones that will affect people very quickly, if not properly dealt with. And so I think that process has started, but I think as people are looking perhaps maybe a little too siloed in their own countries and their own states and in their own regions of the world, that I think that that's a force we have to push back against. I think the academic environment, and I think the nonprofit sector is the best place to

Lauren (26:58):

Have that kind of collaborate, like open communication and collaboration. Exactly.

(27:07):

Many thanks to Arnab for joining us today and sharing more information about H5N1, including why investing in the best science now will save countless lives and resources in the future. Be sure to check out the show notes for more information on our work and other behind the scenes scripts research content. If you liked what you heard today, please subscribe, rate, or leave us a comment. Your feedback helps us bring more exciting content your way. Have a question or topic you'd like us to explore. Connect with us on our social platforms and leave us a message. We'd love to hear from you. Stay curious out there, and we'll see you next time on Science Changing Life.