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#385: Outbreak! Human pandemics and how to manage the inevitable

VOICEOVER

This is Up Close, the research talk show from the University of Melbourne, Australia.

ANDI HORVATH

I'm Dr Andi Horvath. Thanks for joining us. Today we bring you up close to viral and bacterial pathogens like Ebola, the plague, avian flu and others that already have or could potentially devastate human populations.

Only a century ago the Spanish flu, an influenza virus epidemic, took millions of lives across the globe. The emergence, evolution and spread of pathogens like the Spanish flu continue to pose a significant threat to global health. Some of these pathogens are masters of disguise and survival: they evolve in different hosts and are able to cross species barriers. Viruses like AIDS and influenza evolve one million times faster than our own human DNA, which is how they become so easily resistant to our vaccines and drugs.

Pandemics are unpredictable and yet inevitable, but as our guest in this episode describes, genomic sequencing and analysis are providing insights into these pathogens that at least enable us to move towards a management system. Professor Edward Holmes is a globally recognised expert on viral evolution. Eddie describes himself as a cheerleader of the many research teams that investigate the biodiversity, origins and evolution of these pathogens, and as we will hear, it pays to take a historical view of virus transmission, sometimes dating as far back as Ancient Rome. Eddie Holmes is currently professor at the Marie Bashir Institute for Infectious Diseases and Biosecurity at the University of Sydney.

Welcome to Up Close, Eddie.

EDDIE HOLMES

Thank you.

ANDI HORVATH

Eddie, let's get some semantics out the way. What are the differences between endemic, epidemic and pandemic diseases? Give us some examples.

EDDIE HOLMES

Okay. So when they say the word endemic, they normally mean that the pathogen is continuously in the population. So normal human seasonal flu that we get every winter, that would be an endemic disease; we always have it. An epidemic would be one that is suddenly growing a lot faster in the population, maybe completely new. So for example, if there was an outbreak of avian flu and that spread through a few countries, that would be an epidemic. So that's a big increase in growth rates. Pandemic is a bit more subtle, and it's a word that sounds good but it hasn't really got a concrete definition. Pandemic just means it's an epidemic thing that's spread further, so it's got to more countries than an epidemic normally.

ANDI HORVATH

Right. So tell us about the infection of humans by pathogens, things like bacteria or viruses. How do they actually enter the cells of our body and do damage?

EDDIE HOLMES

Viruses are by definition almost intracellular: they have to replicate inside the cell of their host because they have no metabolism themselves, they're basically bags of genes that replicate. So they need to steal the host cell machinery. So what a virus would do, if I cough on you now and a virus flew across this table into your throat it would then bind onto your cell, inject its nucleic acid, its genome into your cell, get into the cell nucleus and then it would replicate, it would use the cell enzymes and copy itself, and then it would construct itself and leave the cell. As it leaves the cell it can sometimes kill that cell because it's kind of cut a hole, or it makes the immune system kill that cell, and that's why you get disease.

ANDI HORVATH

So if you were to cough on me, and please don't.

EDDIE HOLMES

Yeah I'll try not to.

ANDI HORVATH

Does it actually go in via my skin, my eyes, my lungs? Do I breathe it in?

EDDIE HOLMES

Normally for an aerosol one from coughing, that would normally be in your lungs, so you'd breathe it in. So take for example influenza, it's quite likely that a high number of flu transmissions occur just by normal breathing in and out. So me talking to you now, I'm shedding these very small water particles in an aerosol that's going to float away and may infect you as you breathe in. So that may well happen. So it depends on the type of virus you are, but for an airborne one, you're going to breathe it in.

ANDI HORVATH

Let's just tease out the bacteria/virus difference. Tell us about that.

EDDIE HOLMES

So unlike viruses that have to steal parts of the cell replication to survive, bacteria don't. They're autonomous living things. Viruses are not; viruses are really ultimate parasites. They cannot live without a cell. Bacteria can. They have their own metabolism and their own replicating system. Some people argue are viruses really alive because they can't complete their own lifecycle without the help of something else. They have to infect a cell. Whereas bacteria can. They're autonomous living things like we are. Viruses are very different; they're absolute parasites.

A very important practical distinction between the two of them is that if you have a bacterial infection, you can take antibiotics. If you have a viral infection, you can't. So if your doctor says oh you've got the flu, I'll give you an antibiotic, change your doctor because that is not going to work. So antibiotics are only for bacteria.

ANDI HORVATH

Right. Black Death, bacteria or virus?

EDDIE HOLMES

The Black Death is a bacteria. It's caused by a thing called Yersinia pestis.

ANDI HORVATH

And smallpox, virus or bacteria?

EDDIE HOLMES

Smallpox is caused by a virus called variola virus.

ANDI HORVATH

But we no longer have it of course.

EDDIE HOLMES

No. So in the past century smallpox was one of the most serious infections humans have ever faced, but luckily it was
very obvious who had smallpox because of these pustule growths, lesions on your body. So it made it very easy to see who was infected, and also it was actually quite easy to make a vaccine. So we were able to vaccinate and eradicate smallpox in about 1978 or so. So we've not seen it for 30, 40 years.

ANDI HORVATH

Now some of your research collaborations, they actually aim to reconstruct the evolutionary history of pathogen genomes like malaria. So how is it possible to find a malaria genome from samples of mummified human remains from people who died centuries ago? How does it work?

EDDIE HOLMES

Yes, so what many people do to reconstruct the evolution of pathogens is take contemporary genomes, contemporary pathogens, bacteria, viruses, and reconstruct their ancestry. But now, with the wonders of modern genome sequencing, we can start to look at ancient human remains of people who may have died of some disease and then we can extract the nucleic acid, the genome that's left from the things that have infected them, sequence it and kind of glue it together.

It's tough because, as you will imagine, DNA degrades through time and RNA degrades through time. But if you're lucky, you've got some residual, very small

fragments of DNA from the pathogen that's left, and then we can kind of glue them together. It turns out for example that the Black Death turns out to be a relatively straightforward thing to look at in that ancient human remains, you often find teeth. In that teeth, there's dental pulp, as you might well know, and you can drill down into that dental pulp from these ancient human remains, pull out the pulp that's left, and if you sequence that, you find in there bacteria, including Yersinia pestis. So teeth, it turns out bizarrely, are a remarkably good kind of reservoir for ancient pathogens. Many people have done this now and it's very successful.

ANDI HORVATH

Is there a problem with contaminants when you examine the dental pulp of human remains?

EDDIE HOLMES

Absolutely. So because we handle ancient DNA, we're looking at archival samples, and there's DNA everywhere, we can put our own DNA or DNA from the environment on those samples. Also of course they're in soil or wherever they are in a mummified remains setting. They pick up whatever's in that environment too. So contamination is absolutely the number one concern of this work.

ANDI HORVATH

Tell us about the signatures you saw of the malaria pathogen with your collaborators who actually looked at ancient Roman burial sites.

EDDIE HOLMES

The story there was that many people have claimed for a long time that the Romans in Italy had a very large malarial problem and that they famously drained swamps in an attempt to control malaria. That's a good story, there's some historical evidence for it, but really you can't prove that until you actually see the pathogen itself. So with some archaeologists we have recovered Roman remains dating to 2000 years or so ago from various sites in Italy, and as I said before, they have very good teeth. We can drill down into that teeth and we can pull out the genome of the malarial parasite, and that's not a bacteria or a virus, it's a protozoan parasite called falciparum.

In this case, it was extremely low frequency in the sample and it was very damaged. Our own DNA is one long string of contiguous bits of biological material; in these ancient samples, they're very broken up, and this was really broken up, which is a really good signature that it really was old.

What it did tell us though, we could absolutely say that they had malaria in Ancient Rome and the strain they had is called plasmodium falciparum, which today is the most serious form, so it causes cerebral malaria mainly in Africa. So we know the Romans had that.

ANDI HORVATH

Eddie, let's return to the Black Plague. I understand there's been more than one episode in human history?

EDDIE HOLMES

Again, historical record suggests that humans have had three pandemic waves of plague, three big semi-global outbreaks of plague. These are just described from symptoms, not from any biological materials until we came along. The first one was called the Plague of Justinian at the time of the Roman Emperor Justinian who was right at the end of the Roman era, so about 550, 540 AD, and that may have killed a third or so of Europe's population, so devastating.

The second one was the Black Death, and in fact that wasn't one outbreak. That lasted for about 300 years. So it starts with the Black Death in 1347 and it goes on until the 18th century. Every few years there's a kind of spike in plague and people got used to living with it. Again, when it first appeared in the Black Death 1347 or so that may have killed again a third of Europe's population, so an amazing devastation.

Finally, the modern one starts in China we think at the end of the 19th century, and that's the one we know best, we kind of followed. That got to Australia in the early 20th century. They knew that rats are the major reservoir. They knew for example in Australia in the early 20th century if they got rid of the rats, they would stop the plague. So there were these people going out and capturing rats around our cities to try and prevent plague transmission.

So the reservoir for Yersinia pestis, the bacteria that causes plague, are rodents like rats. Marmots too are a kind of rodent-like thing, live in Asia and the Americas, and they are also a reservoir. From them it jumps to humans. That jumping probably happens all the time; we're exposed to these rodent plagues all the time. But normally they go nowhere: one person is infected, there's no onward transmission. But at least three times in history it's taken off and caused these pandemics.

Now they're the three we know about, but there are possibly others too before those. So that's what we're investigating now: can we recover remains from these earlier outbreaks to see really are they Yersinia pestis, the plague.

ANDI HORVATH

It doesn't make sense for a pathogen to be fatal to its host, because it was quite a fatal disease.

EDDIE HOLMES

You might think that, but the key metric is really natural selection, so what's beneficial in evolutionary terms. So what selection is going to favour is just onward transmission. It's just a numbers game: who has more offspring. So for us that's kids and for a pathogen it's the number of people you infect. So what natural selection is going to favour is just you infecting more and more and more people. It could be being more virulent, killing more people, is actually beneficial for transmission.

So let's say for example that the more sick you are, the more virus you give off, then not only will that kill you more frequently but it'll infect other people more frequently. So in fact, it can quite often be that being nastier is actually beneficial for evolution.

ANDI HORVATH

I'm Andi Horvath and you're listening to Up Close. In this episode, we're talking about pandemics and infectious disease with evolutionary virologist, Professor Eddie Holmes.

Now tell us about these pathogens and their ability to jump species. It seems to me that bats and chickens get a really bad rap. What is it about bats and chickens?

EDDIE HOLMES

So my main interest in this field is trying to understand how diseases emerge in humans. What that normally means, as you've alluded to, is they jump from an animal host into humans. Now I should also say that humans can also give the pathogens to animals too, and that has happened. So we are a risk to them, as they are to us. Animals can carry an enormous number of pathogens, bacteria, viruses, other microbes, and so as we've changed our ecology as a species, we cut down rainforests, we open up new lands for agriculture, we have these animal markets, we keep animals, different species together. As we've done that, we've exposed ourselves to these animal pathogens.

So let's say a chicken has a flu virus. We get up close to a chicken and that virus comes to us. Most of those times it's going to go nowhere. Occasionally they get going, like my plague story. So why? Why is it that some take off and some don't? That's the million dollar, billion dollar question these days.

I think what we're learning is that animals do carry an enormous number of pathogens, and the more dense the population of animals there are, the more things

they carry. So bats obviously quite often roost in huge numbers, which means they can just carry more pathogens, as do rodents. Whereas let's say a counterexample, like an orangutan for example, kind of solitary animal living in the jungle, that's not going to carry as many pathogens because it's just a solitary thing, there's not much transition going to be allowed to happen. But if you live in a big dense population, you're going to get more of them.

Chickens can be both very, very dense and we interact with them very, very directly. So bats get a really bad rap. They do carry a lot of bugs but we don't really interact with bats that often as a species. Chickens, again these big poultry industries, we have all these birds together, it's no surprise that we will get some bird viruses occasionally.

ANDI HORVATH

Eddie, I believe camels are also a vector for human pathogens?

EDDIE HOLMES

One of the most surprising observations in recent years has been that MERS virus, Middle Eastern Respiratory Syndrome virus that came out a few years ago in Saudi Arabia and that's got into Korea, its reservoir appears to be dromedary camels. Amazingly it turns out that camels carry a lot of these respiratory pathogens.

ANDI HORVATH

What's the deal with camels? What's the mechanism? Is it their spit that is dangerous?

EDDIE HOLMES

It could be. We're not entirely sure. It's spit or some respiratory particles. So when a camel breathes, when a camel sneezes or spits, there's a lot of material going to come across. So it's something in the respiratory tract that's pushing the virus out, which shows us that we shouldn't just think about bats and chickens but other animals that we interact with on a regular basis. They could give us infections too.

ANDI HORVATH

Are there reservoirs on the planet for the plague and avian flu virus?

EDDIE HOLMES

So the plague reservoir would be various rodent species. They exist in North America, Eurasia, there are plague reservoirs. Flu is a bird virus and so many, many wild waterbirds naturally carry influenza all over the planet. Now most of those waterbird strains, most of them are actually very benign; it's only a few that cause real damage and only a few have ever got into humans.

ANDI HORVATH

Eddie, you talk about how the scientists of the 19th and 20th centuries investigated the pathogens that they found in plants and animal species that were compromising human health and human food resources. Now those species are just a handful of the vast biodiversity on the planet, and in the 21st century, with the ability of high volume gene sequencing and analysis, we were able to look at other species like sea sponges, fish, worms and snails, to get that complete picture of the so-called virosphere, that is all those places where viruses are found or in which they interact with their hosts.

EDDIE HOLMES

So as you said, for most of its history, virology as a subject has focused on things that we're interested, humans and our cattle, things we eat or things that we grow, like plants. Also, what we've tended to do is culture things, so take them and kind of grow them in petri dishes in laboratories. What we can now do with modern genomics is just take a sample of any living thing we want, grind it up and sequence all the DNA and RNA in there. Metagenomics they call this. This new technique of unbiased just what's out there discovery, it's finding an enormous diversity of varieties that we didn't ever imagine were ever there before. Our whole notion of viruses - when I say the word virus, your automatic assumption is it's a bad thing, it's going to end in your illness or perhaps your death - that may not actually be true.

I work on insects and things a lot and they carry an enormous number of these viruses, and it's probably true of many, many things as well: we just haven't looked before. It's quite possible that those viruses may not harm them in any way whatsoever. It's also very obvious that the food we eat, the plant matter, contains lots of viruses. You go to your local market and you buy some food for a salad and you eat that, you may be ingesting viruses and they will do nothing to you and you just pass it out, but they're there. They're actually ubiquitous and it's probably almost certainly true that the number one source of DNA and RNA on this planet is virus, it's just we haven't looked before.

ANDI HORVATH

Eddie, can we identify the various host genes, like our genes, in the gumbo diversity of viruses as you describe it?

EDDIE HOLMES

Yeah so the difficulty of working with viruses is they are genetically extremely diverse. I suspect in fact that there are viruses that are so diverse in their genome sequence we can't even recognise them. However, because our own genes are actually quite recognisable in that background, we can normally see our own genetic material quite easily.

What concerns me is this virosphere you've mentioned is actually way bigger than we even can imagine. We can't actually see it. To look for a virus what you do is you get all your sequences and you compare them to little markers that you have, so it's a similarity match. If the virus is too diverse, you just can't see it. So I suspect that the virosphere is actually even bigger than we can possibly imagine.

ANDI HORVATH

Why does the virus pick up bits of the host DNA? What does that do to the virus?

EDDIE HOLMES

It depends on the virus. Sometimes it's probably just chance, it has no real impact. In other cases, some viruses, like pox viruses, like the cause of smallpox, they capture bits of host DNA that allow them to evade host immunity, like a decoy. It's a strategy of the virus to survive inside its host.

ANDI HORVATH

By examining the virosphere, did this give us more insight into species jumping?

EDDIE HOLMES

They're hoping it will. That?s a very big topic for the future. The biggest question in all this work - and it's almost an unanswerable question - is what will emerge next. Can we predict what's going to happen next? One way people are trying to answer that question is by sampling every bat species or every rodent to see what's there. Now the problem with that approach I think is you will find a lot of viruses, you'll find an enormous diversity of viruses, but which of those will then jump to humans is much harder to predict, if you can predict it at all. These virosphere studies that I do, all I'm interested in is evolution, basic diversity and evolution. The practical benefit of

that for predicting epidemics, pandemics, I'm less clear on.

ANDI HORVATH

Landmasses like Australia, Eddie, have been cut off from other parts of the world, so would marsupials give us insights into the virosphere?

EDDIE HOLMES

Absolutely. I would very strongly predict that marsupials and monotremes will carry viruses that are completely novel and undescribed. Everyone knows Ebola. Ebola is a filovirus. Modern day filoviruses like Ebola are only found in Central West Africa. They're found in a few species of bats and humans and a few deer-like things. So very, very fragmentary isolation now in parts of Africa. But we know that filoviruses, segments of filoviruses are also in the genomes of marsupials. Quite extraordinary.

If you go and sequence I think it's wallaby genomes, you will find in there fragments of filoviruses. So way back in evolutionary history these filoviruses have been all over the planet. That must be millions and millions of years ago. They've died out now, but we see the remnants, the living ones of those, in Africa causing Ebola.

ANDI HORVATH

I'm Andi Horvath and our guest today is evolutionary virologist, Professor Eddie Holmes. We're talking about the evolution and emergence of infectious diseases here on Up Close.

Eddie, let's explore the dynamics of the contemporary epidemics and future pandemics. Let's return to the Ebola virus in Africa. How did it emerge and how did it spread?

EDDIE HOLMES

Ebola we've known about since 1976 and it's sporadically caused outbreaks in Central West Africa in a kind of belt across the continent that reflects where the bat hosts come from. This really is about a virus. Ebola in the past though had only ever caused very sporadic isolated outbreaks in small populations, and it was stamped on very quickly and controlled. The last one, the one in Africa that everyone knows about, that got out of control because for the first time the virus got into these big urban areas in Africa and it went underground effectively so we lost track of the transmission, we lost where it was in the population.

That obviously led to the big outbreak that we saw. Now the good thing is you need

to be symptomatic to pass it on. So not until you're ill are you shedding the virus, making discrete particles pass to other people. That means we can look for ill people, isolate them and then break the chain of transmission. So that's how we control Ebola.

Ebola was a terrible thing for West Africa, it caused a huge problem, but globally it was never going to be a big pandemic because we could always control it. Influenza is the kind of hardy perennial of this world and it's much more insidious because you don't know you're infected. This is the critical thing.

So if I go off around the world and I come back to Australia where I live, and I may have got infected and I don't know that for a few days, but I'm shedding virus. I'm on the train system in Sydney, I'm on the bus system, I'm passing the virus on and I don't know it. People I've passed it on, they then pass it on and they don't know it, and then suddenly within a few weeks it's gone. So they're the ones we need to worry about, these ones that are silent transmission. That's much, much harder to control.

ANDI HORVATH

Is eradication by vaccine possible or will some viruses always remain elusive in the sense that they are just a different type of virus?

EDDIE HOLMES

Vaccine eradication is possible when you can absolutely work out who is infected, when you can make a vaccine obviously that can work, and there's no animal reservoir that can continue reinfecting. So for example, flu I don't think we could ever really eradicate because birds have it in such high numbers and it's very, very diverse.

Also, I have to say in some cases would you really want to eradicate these things? To me it may not even make sense. Let's say you have a mild flu that has extremely low mortality rate. That flu actually may protect you in a certain way against other more serious flus. When you're infected by flu it's like having a vaccine: it gives you some immunity to what's in the population. This idea that we should eradicate every virus, I think that's probably a little bit misguided. Some of them may actually have some hidden benefits in giving you immunity to other things. It's actually a much more nuanced thing than you might expect.

ANDI HORVATH

Now Eddie, some label mosquitoes as the deadliest creatures on earth because they transport disease. As climates change, there is a slow creep of insects like the

mosquitoes to new parts of the world. Now what does that mean for the threat of things like Zika and other mosquito-borne viruses?

EDDIE HOLMES

So many people have suggested that climate change will change the geographical range of vectors like mosquitoes, that will change disease patterns. I think that?s true that if climates warm then mosquitoes will be able to overwinter in more temperate regions, and I'm sure that's going to happen. I think though it really depends on how good your mosquito control really is. In Western countries that have good mosquito control, even with climate change we will hopefully be able to control most of those infections.

Zika, Zika infection is an extraordinary thing at the moment because we've known about that virus for many years and it was a very benign thing. Zika, you would never worry about Zika. Suddenly the virus, for reasons that are still bizarre, has got to the Americas and just completely changed its behaviour and it's causing this microcephaly in infants if you're infected at a certain time during your pregnancy. Again, it depends on the kind of socioeconomic status of the country involved. For poorer countries, vector-borne diseases are a much bigger problem.

ANDI HORVATH

I want to ask you about international cooperation surveillance diagnostics and biosecurity controls.

EDDIE HOLMES

It's certainly an extremely important aspect, and I think there are two epidemics in recent history that kind of illustrate that. So the first was SARS. SARS broke out in Southern China, got to Hong Kong, Singapore, then went to a few other countries. The world acted very quickly on that and it was a pretty good response, about 8000 cases, 800 deaths. China was given a lot of criticism for not responding quickly enough and they have done a fantastic job in China since SARS. They've built this amazing disease control system that every province and every city works on.

Ebola gives us the converse of this in that basically we dropped the ball. The virus was there, people didn't respond quickly enough, the WHO did not do a good job, and that outbreak was far bigger than it should have been. We should have stamped on that way, way quicker.

So I'm hopeful that if we take the SARS model and there's very efficient sharing of data and global action, I think we can act pretty well to control things. Another thing I should say also is that our ability now to identify the cause of a disease is so good

these days. So it took for example - when AIDS first came along it took two years from discovering the disease AIDS to finding the causative virus agent, two years, which at the time didn't seem like a long time. Now we can reasonably expect that to do it in two or three days, if not 24 hours, because the techniques we have now for discovery are so good.

ANDI HORVATH

So can we predict an epidemic or a pandemic to some degree? Are they forecastable? Can we put odds on them?

EDDIE HOLMES

This is a big debate at the moment and I am in the more pessimistic side of that. There are some various traits that we can see that may allow us to give you some generalities about what might emerge in the future. So for example, many people have suggested there are hotspots, places where things tend to jump species boundaries and spread: West Africa, Southeast Asia maybe. If they're hotspots, we should go look in them more carefully. But then MERS, MERS emerged in Saudi Arabia which was the coldest spot you could imagine. So it's very, very difficult to predict.

I don't think prediction - nice word to say, it may not be that helpful. To me, the best way to stop a pandemic is to have extremely good surveillance, and I would particularly look at people who work at this human-animal interface, because they're the people who have been exposed, people working in live food markets in Asia or deforestation in Africa, where they're interacting with animal species intimately, they're at the frontline, the kind of fault line for transmission. If we monitor those, sample those people to see what's spreading, that's our best bet.

On top of that we have a really unified global response system where every country is reporting accurately and every country is taking part. That would really help.

ANDI HORVATH

When it comes to epidemics and pandemics, we depend on the insights from researchers like Eddie Holmes and his extensive network of collaborators and colleagues. I guess we're only ever a hazmat suit or face mask away from many diseases, so may the immunological force be with you. Eddie, thanks for being our guest on Up Close.

EDDIE HOLMES

My pleasure.

ANDI HORVATH

We've been speaking about the evolution and emergence of unpredictable but inevitable pathogens responsible for human pandemics with Eddie Holmes, professor at the University of Sydney and NHMRC Australia Fellow. You'll find a full transcript and more info on this and all our episodes on the Up Close website. Up Close is a production of the University of Melbourne, Australia. This episode was recorded on 15 November 2016. The producer was Eric van Bemmel and audio engineering by Gavin Nebauer. I'm Dr Andi Horvath. Cheers.

VOICEOVER

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