

The discovery, origins and evolution of SARS-CoV-2 (COVID-19)

Edward C. Holmes

Marie Bashir Institute for Infectious Diseases and Biosecurity,
School of Life & Environmental Sciences and School of Medical Sciences,
The University of Sydney
Email: edward.holmes@sydney.edu.au

Abstract

This transcript comes from a presentation Professor Holmes gave on 31 March 2021, at the NSW Science & Research Breakfast Seminar Series, hosted by Hugh Durrant-Whyte, FRSN. See <https://attend.mediahouse.com.au/breakfast-series/view/Professor-Edward-Holmes>

Introduction

*Introduced by Professor Hugh Durrant-Whyte,
NSW Chief Scientist and Engineer.*

Hugh Durrant-Whyte: We are all acutely aware of the COVID-19 pandemic that has prevented us holding a large in-person seminar for the last 13 months, and perhaps none more so than today's speaker, the 2020 New South Wales Scientist of the Year Professor Eddie Holmes. Eddie is a global leader in research on the emergence, evolution, and spread of viruses.

He has a particular interest in investigating how viruses are able to jump species boundaries, occasionally causing disease, epidemics and pandemics. In January 2020, Eddie became the first person in the world to publish the genomic sequence of SARS-CoV-2, enabling urgent work to commence globally on both virus detection tests and vaccine development. He followed this with fundamental research into the animal origin of SARS-CoV-2 helping to demonstrate the presence of related viruses in bats and pangolins and showed that coronavirus can jump species boundaries and emerge in new hosts.

It's no exaggeration to say that Eddie's work has been instrumental in helping the world get to the point where vaccines are now being rolled out and the future can be viewed with a degree of optimism. In Eddie's career, he has made major contributions to our understanding of the fundamental mechanisms by which viruses evolve and helped to pioneer the use of phylogenetic methods to track the spread of viruses within populations. His other major research themes are using genomics to understand the epidemiology of major human and animal pathogens and revealing the extent and structure of global virus diversity, the so-called virosphere. His work has led to fundamental insights into the origin and spread of numerous viruses that have had a major impact on human and animal health, including hepatitis C, HIV, influenza, West Nile, dengue, Zika, and Ebola.

Befitting his achievements, Eddie has received numerous accolades. In 2003 he was awarded a Scientific Medal by the Zoological Society of London. In 2008 he became a Fellow of the National Academy of Sciences,

USA. In 2010 he won the Faculty Scholars Medal in the Life and Health Sciences at Pennsylvania State University. In 2015 he was elected a Fellow of the Australian Academy of Science, in 2017 he was elected a Fellow of the Royal Society of London and won the New South Wales Premier's Prize for Science and Engineering in the Biological Sciences, as I mentioned in 2020. He was also honoured as the New South Wales Scientist of the Year at the New South Wales Premier's Prizes for Science and Engineering. Now I will be joining the seminar online, but I would like all of you in person, please join me in welcoming Professor Eddie Holmes from the University of Sydney as he presents the discovery and origins of SARS-CoV-2.

Smallpox

EH: Good morning. As Hugh said, we've all been giving virtual seminars over the last year. This is the first I've given in person for over a year, so I may be a bit rusty. What am I going to do today? I want to talk a bit about how we found this virus and where it may have come from. I added the words "and evolution" to my title, because I'll also talk a little about where we are now as we're hearing about how the virus is evolving, and new variants are appearing. I want to discuss what that means for how we might handle this virus.

Before I get to SARS-CoV-2. I want to give another story, that sets up some of the key topics. It's a different virus, and I wind the clock back to 1978. I have a page from the London *Daily Mirror* newspaper. The top two stories are discussing the sad tale of a person who's just died. There's a photo of her in a wedding dress. At the top it talks about the mystery of the smallpox leak, which is

referring to the very last case of smallpox ever recorded anywhere on Earth.

Bizarrely, that occurred in Birmingham, UK.

It's a very sad story of a person called Janet Parker. She was a medical photographer at the University of Birmingham, and she was exposed somehow to a smallpox virus that they were working with on the floor below hers. Somehow the virus got onto her floor, she got infected and she died on September 11, 1978, in a quite miserable place, the Catherine-de-Barnes Isolation Hospital. It's a very sad story. There's a very good book you can read by Mark Palin called *The Last Days of Smallpox*.

I have discussed smallpox very briefly because it is an extremely important virus in terms of human history for a number of reasons. And it's the only human virus that we've eradicated from our species. It was eradicated by vaccination.

Everyone knows the story of vaccination for smallpox. It was first developed by Edward Jenner in 1796. And you all know the story of cowpox and the milkmaids. There's a Hogarth painting of Jenner vaccinating someone: it's an 18th century celebrity thing. The terms vaccine and vaccination actually come from the phrase *Variola vaccinae*, or smallpox of the cow. That's the history of vaccination.

I've worked with my colleagues for many years, trying to understand the origin and evolution of smallpox. We've gone to various locations globally to try and find old smallpox samples. So, for example, we went to Vilnius in Lithuania. In Vilnius, there's an old church, the Dominican Church of the Holy Spirit of Vilnius, and in that church there's a crypt, and in that crypt, there are coffins, and in those coffins, there are mum-

mies. Some of those mummies are child mummies. And some of those children died of smallpox. What we did was sample the lesions of smallpox from these mummies, to extract any nucleic acid, and sequence it. We managed to sequence the complete genome of variola virus from a sample that's from 1650. 400 years ago. At the time, that was the oldest known smallpox strain.

That's what we can do with genomics. Once we've got that genome, we can then start to look at its evolutionary history.

That's what we've done for SARS-CoV-2. Now, the way we look at evolutionary history is we draw things called evolutionary trees, or phylogenetic trees. They are exactly the same as family trees. We all know family trees and pedigrees. You can easily track the lines of ancestors and descendants in a family pedigree. Evolutionary trees are exactly the same. They're stretched in time. There are hundreds or thousands of years, but exactly the same principle. Figure 1 is such a tree. I've spun the tree on its side so

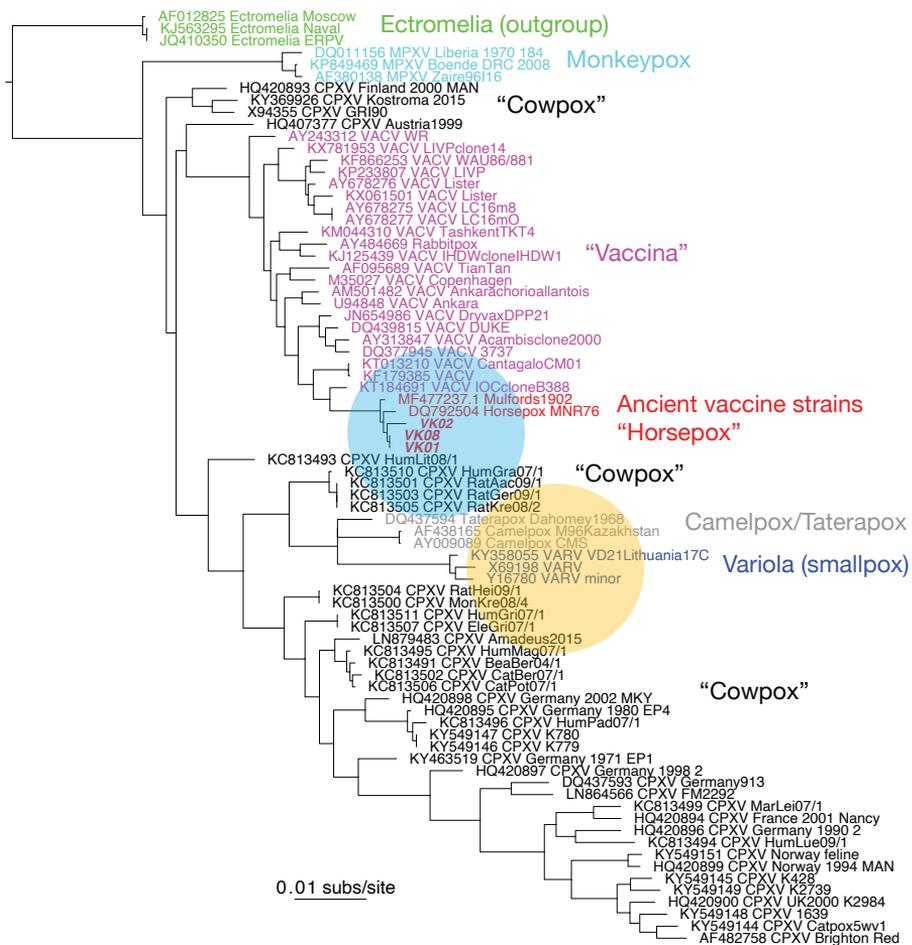


Figure 1: Evolutionary tree. Adapted from Fig. S5 in Lu et al. (2020), published under Creative Commons.

you can't really see so the base of the tree on the left. This tree is not a random tree: it's a tree of the pox viruses that includes smallpox. There a yellow circle, the smallpox virus. That little cluster of brothers and sisters is smallpox. It is labelled Lithuania since my Lithuanian strain falls in that little cluster.

And the idea is, these are all animal viruses. Jenner very famously used cowpox. Now, one of the questions we were interested in is what did Jenner actually use when he started vaccinating. During the 19th century, there was a big vaccination campaign against smallpox, like the campaign which we're now entering for SARS-CoV-2.

What vaccine strain did they actually use when they vaccinated people with smallpox back in the 19th century, and late 18th century? From a museum in the US, from the US Civil War, about 1860, we managed to find some old vaccination kits. In those days, there wasn't a needle. Instead there was a little pad and a little knife. Basically they cut you and they rubbed in the vaccine. That would be your vaccination.

We took those pads, washed them in water and residual comes off, which actually contains the vaccine strain that they used in 1860. We sequenced that. And that is where the blue circle is in Figure 1. It turns out the vaccine that they used was not cowpox or vaccinia. It's a thing called horsepox. All these names are actually very misleading. Horsepox is not from horses. It was found once in a horse from Mongolia. But we don't know where it comes from. Cowpox is not from cows, either. It was once in a cow, in Gloucestershire in 1798. But it does not necessarily come from cows.

Figure 1 shows all these pox viruses. They are animal viruses. We don't know exactly where they come from. It's the same story as with SARS-CoV-2. Are they bats? Are they rodents? The animal kingdom carries lots of viruses, and occasionally they jump into humans with disease, like smallpox did back then.

So we're now actually going to try and find more about the origins of smallpox. Jenner had a very famous cow that he used to get the first cowpox extract. That cow was called Blossom, a celebrity cow. There is a painting by Hogarth of Blossom. And amazingly, Blossom's hide is still around. If you go to St. George's Hospital in London, in their library, there's an exhibit about smallpox vaccination. And behind the glass cabinet is Blossom's hide, or supposedly Blossom's hide. The hide looks a little bit like the painting. It may or may not be Blossom. We've actually managed to take a swab of Blossom — this hide — to see if we can sequence it, to see whether it actually has a virus in it that might be like cowpox.

We've also been trying to get hold of an even earlier celebrity smallpox victim. And that's the Pharaoh Ramesses V, from the Twentieth Dynasty in Egypt.¹ A very famous textbook says Ramesses V may have died of smallpox. And we've actually got samples we think are from Ramesses to try and see whether he really died of smallpox.

Emergent diseases

I have mentioned smallpox for a couple of reasons. First, it's a classic case of emerging disease. And it's one that's come from animals to humans. And all examples of disease emergence like smallpox or flu or

¹ Ramesses V died in 1145 BC. [Ed.]

COVID-19 are about pathogens jumping from animals to humans. I also mentioned smallpox because, as you would have been aware, the Janet Parker story is also a story about a virus and laboratory escape, which I'll get to with SARS-CoV-2. Smallpox and COVID-19 are actually examples of these emergent diseases.

You can find online maps of the world that show you where these jumps of a pathogen for animal diseases have occurred in recent years. And there are a myriad of these. In Australia we've had Hendra. We've had Ebola in Africa, Zika in the Americas. Flu comes from Asia. We had the movie "Contagion." There's a book called *Spillover*, by David Quammen. If you actually want a good general book about disease emergence, it's very good.

And what I do for a living is try to understand how diseases emerge. So I take the natural world, and I look at the places where humans and animals interact, because that's the fault line. It's a very simple analogy from earthquakes. The tension point where jumps occur are where people interact with wildlife. That's where viruses can jump. So what we try and do is sample across that natural space.

For example, where people work with livestock or where humans have encroached into green belts and they're exposed to animals, what's jumping between humans and animals? What's in the animals and what's in the humans? What moves across? That's where we sample. And then we use genetics to work out what viruses are there. I won't go into the genetics in any great detail. Suffice to say, we use a very simple technique, with a fancy name. It's called meta-transcriptomics.

Let's, for example, take one thing I'm working on with which you are familiar — tick-borne disease. In New South Wales, people get bitten by ticks. Ticks sometimes cause disease. There's been a big question: what's the causative pathogen? What's doing this? What we do is take blood sample, skin biopsies at the lesion when we have been bitten by a tick. And then we can sequence all the RNA — not the DNA — RNA is the kind of information molecule in the sample. So we can sequence all the genes expressed in that tick bite. And the genes that are expressed come from the host, like our immune genes, for example, or from the bacteria or from the virus or fungus or parasite. We sequence all that. Then we try and work out what can we see. Can we see a pathogen in there? Can we see a new virus or bacteria? That's the technique.

And that's the technique that we used to discover SARS-CoV-2. Meta-transcriptomics is just basically sequencing all the RNA and using computers to work at what it means. One thing you realise from doing that is that the number of viruses out there is just absolutely astronomical.

The number of human viruses that are known is about 200, 250 or so. The number of viruses that have been classified is now about 6000 or 7000. But it's estimated that 99.995% (or about 87 million) viruses are unknown. We have basically scratched a tiny, tiny fraction of the virosphere. Viruses are absolutely everywhere. If you go and sample wildlife in Sydney; you go to a food market; the plants that you buy; the food that you buy will have viruses, they're everywhere.

So that's the kind of background I want to get onto SARS-CoV-2. So for a number of years, when I do this, the core of my work is going out there and looking at places

where humans and animals interact to see what viruses are there and what could jump species, and a lot of work I do is in China, which is actually a very good place to work on this.

Bat viruses in China

For example, I went to Zhejiang Province in south-eastern China a few years ago. There are very old villages and you walk around a mountain for a couple of hours and you get to a cave and then people have to put their PPE on. There's a cavern and in these caverns there are bats, lots and lots of bats. Our group and many others, for a number of years, have been sampling bats in China and other locations too — I've done it in Australia as well. And then you use meta-transcriptomics to sequence sometimes faecal samples, sometimes tissue samples. Bats carry one hell of a lot of viruses. They're absolutely full of viruses, partly because their immune systems may be different, partly because there's a lot of bats.

There's a paper we wrote in 2017, showing the diversity of bat viruses in China. And there's lots. We were already sampling these bat viruses from China. In that paper we wrote prophetically that these things can and will emerge: "The ongoing emergence of these CoVs in humans means that CoVs will likely remain a key public health threat for the foreseeable future." There's a lot of viruses in bats, a lot of viruses that look potentially dangerous, like coronaviruses. So there's a chance that this could happen. We could get an epidemic.

And so COVID-19 was of absolutely no surprise me whatsoever. It was clearly going to happen because we could see the viruses out there. We knew they were jumping. It was an accident waiting to happen. As well

as Zhejiang Province, we've been doing a lot of work in other parts of China, and over the years, one of the locations we'd also sample a lot in was Hubei Province in the middle of China where the Yellow River runs. We'd sample lots of wildlife around the city of Wuhan in Hubei. We've sampled lots of bats and insects and mice around Hubei.

But we'd also sampled patients in the city of Wuhan. And in particular, we went to a hospital called Wuhan Central Hospital. This is the hospital you saw in Wuhan last January. This is the epicentre of the epidemic. Wuhan Central Hospital became very famous. And I was there in 2016 when I gave a talk. What we, in fact, were doing sounds quite prophetic. We were taking people who had pneumonia and acute respiratory disease to see what microbes could be infecting them. This is two years before COVID. We wanted to know what was there. People get pneumonia very often and it's often undiagnosed. It's a very common disease.

The question we were trying to answer is what was responsible for pneumonia. It's an acute respiratory disease in Wuhan. We were doing this two years prior to the outbreak. We had about 408 patients plus loads of controls. And we took a sample called bronchoalveolar lavage, a lung wash. That's quite a good sample for looking for respiratory disease. We took these lung wash samples and then used meta-transcriptomics to see what these patients had, in this hospital in Wuhan a couple of years ago.

This is a bit technical, but basically they had a ton of stuff, as you might expect. There's bacteria, there's fungi, there's viruses. There was nothing novel. This is 2016, 2017. Basically, they had lots of common cold coronaviruses, influenza, parrot influenza,

respiratory viruses, a whole bunch of the standard stuff you'd expect. They had a whole bunch of bacteria you'd expect. There was nothing novel at all.

Critically, there was no SARS-CoV-2. Or the first SARS virus. That wasn't there at all. That's two years prior to the outbreak. We stopped sampling in December 2017. And the evolutionary trees show the viruses that we discovered and where they fit. They're linked to global sequences. Wuhan is a really global place, a big city, in the middle of China, very well connected. And so it's getting a global mix of viruses. Because it's a hub, a real big hub.

In fact, the only thing that was unusual we found is a zoonotic pathogen. It's a bacteria (*Chlamydia psittaci*) that causes psittacosis, often called parrot fever. People who work with birds sometimes get psittacosis. We had one person who had pneumonia because they got this parrot fever, which is kind of strange. That was the only thing that was unusual. There was nothing else there. But the key thing was we were on site in Wuhan collecting these respiratory samples in the hospital prior to the outbreak. So by chance, we were on site.

COVID appears

The end of 2019. The first I heard about this outbreak was on a website called ProMED, a really great free tool. You can download it on your phone, it's on Twitter, it's on the web.² It provides a daily update of outbreaks of disease globally. It could be animal disease or human disease, anything. Figure 2 is the actual original ProMED post. I saw this on New Year's Eve, 2019. It basically says there are four cases of pneumonia in

China associated in Wuhan with the South China Seafood Market. Now I'd been to that market. I'll discuss that below. But I was immediately interested because it's pneumonia in Wuhan that I was working on and a market that I've been to. So I thought, okay, this is really cool. So at that point, we were not worried. So then I contacted my friend and colleague, Professor Zhang in Shanghai, to see whether he was going to work on this.

And a few days later, on January 3, Professor Zhang, at Fudan University, was sent seven lung wash samples to sequence in his lab. These seven samples were all people presenting with pneumonia. And they were all people associated with the Wuhan seafood market. That's on January the third. On January the fifth, 40 hours later, he managed to sequence all those samples using meta-transcriptomics. Of those seven, one of them had really lots and lots of matches of a sequence of SARS-CoV-2. So it took 40 hours from the virus sample arriving in his lab to us sequencing the virus. 40 hours. To put this in context, it took two years to find that HIV caused AIDS. So it is quite extraordinary what we can now do with modern genomics.

That sequence was finished on January 5, 2020. Zhang and I were talking on the phone that day, and, on the same day, he wrote to the Ministry of Health in China and said, basically, this is what it is. It's a new coronavirus. It looks like the first SARS coronavirus, very similar to the one of 2000 to 2003. And because it looks like that, we knew automatically it was going to be respiratory. Because coronaviruses are respiratory. That absolutely is their defining feature. So, Zhang and I discussed it. He wrote

² <https://promedmail.org/about-promed/>



Published Date: 2019-12-30 23:59:00

Subject: PRO/AH/EDR> Undiagnosed pneumonia - China (HU): RFI

Archive Number: 20191230.6864153

UNDIAGNOSED PNEUMONIA - CHINA (HUBEI): REQUEST FOR INFORMATION

A ProMED-mail post

<http://www.promedmail.org>

ProMED-mail is a program of the
International Society for Infectious Diseases

<http://www.isid.org>

[1]

Date: 30 Dec 2019

Source: Finance Sina [machine translation]

<https://finance.sina.cn/2019-12-31/detail-iihnzakh1074832.d.html?from=wap>

Wuhan unexplained pneumonia has been isolated test results will be announced [as soon as available]

On the evening of [30 Dec 2019], an "urgent notice on the treatment of pneumonia of unknown cause" was issued, which was widely distributed on the Internet by the red-headed document of the Medical Administration and Medical Administration of Wuhan Municipal Health Committee.

On the morning of [31 Dec 2019], China Business News reporter called the official hotline of Wuhan Municipal Health and Health Committee 12320 and learned that the content of the document is true.

12320 hotline staff said that what type of pneumonia of unknown cause appeared in Wuhan this time remains to be determined.

Figure 2: The original ProMED post announcing the four "pneumonia of unknown cause" cases in Wuhan.

a letter to the Ministry of Health saying this is likely a respiratory pathogen. It's likely to be dangerous. People should take precautions. That was the same day.

Now, one of the unfortunate things that was not done was that human-to-human

transmission was not officially recognised until about January 20. A two-week gap between the virus being sequenced by us and the authorities realising that there was human-to-human transmission. But, to Zhang and me, it was obvious from day one.

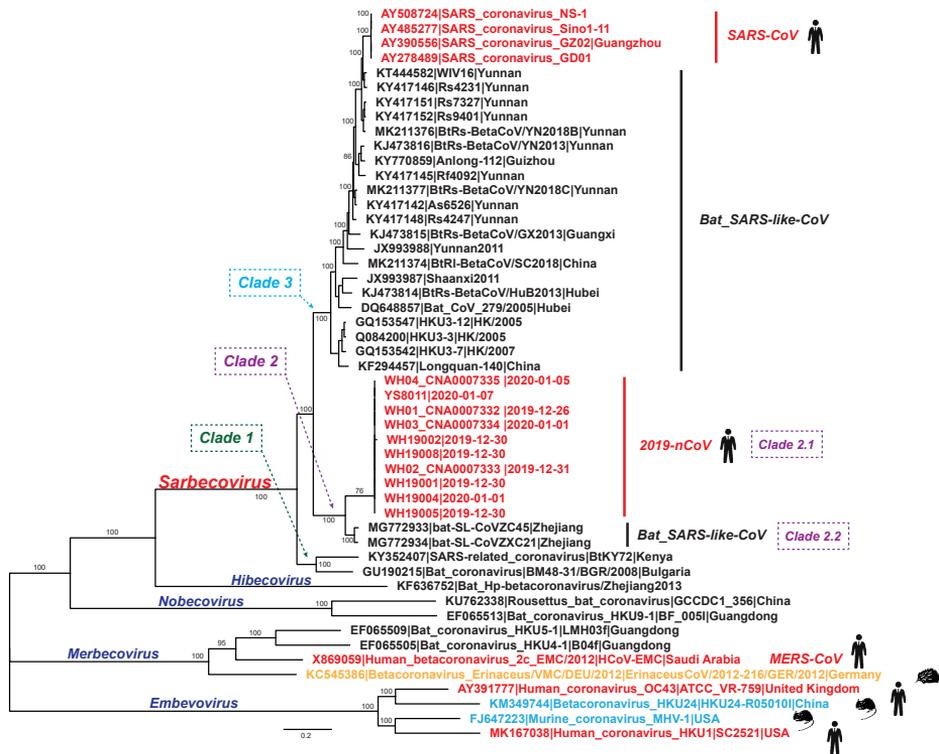


Figure 3: SARS coronavirus tree. Reprinted from *The Lancet*, Vol. 395, Duggan et al. (2020), pp. 565–574, Copyright (2020), with permission from Elsevier.

In fact, we have emails, and we’re asking is the transmission asymptomatic or symptomatic, because it’s a coronavirus. Coronavirus is respiratory. So unfortunately, the ball was dropped for a bit there.

Yes, we were the first people to release the sequence. But we were not actually the first people to sequence it. Prior to us, there were a number of other groups — you can find this online. Other groups had been sequencing the virus. The first actual sequence came from a company called Vision Medicals on 25 December. These doctors in Wuhan saw they had something. Their diagnostic tests weren’t working. They didn’t know what it was. They sent it quite reasonably to a local sequencing company and asked, Can you figure out what this is?

And that company first saw the data and they sequenced it on 25 December, and they got hits for SARS virus, and they basically went, oh dear, it’s SARS back again. And that SARS was back went all over social media in China. Of course, that was a toxic thing. People didn’t want to have SARS back. All it did was cause pandemonium. Then a second company confirmed that and re-sequenced it. But when they said SARS was back, what they couldn’t see was that it wasn’t exactly SARS. It was related to SARS, but it’s a different virus. There was some confusion early on, a lot of toing and froing in late December. The last week in December is when people really started getting a number of groups of sequencing. We were one of them.

But as soon as we had the first sequence in detail we knew exactly what it was. It was pretty obvious this was a coronavirus related to SARS. Figure 3 is one of the first trees that we did. At the top in red, that's the first SARS coronavirus, and a bit further down in red, that's the new one. Halfway down, it says 2019 human symbol nCoV. That's what we called it then. You can see that the two red bits are quite similar. So we knew right from day one, it was closely related to SARS virus. And that's what we said. It's respiratory. Also the bottom shows other coronaviruses that infect humans.³ We knew it was a kind of human coronavirus. Critically, the branches in black, they're all from bats. So we knew right from the start it was like the first SARS virus, only a bit different. It was related in evolutionary terms. Its family tree had bats very close. I won't talk about the gene structure in any great detail.

Now the virus looks like a big ball. On the ball outside there's a protein called the spike protein. That's the bit that attaches to the host cell. And there was lots and lots of interest about the spike protein. In particular, the spike protein had some little bits of sequence that looked quite unusual. The sequence is called a polybasic or a furin cleavage site. It's actually four amino acids, four bits of sequence that are unusual in SARS-CoV-2. Again, it's a standard coronavirus. We could see it was like the first coronavirus and a bit like bat viruses.

The big question is, where does it come from and what's the animal reservoir? I've already noted that, from day one, we could see it was closely related to viruses in bats. That was very obvious. And not just any old bats. It's particularly horseshoe bats. Their

nasal structure looks like a horseshoe, so it's obvious why they're called horseshoe bats.

They're from a genus called *Rhinolophus*. And it turns out that horseshoe bats are very common reservoirs for coronaviruses in China. They are full of coronavirus very, very commonly. So that was not a surprise. What was a surprise is that pangolins also have a related virus. No one was expecting pangolins to have a virus. No one had worked on pangolin viruses ever previously. Pangolins (*Manis* sp.) are nocturnal solitary animals, massively endangered because they're trafficked all the time for their scales, used in folk medicine.

What happened was the customs authority in China, in two provinces, Guangdong and Guangxi, had confiscated pangolins that had been smuggled in for their scales. And these pangolins were sick. They were not healthy pangolins. So the customs authorities alerted the vets to say there's something wrong with these pangolins. And so my colleagues then did genomic sequencing on the pangolins. And, bizarrely, they have a virus that's very closely related to SARS-CoV-2. You would not have predicted that.

There's one bit of sequence called the receptor binding domain. That's the bit of the virus that attaches to the host cell. The virus binds the cell to get in. Where it attaches, that bit of sequence, bizarrely, in the Guangdong pangolins confiscated by Guangdong customs, is almost identical to the human sequence. It's very strange. So bats have it. Pangolins have it. But there's a gap. There's an evolutionary gap. In evolutionary terms, it's about 20 years or so of missing evolution. So you have the human virus, the animal viruses. And there's some-

³ SARS-CoV-2 is the seventh documented human coronavirus; four cause common colds, three cause severe disease (SAR-CoV, MERS-CoV, SARS-CoV-2); bats are involved with the emergence of five.

thing in the middle we haven't sampled yet. And we don't know what that is. I'll come back to that.

Bats carry an awful lot of viruses. It is quite startling to see how many viruses they carry. We just did another study. My colleagues went to the Xishuangbanna Tropical Botanical Garden in Yunnan in southwestern China. And in this garden the bats are not in caves, they're in trees. They managed to sample 26 new bat coronaviruses, novel, completely new, in a 1000 hectare area. So you can just imagine the number of viruses that are out there in nature. The number of coronaviruses is absolutely astronomical. In fact, *Rhinolophus* horseshoe bats are widely distributed across all over Southeast Asia, and this part of the world has lots of horseshoe bats. And they're going to have absolutely buckets of virus. There's an amazing diversity of viruses out there.

One thing people haven't really cottoned on to about the pangolins is they were ill. They were not healthy animals at all. They were diseased. Basically, when a human has COVID-19, various immune genes are turned. The same genes are turned on in pangolins. It turns out it's a very similar disease presentation. So pangolins get a very similar kind of COVID thing as do humans. But, to repeat, there's a gap between the human ones and the closest animal ones.

And the question is what goes in that gap? And what the WHO have just announced in yesterday's report is they think the most likely scenario for how this virus emerged is it comes from bats through an intermediate host to humans. So the question is what's that intermediate host? And the animals that I think are most likely are mink and raccoon dogs (*Nyctereutes procyonoides*). Mink you all know. These animals are fur

farmed in large quantities in China. They're wildlife that are farmed. And I think they're pretty likely to be the intermediate host. We know mink carry the virus. The virus in Europe has gone from humans to mink, and then from mink back to humans. So mink are a really good source of virus. The other animals, I think, are very likely raccoon dogs. They're my personal favourite. And I say that because, in 2014, I went to the Wuhan seafood market.

It's a pretty confronting place. It's kind of sweaty, it's steamy. There's lots of internal roads. There are lots and lots of animal stores. In their recent report the WHO have produced a map of the market and the different stores. They swabbed the surfaces, be it a wall or a bench or the floor or a grate. And they found virus on those surfaces. And they're all clustered on one side of the market, on the west side of the market. And that's the side where the animal traders were. The fruit and veg people are on the east. The animal people are on the west and it is the west side that has the virus. There is clearly mass transmission going on in that market.

Now we don't know whether it's going from just between humans or whether animals are involved. But there were lots of transmission. When I was there in 2014, I took photographs of wildlife in that market, including raccoon dogs. They're very strange. They're kind of photoshopped animals, but they really do exist. And the raccoon dogs were in cages stacked up in the west side of the market.

And that's where most of the positive environmental samples were. I suspect that's a really important avenue for this virus. My bet is on the wildlife, farmed wildlife trade being brought into this market. That, to me, is the most likely scenario. And that's

what WHO have decided. We're lacking the smoking gun, or smoking raccoon dog. We don't quite have it yet. But I think, tellingly, these animals have not been tested in China, nor have mink, and I suspect they're the most likely intermediate.

Lab escape or wild transmission?

So now the million dollar question. Did this virus escape from a lab? It's something that I thought about immediately, as well. It's not a strange question: in the middle of Wuhan is a very big virus lab called the Institute of Virology. And they were working on bat viruses in that lab. And one of the closest relatives to SARS-CoV-2, called RaTG13, is from that lab, which has led to an enormous amount of debate. But here are a few facts.

First, there is no evidence that SARS-CoV-2 is engineered (and no reason to bio-engineer a random bat virus). Any talk of covert military operations is rubbish.

Second, bat virus RaTG13 is not the direct ancestor of SARS-CoV-2, it's a relative, but not that close, and all the components of the SARS-CoV-2 virus exist in nature, including the furin cleavage. There is nothing unusual in the SARS-CoV-2 sequence at all.

Third, there is no evidence of a secret SARS-CoV-2-like virus (closer to SARS-CoV-2 than to RaTG13) kept at the Wuhan Institute (and no reason to keep it secret before the pandemic) — they have previously published all their viruses.

Fourth, SARS-CoV-2 is not necessarily from bats and not necessarily from Yunnan Province. It's just that Yunnan is a great place to go and sample bats. Indeed, bats are probably an intermediate species.

Fifth, SARS-CoV-2 was not perfectly adapted to humans on first emergence and appears to be a "generalist" virus: it does

well in humans but it does well in other species too. Indeed, a paper in *Nature* reports that the pangolin virus itself works really well in humans. So you didn't need to adapt this virus for humans: it was going to work already. The ones from nature are very, very good human viruses.

Sixth, cases near the Wuhan Institute only appeared later in the outbreak, cases appeared near the seafood market earlier. So the spatial distribution fits the market first, then the lab quite clearly later.

Seventh, there is no evidence of SARS-CoV-2 infection at the Wuhan Institute: they claim their staff were PCR- and antibody-negative, so no one is infected. And, if that's true, that rules it out automatically.

So either this is the biggest cover up in history and they're all lying. Or there is no evidence at all. I'm very prepared to believe it's out of a lab. But give me the evidence. At the moment, there is absolutely none. This is going to go on for a very long time.

The virus mutates

So the virus has then emerged. We're now sequencing it frantically. You've heard about that. We have now sequenced something like 900,000 genomes globally. Just extraordinary. Soon, within the next couple of weeks, we'll have a million genomes sequenced. And the virus is gradually evolving. It's actually picking up about two mutations a month, on average, as it evolves through populations. What we've been doing is trying to classify the virus as it spreads globally. And we developed a very simple online tool where you can take your sequence, your virus, and you can work out what lineage it is. You take the tree of the virus, you can divide it into lineages. I'm using very technical names: A-B-C, things like that. And A1, B1.

It's very simple lineage classification system. There is a little tool called Pangolin⁴ that allows you to find out what lineage your virus is. We have classified something like 887 lineages so far, but there are three of them you're hearing a lot about in the news at the moment. And they are the so-called lineage "variants of concern."

There are three that you want to know about. One is called B.1.1.7.⁵ And it's often called the UK variant, because it was found first in the UK. The outbreak in Queensland is B.1.1.7. One's called B.1.351.⁶ That's the one that's found in South Africa. And there's one called P.1 and that's from Brazil.⁷ They're the three that people are most worried about because they're spreading very quickly.⁸

The mutations in those three variants are mainly clustered in the spike protein. Now, the key thing is all those variants are characterised by lots and lots of mutations, which is very unusual. And you've heard about these mutations. And the key thing is the same mutations are appearing in all these different variants.

And to make it easy because they're so complicated, we've given them stupid nicknames in the group. So, for example, the first mutation we saw was amino acid 614 in the spike protein. It's a D amino acid to a G, so asparagine to a glycine change. D614G. So we called it Doug. We've also got an N501Y — we called it Nelly. I apologise if you're one of these names. The mutation that looks worse is one called E484K. Originally

we called it Eric. We now think it's actually the worst one. We call it EEK.

And the key thing is that the same mutations are appearing independently in these different lineages. And so the big question is, what's driving this? There are a variety of theories on why suddenly all these variants of concern are appearing. Is it increased transmissibility? Is it immune escape or evasion? Is it mounting interferon resistance (evasion of innate immunity)? Is it the impact of population lockdown? Is it because people have chronic infections so they don't shed, don't clear the virus? Are they generating the virus? I suspect it's the top two. It's immune evasion. So as the virus is spreading globally, people are gradually getting vaccinated and gaining immunity. And that's putting selection pressure on the virus. And I suspect all these variants are actually in some way immune escape. I suspect that's what's going on. This is going to happen. The more immunity rises, the greater the selective pressure on the virus. It's going to happen. And we will likely have to update the vaccines.

Now, of those three lineages of concern, the one that's most concerning is B.1.1.7. That's the one that's in the UK, and that's the one that's now broken out in Queensland. And it's concerning for two reasons. First, it does appear to have an increased transmissibility compared to the other variants. There's a 43% to 90% increase in transmissibility of this variant compared to

4 <https://virological.org/t/pangolin-web-application-release/482>

5 The Alpha variant, also known as lineage B.1.1.7. [Ed.]

6 The Beta variant, also known as lineage B.1.351. [Ed.]

7 The Gamma variant, also known as lineage P.1. [Ed.]

8 The Delta variant, first seen in India, also known as lineage B.1.617.2, was named on 31 May 2021. The Omicron variant, also known as lineage B.1.1.529, was named on 26 November 2021. [Ed.]

the original. So it's much more infectious. Even more of a concern is the hazard of death, which is a nice way of saying mortality rate. It's between 42% to 80% higher if you have this variant. So it spreads faster and it's more serious. Actually for people over 80, the mortality rates are really high, over 15%. This is a concern. The good news is, as far as I'm aware, the vaccines that we have, although they don't always protect against transmission, are very good at stopping death and serious disease against all the variants, including the UK one, B.1.1.7.

So the vaccine is critical. It should massively reduce the mortality. It may not stop transmission, but it will definitely reduce mortality. It's not just the UK variant. This variant is spreading, and there's absolutely no surprise it's spreading all over the place. It will become the dominant strain globally. And I'd say, luckily, we can vaccinate against this strain pretty well. People in hotel quarantine that come into Australia are now very commonly B.1.1.7. It's no surprise that's the one that's escaped because that's the one that's spreading all over the place globally. But the vaccine should control it.

Future prevention?

So how can we stop this happening again? I think there are three things you need to do. First, emergence. I have tried to show it is all about human-wildlife interaction. Somehow we need to stop emergence happening again by monitoring, reducing our exposure to the wildlife trade, live animal markets, with better zoning. That's the fault line. That's where we get viruses from. So not building on areas where bats live, for example, like councils tend to allow. We need to stop doing that.

Second, we need to have much better surveillance mechanisms. We should establish global genomic, serological and social media surveillance of people at risk: those living and working at the human-animal interface. People who work at the human-animal interface, whether an abattoir or an animal market, and in animal trade need to be screened absolutely regularly, because they're on the front line. They're being exposed. If we can survey them and detect any disease early, then we can stop the next thing happening. But that also requires data sharing, and politics to get out of the way. And unfortunately, politics is undermining this at the moment.

Third, finally, the kind of critical thing is we need to develop and stockpile universal vaccines or cost-effective vaccines and antivirals that recognise all the viruses out there. There are certain viruses that always jump. Coronaviruses jump, influenza viruses jump. There are other families that jump all the time. We need to make new vaccines and antivirals that can protect against a broad range of those. I've been trying for a few years to make a universal flu vaccine. The same thing needs to happen for lots of other viruses, too. That's the kind of Apollo Project for virology. That's what we need to do. Massive investment. That's where science needs to be.

I'm going to stop there. Lots of people have been involved. Thank you.

Q and A

Q: With these new viruses, can sewage testing be used to detect new crossovers, new pathogens, which crossover to humans from animals, since not everyone is going to get tested or going to be eligible for tests?

EH: It's a good idea. The question is, can you do sewage testing, waste water testing? You can if you know what you're looking for. The problem with sewage testing is the virus is very, very fragmented when you get there. So doing a simple PCR test, that's what you use now to test whether you're coronavirus infected or not. That works. To do the genomics that I do to find unknown viruses, it won't be as good because the material is so complicated and broken up. So I think it's definitely a useful thing. But if we know something's there, we can track it. Finding a completely novel thing, at the moment, things are a bit harder.

Q: I guess the simple question to me is, where does it end? Fauci tells us that the only way out of all this is the vaccine. We have to build up herd immunity, but we isolate. So we're not building up herd immunity, but we need the vaccine. But you look at the Spanish flu. You look at the Hong Kong flu. They eventually burn themselves out. But everything we hear indicates that this is going to go on forever. What's your opinion?

EH: Yes. I think this will become an endemic human virus. There's no doubt whatsoever. And flu has never died out. I mean, flu is an endemic thing, we've had it for years. My guess is the virus will gradually evolve into a seasonal respiratory infection, and that we'll need to vaccinate every year or every two years, as we do for flu. There's no way — eradication is impossible since not every country is going to roll the vaccine out, it's not going to happen and the virus will evolve around it. So I think it will be an everyday part of our lives, and we'll just have to get used to being vaccinated.

Luckily, like I said, those variants, or "scariants" as they're often called now, are

coming up all the time, and the vaccines have different efficacy against them. The good news is they all seem to control mortality pretty well. So you get vaccinated, you might get a bit ill, but you should stop getting the lung and serious lung infection. So it's going to be part of our lives.

Q: Look, I was just wondering, could you give us an indication of what your feelings are on the apparent claim of the Chinese government that there only have been about 4300 deaths due to COVID-19 in China?

EH: There's a lot of politics in this thing. I think there's a number of countries where the numbers claimed may actually not be real. In Wuhan, the modelling suggested very early on the number of cases was far higher than reported, potentially hundreds of thousands of people in Wuhan were infected. So I don't know the data, but I think a lot of these things you need to be very careful about.

Q: Thank you. I'm enjoying the splendid isolation of Australia, and it seems that we have zero tolerance to COVID coming into the country. This is great, short term, but, long term, I can't see that it's a feasible position to take. What do you think it will take for that position to change politically?

EH: Yes. At some point, the federal government will decide enough people have been vaccinated and they will open up the borders. We can't be an isolate like this. We've done extraordinarily well: I think there's a case that New South Wales has done better than any place in the world, because we've had 56 deaths from COVID in New South Wales. Extraordinary. And we've not had a really hard lockdown. So I think we've done better than anywhere. But it won't continue.

My guess is once we've reached the level when most of the adults over a certain age have been vaccinated, I think that that's when they'll start to open up. The kids, I don't think, will come into it. I think they might leave those alone a little bit. I think they're looking for a portion of the adult population to be vaccinated. What proportion is that going to be? I don't know. Unfortunately, the vaccine roll-out's not going as quickly as I hoped it would. I think they've been too slow. I was hoping by the end of October, but they're now kind of hedging their bets, so it's hard to tell. It really is hard to tell, but I think they'll have to come out, certainly by the start of next year, if not this year. It has to happen.

Q: What is the evolutionary role of the furin cleavage site? How did it get inserted into the SARS-CoV-2 virus?

EH: This furin cleavage site has been contentious — four amino acids of such absolute contention. And so there's been an argument that it's been deliberately inserted. If you look at viruses, lots of them have furin cleavage sites. It's very, very common. Serious influenza viruses have them. In coronaviruses, they are all over the place. They come and go all the time in evolution. We've actually found some bat viruses that have quite similar sites, so I think it's a hot spot in evolution. It changes all the time. In itself it means absolutely nothing. It appears to increase transmission of the virus, but I think no more than that. One more thing. If you use cell culture, if you try to grow in the lab in cell lines, you only ever lose the site. You don't gain it. So if it's engineered in the lab, the result you're getting is the opposite you actually get because you tend lose the furin cleavage in the lab. So I think it's a natural piece of coronavirus and virus

evolution. And no more than that, there's no engineering going. On that I'm pretty sure enough.

Q: Why did you and Professor Zhang not release the genome on January 8th, 2021? GenBank had already processed it.

EH: We got the sequence on the 5th of January, and I released it on the 11th. Over that week, I didn't have the sequence myself until about less than an hour before I released it. I was trying to get Professor Zhang to release it, but they were under great pressure in China not to release any data. Other groups had the sequence as well, and essentially, there were instructions that there should be no publicising of the outbreak. So we kept it to ourselves. But we told the key people in China — people actually on the ground during the outbreak, but we were told not to release the data. As that week wore on — and I said other groups had it as well — as that week wore on it became untenable to keep it to ourselves. As soon as they said it was a coronavirus and the pressure grew online to release it. So it got to kind of breaking point.

And I then persuaded Zhang to give me the sequence, and I released it. I think it's very hard to judge these people because the politics are very complicated there. It's not a simple thing. If it's a Western thing, it'd be different. It's not so easy dealing with China.

Q: Have we understood the long-term impact of the virus infection?

EH: No. In terms of disease, no, I don't think we do. I think there'll be this long-COVID phenomenon. I think there are long-term implications of this that we don't know. We've learned an awful lot. I mean, the number of papers on COVID-19 is just unbelievable, right. My citations did really

well last year, but there's clearly a lot more work needs to be done on that. I think it'll take years to kind of really come out, unfortunately.

Q: Can you treat coronavirus by using the inhibitor of the protein that it binds to?

EH: Yes. There's a lot of work on antivirals for coronaviruses using drugs. I don't think they've got one yet that works that way. Most of the drugs that we've got — and then none of them are actually that good at the moment — they're all old drugs have been repurposed. They're drugs they had lying around. They've been used against coronaviruses, and sometimes they said they worked okay. At the moment, I don't think we have a really good antiviral that works. People have touted hydroxychloroquine and ivermectin. They just do not hold up at all in clinical trials.

People are trying to do what you say. At the moment, the drug research hasn't really been as successful as the vaccine research, and the vaccine research has been spectacularly successful. We do need an antiviral, like you say, but unfortunately, at the moment, we haven't quite got there.

Q: My question is with the history of the wet markets, how did it take so long for it to spring over to humans? I mean, the last big dynamic that we can think of, that I can think of, is the Spanish flu. How did it take so long to kind of come over to humans?

EH: No, people are exposed all the time. They've tested people working in the market trade in southern China, and I think like 3% of them have antibodies to SARS-like coronaviruses. So people have been challenged all the time. 99 times out of 100, these things go nowhere. They go absolutely nowhere. But that one time they don't. SARS-CoV-2

is the seventh human coronavirus. Five of those have appeared in the last 20 years. And some of them have very similar stories to SARS-CoV-2. We have no idea where they come from.

There's one called HKU1. That was discovered in Hong Kong/Shenzhen from an animal reservoir that's unknown, initially associated with pneumonia. And it has a furin cleavage site in the sequence. That's now spreading. Luckily, now it turns out to be similar to the common cold virus. So this emergence process is happening all the time. Absolutely all the time. Luckily, most of them don't go anywhere.

Unfortunately, SARS-CoV-2 — the problem was it's pretty transmissible, also it emerges in a big city in China just before Lunar New Year, which is the worst possible situation. And then you get millions of people moving literally the week after. It's all over China very quickly. And because Wuhan is an international hub, it's out of Wuhan very quickly. That was a problem. So it's the worst possible place for it to happen. Unfortunately, it happened.

Q: Why were the four studies on pangolins all released within the same two- to three-day period?

EH: I can only speak from our study. We had our paper published. We were working on pangolins. And then as our paper was being written, we heard that there was a press release by another group claiming they had a pangolin virus as well. I can't say anymore. I wasn't involved in the other studies.

Q: You showed a lot of data about the virosphere and how many viruses are out there. So can we actually prevent the next pandemic? What do we need to do to be able to do so?

EH: The number one thing, I think, is better surveillance. Absolutely better surveillance. And then data sharing. And unfortunately, those things didn't happen in this particular circumstance. It's become overtly political. All those sorts of things have meant that we've not been able to share data under political pressure now: Zhang has been under huge political pressure in China, and I don't think people really appreciate what it was like. And so the number one thing we need to do is to build data-sharing mechanisms. We have surveillance and that data is shared globally.

That's the number one thing to do. But we've got to cut through the politics, right?

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Postscript

Professor Eddie Holmes FRSN on ABC's Radio National Breakfast on 4 November 2021, with Fran Kelly.

Fran Kelly: The sequencing of the COVID-19 genome in March last year was a critical breakthrough in the fight to contain the virus. Australian scientist Professor Eddie Holmes' work and the decision to share that research with the world allowed labs around the globe to start work on a vaccine. It's been described as one of the most important acts of data sharing in human history, saving millions of lives. Last night, Eddie Holmes was honoured for his work and awarded the 2021 Prime Minister's Prize for Science.

Professor Eddie Holmes, welcome back to RN Breakfast, and congratulations.

Eddie Holmes: Thank you, Fran. It's nice to be here.

FK: Described as one of the most important acts of data sharing in human history, when you cracked the code and decided to share it with the world, did you know that you were doing something that could set us on a path to the quickest sort of development of vaccines ever? Why did you decide to do this?

EH: No. That actually was a big surprise. If you wind your mental clock back to January last year — it seems like a long way back — at that point, this outbreak was in Wuhan. There weren't that many cases. It was localized around this market. It was growing. It was clear we had to get the data out there. And that's why I shared the data at that point. But the fact that then it turned into this horrendous pandemic, I didn't see that coming at that particular point. So that's all been a bit of a surprise.

FK: You were on it pretty quickly. The genetic code you published just barely

months, hardly months after the virus really emerged and came into our consciousness. Does the fact that you decoded it and shared it with the world does that also mean you were the first to decode it?

EH: No. What actually happened was — it's quite a complicated story that's gone on — the first people actually to sequence the genomic sequence of the virus was actually a biotech company in China. What happened was some of the doctors in Wuhan noticed that they had these patients with pneumonia. They couldn't figure out what it was. Their standard tests weren't working. They sent their samples to a local biotech company, and they then did the first sequence and they showed it was a new coronavirus. Then a whole number of groups worked frantically to try and confirm that and get more data. And I'm working with one of those people. That's your first point about how quickly it happened. It's really an interesting thing. We all remember the AIDS panic. It took two years to discover that HIV was the cause. Two years. It took 40 hours from the samples arriving for us to work out that this virus was the cause of COVID-19. So the change in technology over that time period is really quite staggering. Extraordinary, isn't it?

FK: Now, since then, there's been a lot of politics, but also an immense international effort to work out the origins of this virus. The Office of the US Director of National Intelligence has concluded that a natural origin and a lab leak are both plausible hypotheses. You've been at the forefront of global research on the origins and the development of COVID-19, and I think it's fair to say you've been a major voice for the natural origin theory of COVID-19 rather than the lab leak. Is that still your view? Even after

the investigation, the global investigation and those findings of the Office of the US Director of National Intelligence?

EH: Yes, it very much still is. I'm a scientist. My job is to evaluate data, interpret data on the evidence we have. If there was evidence of a lab leak, I would happily put my hand up and say there's a lab leak, that's what happened. At the moment, though, there is really no evidence and that US intelligence report that you alluded to actually does not provide any evidence for a lab leak either. That's 20 months of the best intelligence agency in the world looking at, and they can't find any evidence.

They say it's still possible, but they can't actually show it. So I still think this is due to the wildlife trade, animal markets. I still think that's the most likely but we can't prove that. Obviously, we need to keep looking. We need to go back and investigate in more detail. At the moment, I still think it's most likely of zoonotic origin.

FK: That position has attracted a fair bit of controversy. I mean, the whole debate about where it's come from: a lab in Wuhan or wildlife, there's a lot of controversy and heat around it. You and your team have been condemned in some quarters for links to the Wuhan Institute. How tough has that been for you?

EH: Yes. That's one of the biggest surprises of the whole pandemic — quite how vitriolic and political it has been. I should say I have no link to the Wuhan Institute at all. I have collaborated in China, but not with that Institute.

FK: So you've collaborated in China, but not with the Wuhan Institute?

EH: Yes. That was a surprise. You have to grow a thick skin pretty quickly. I think

the difficult thing now is it's become just so political, both in the east and the west, and both sides are shouting at each other. I understand why that's happening. The politics is like that, but we need to throw that away and get back to the actual science. My concern is that we might lose our focus. This really is a scientific question. We may lose our ability to answer the science question because of the politics. So, I never thought it would turn into quite the political football it has turned into.

FK: And last month, the WHO formed a new body to investigate the origin of the pandemic. In scientific terms, how important is it that knowing where it originated from gives us more ammunition against future variants or against future pandemics?

EH: Yes, I think origins is critically important. I think we need to know exactly what the route was — how the virus got into humans — and then whatever that gap is, we fill that gap. If it does turn out to be the wildlife trade, then that clearly needs to be subject to much better regulation. So I think the origins is absolutely critical, and I hope the governments involved let the WHO team in, let them do their job and let us find the origin of this virus. Then we can all move on and put in place what we've learned from this one to stop this ever happening again.

FK: And I'll come to that if I have time. But really, what's important now is what happens with this virus. You've said, well, we know it's a constantly evolving virus. The world is trying to deal with the Delta variant at the moment, but there's a beta variant out there which you and others, I think, are already warning, is vaccine resistant. What can we expect, do you think, as more of the world gets vaccinated — though we are still a long way from global vaccination?

EH: Yes. So what's going to happen as we get more vaccinations? Obviously, this is a great thing to do that's going to push the virus. The virus is going to find it harder and harder to infect people, so it's going to get pushed. Evolution is going to push it, and it will gradually start to evolve strains that evade immunity. That's what 'flu virus does every year, and the COVID-19 virus will do the same sort of thing. So what that will mean is we will almost certainly need to update our vaccines on a fairly regular basis, but I'm actually pretty optimistic about that. The new technology we have for vaccines is pretty staggering, and I think they should just be able to kind of tweak the sequence of the virus and the vaccines, generate new vaccines, and that will keep us protected. I think it will be a game of cat and mouse for a while — us versus the virus and evolution — but I'm optimistic that we'll manage to dampen this down effectively.

FK: Just finally, you're a world beater when it comes to viruses and beating viruses. You've helped determine the origin and spread of Hep C, HIV, dengue, Zika, Ebola virus. You're calling for some kind of global radar to stop new viruses when they first appear. What do you mean by that?

EH: It's not just me, actually. I think a number of people now have thought this was a good idea. Boris Johnson actually announced it at the G-7 in Cornwall a few months ago. The idea is that countries work together. They have surveillance radar techniques built in. So if you see outbreaks very early on — people with unusual diseases or you see animals dying off of something — that information is then very quickly fed to all the people who need to know, all the health people, all the vaccine developers, the anti-viral people, the government.

And then we just act much quicker. And the single biggest thing I've learned in this whole pandemic is, you can have all the technology you want but unless you share your data, it counts for nothing. So sharing your data as quickly as possible globally is the most important thing. That's what the global radar is designed to do.

FK: You need global governments to sign on to that and follow through. Congratulations. It's well-deserved. Australia is very proud of you. Thank you.

HE: Thank you very much.

FK: Professor Eddie Holmes is the winner of the 2021 Prime Minister's Science Prize.

