



## Edward Holmes

National Health and Medical Research Council (NHMRC) Leadership Fellow & Professor of Virology, School of Medical Sciences, University of Sydney, Australia

“All human viruses ultimately come from animals, and humans transmit viruses to animals too”

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### Q1 What first drew you to virology, and how did your early experiences influence your focus on viral emergence and transmission?

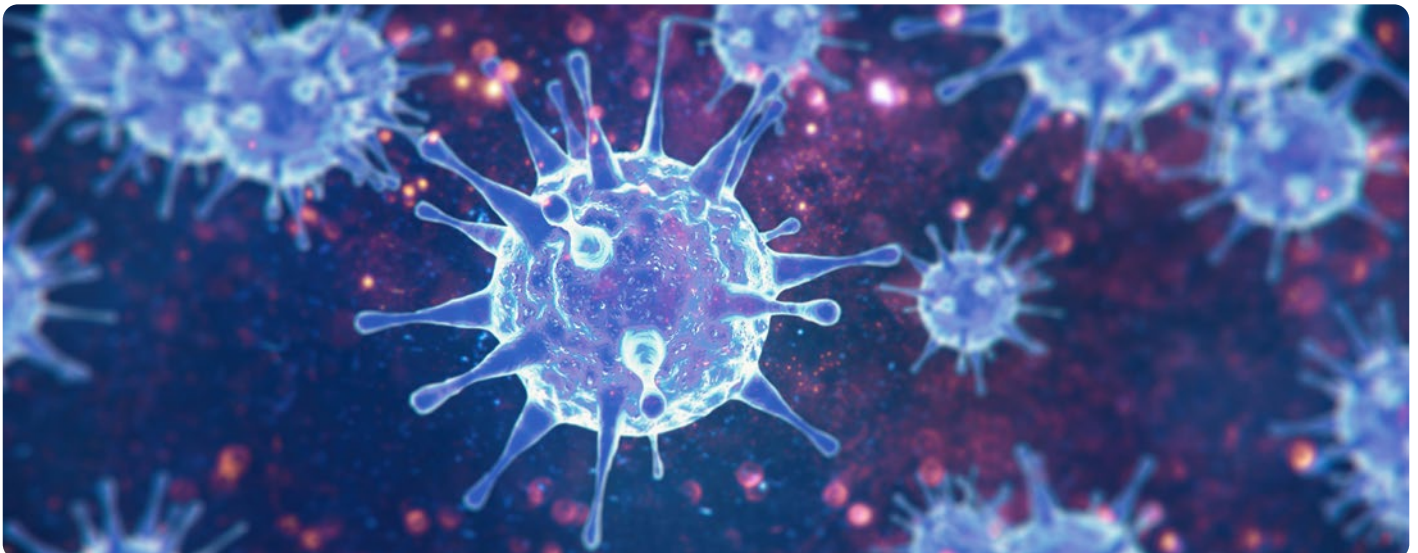
In 1990, I finished my PhD on primate evolution and went to my postdoc in Davis, California, USA. It was meant to be on fruit fly genetics, but I wasn't really into it. We drove a lot to San Francisco, California, USA. This was during the peak of the AIDS epidemic: there were no therapies that worked, and the number of deaths was very high. Seeing it close up, I thought this disease was a lot more important and interesting than working on fruit flies. I heard someone give a talk about looking at HIV sequence data and how the virus evolved, and I thought, I should be doing that instead. That experience was really formative.

Then I went to Edinburgh, UK, and worked on HIV. Edinburgh had a big HIV outbreak in the 80s and 90s, especially in communities with injecting drug use. HIV also really brought the study of disease emergence into

focus. People wanted to know where it came from. I realised that an evolutionary approach was natural for thinking about how viruses jump species and emerge. Essentially, every human virus ultimately comes from an animal reservoir at some point. It could have been long ago in our evolutionary past, such as herpesviruses, or recently, like COVID-19. Evolutionary biology has some fantastic tools to study this process.

### Q2 Your research has significantly advanced our understanding of how RNA viruses jump from animals to humans. From your experience, what are the key factors that allow some viruses to make that leap while others stay confined to their animal hosts?

All human viruses ultimately come from animals, and humans transmit viruses to animals too, so it's a two-way traffic. Perhaps the most important factor shaping the likelihood of emergence is how close the animals are to humans in evolutionary (i.e., phylogenetic)



terms. The closer they are, the more likely the virus can recognise and replicate in human cells. For example, HIV comes from chimpanzees, which are obviously very close to humans. So, the virus didn't have to adapt much to infect humans. In contrast, we're constantly exposed to plant viruses as part of our diet, but we don't get infected. Most of our viruses have mammalian origins as they are biologically similar to us.

The virus also needs the right mechanisms to enter and exit cells. Cell receptors that are conserved between species are easier for viruses to exploit. The tissue the virus infects also matters: the virus has to replicate in the right location for transmission. For example, avian influenza virus preferentially replicates in the lower respiratory tract, which is good for disease but poor for transmission.

Finally, ecological and epidemiological factors matter. Even if a virus is genetically suited to humans, there must be enough susceptible hosts to sustain transmission. In a remote area with low population density, the virus may burn out as there are just not enough hosts to pass it on. In a large, dense city like Wuhan, China, even a poorly adapted virus can spread and adapt. All these factors (genetics, tissue tropism, and ecology) have to align for emergence. You can have the best adapted virus in the world, but it won't spread without the right ecological context. HIV, for instance, emerged in central-west Africa in the early 20<sup>th</sup> century, but it didn't spread widely until it reached cities like Kinshasa, Democratic Republic of the Congo.

### Q3 Your current projects leverage metagenomic and metatranscriptomic approaches to explore the virosphere. How do these technologies change our ability to predict or prevent the next viral emergence, and what are some surprising discoveries you've made using them?

Prediction is tough. It's not like forecasting the weather. All the variables we've talked about have to align perfectly. And there are unknowns. But what we can do is focus on high-risk human-animal interfaces, where humans interact with wildlife. HIV emerged when humans logged forests in West Africa and encountered monkeys and apes. SARS 1 and SARS 2 emerged largely because of the wildlife trade. Stressed animals from multiple species

were brought into cities, often sick and shedding viruses onto each other, with humans handling them without personal protective equipment or health checks.

Metagenomics, particularly total RNA sequencing, allows us to see what viruses are circulating in these populations. We can identify viruses jumping between species, which are the ones we need to worry about. Coronaviruses, in particular, seem good at jumping hosts. Surveillance at live markets, abattoirs, or near bat roosts can give us a global system for early detection. However, this is being held back by politics. Open, free data sharing is essential, but geopolitical tensions and blame games make it harder. Technically, it's completely doable. We have the tools; the challenge is collaboration and the political will.



**Q4** You're studying ancient pathogens to understand the spread of past pandemics, like plague and cholera. How can these historical clues inform how we respond to current emerging infections?

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Ancient pathogens don't tell us what will happen because human society is so different now. For instance, plague strains from the Black Death and Justinian's plague are genomically very similar to modern strains. The high death toll then was most likely due to poor living conditions, not higher virulence.

What ancient DNA does give us is insight into how genetic factors have changed, or not, through time. We can see if the same types of mutations occur repeatedly through time when pathogens jump from animals to humans. It also shows the impact of human ecology: when humans became farmers and sedentary, disease exposure increased. Industrialisation, urbanisation, and now global trade all amplify disease spread. Ancient DNA,

therefore, provides a long-term perspective on how ecology and genetics interact in disease emergence.

**Q5** Having studied SARS-CoV-2 extensively, what do you think were the key evolutionary lessons from the COVID-19 pandemic regarding viral adaptation, transmission, and control measures?

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I was surprised by how much SARS-CoV-2 evolved. Genetically, it was pretty predictable, but the phenotypic changes in fitness were immense. Omicron, for example, is thousands of times more infectious than the original Wuhan strain. The first virus wasn't especially well adapted to humans, but in a dense population, it could spread enough to allow rapid adaptation.

Early on, virulence and transmissibility increased in parallel, which is unusual. Later, Omicron became better at infecting the upper respiratory tract, which increased transmission but decreased

lung-related disease, so virulence declined. Watching these traits evolve in real time was remarkable. Population density and ecological context were crucial. Even a virus that can infect cells well won't spread without the right conditions.

**Q6** Are there specific virus groups that you consider most likely to cause future pandemics?

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Respiratory viruses are the biggest concern because they transmit easily, often before symptoms appear. The main groups for these viruses are: paramyxoviruses, like Hendra, Nipah, and measles; influenza viruses; and coronaviruses. Fortunately, paramyxoviruses are usually local and contained quickly. Influenza is perennial, and we've been worried about it for decades. But coronaviruses worry me most. They've appeared repeatedly in the past 20 years, jump species easily, and have incredible potential to cause another pandemic.

“Industrialisation, urbanisation, and now global trade all amplify disease spread”



**Q7** In Australia, you are investigating emerging tick-borne diseases. What challenges do these pathogens pose in terms of detection, surveillance, and predicting their potential impact on human and animal health?

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Globally, tick-borne diseases are becoming more recognised, especially in Asia and Europe. In western China, Xinjiang, Kazakhstan, and parts of Europe, the burden is high. In Australia, the challenge is figuring out what's causing various illnesses linked to tick bites. Lyme disease definitely isn't here; the pathogen doesn't exist in Australian ticks. Despite extensive metagenomic studies, we haven't found an infectious agent for the cases we do see. It may be an immune or tick toxin response instead.

Ticks are increasingly recognised as viral vectors. The good thing is, we now have tools that worked elsewhere. Modern metagenomics allows detection within 24 hours. But in Australia, despite applying these tools, we haven't yet identified a clear pathogen for cases of tick-associated disease.

**Q8** How can understanding the evolution of viral virulence and host range guide public health strategies for emerging infectious diseases, particularly in the context of zoonotic spillover events?

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Virulence is complicated. It can increase, decrease, or stay the same over time. The key to public health is understanding the human–animal interface, where pandemics usually start. Limiting interactions with wildlife, through habitat protection, avoiding wildlife markets, and surveillance, is crucial. Detection and vaccines are feasible, but again, politics

often interfere. Open scientific collaboration is essential, yet data sharing has become harder since COVID-19. Climate change and habitat destruction will only increase risks if we don't address these interfaces.

**Q9** After over 35 years studying viral emergence, what keeps you excited about the future of this field, and where do you think the next big breakthroughs might come from?

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The combination of genomics and AI is transformative. Genomics provides absolutely enormous data sets (many human genomes worth per run), and AI can analyse them to identify new viruses, predict protein structures, viral functions, and risk. AI and genomics together give us unprecedented ways to understand viral diversity, evolution, and emergence like never before. That's incredibly exciting.

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