spike

THE VIRUS *vs* THE PEOPLE
THE INSIDE STORY

Jeremy Farrar
with **Anjana Ahuja**

PROFILE BOOKS

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If anything happens to me, this is what you need to know …

30 December 2020

Known cases: 4

I WAS IN AN AIRPORT lounge on New Year's Eve 2019 when my mobile rang. I was heading back to England from Rwanda and the Democratic Republic of Congo, where I had been visiting the Ebola vaccination centres in Rwanda across the politically fraught border region of North Kivu. I'd spent around a week going around the clinics and I'd had the vaccine myself in Prefegitura ya Cyangugu, a village in Rwanda. I was absolutely knackered and looking forward to a couple of days at home in Oxford before heading back to the office.

I was scanning my phone when I saw a report of a mystery pneumonia spotted by doctors at a hospital in China. I sent a short text message to George Gao, head of the Chinese Center for Disease Control and Prevention (China CDC) in Beijing, and an old friend. George is a very likeable character, as well as a respected scientist, a brilliant impressionist and a karaoke enthusiast. My message was short and simple, just asking if he was OK and that he should reach out if he needed anything.

He phoned me back. Very soon, George told me, the world would be hearing about a cluster of cases of a new pneumonia from Wuhan in China. The cases had already been reported to the World Health Organization. It was, essentially, a courtesy call from one scientist to another. I remember him telling me that we wouldn't need to worry because it wasn't severe acute respiratory syndrome (SARS), and that we must keep in touch.

It was a relief to hear him rule out SARS, a deadly disease that features on the world's worry list and for which there is no vaccine or cure. It first appeared in 2002 – and one of its victims, Carlo Urbani, was a good friend of mine. He died while investigating an outbreak in Hanoi, Vietnam. He was just 46 and had a young family.

Carlo's work helped to identify SARS as a new coronavirus. Most importantly, he spotted that cases of severe pneumonia were being passed on from patients to health workers, who were falling sick and dying. Carlo organised the hospital's closure, alerted the world and, essentially, saved Vietnam. His legacy is honoured, if that is the right word, in the naming of the Urbani strain of the virus. This was the dominant strain that spread across South East Asia in 2003, before being contained, infecting more than 8,000 people and killing nearly one in ten of them.

Having spent eighteen years running an infectious diseases research facility in Ho Chi Minh City, I was badly shaken by Carlo's death. I know what it is like to deal with the science and politics of a new disease. I helped to alert the world to a potentially serious outbreak of H5N1 bird flu in Vietnam in 2004, along with colleagues Tran Tinh Hien, Nguyen Thanh Liem and Peter Horby, then an epidemiologist working for the World Health Organization in Hanoi and now an Oxford University scientist.

Both SARS and H5N1 had a profound psychological impact on me, because of the fear that comes with unknown diseases. They took me back to being a young doctor in London at the start of the HIV epidemic: as medical students and junior doctors we rarely stopped to question the power of medicine, believing unerringly that we could treat people and cure them. But when HIV came along in the early 1980s we could do nothing. Young people would come in to die. The West had not seen deaths from untreatable infectious diseases for many years.

When SARS came, it was the same. You don't know what you're dealing with, you're frightened, friends are dying and it's spreading around the world. Six months later, SARS was finished because it did not transmit readily between people: also, people were most infectious when they were symptomatic. There was little or no asymptomatic transmission, meaning that isolating people with symptoms brought a chain of transmission to an end. Despite lasting only six months, and causing 'only' 774 deaths, the epidemic was estimated to have cost around US $40 billion.

The next year, bird flu struck Vietnam. It never got beyond about 100 cases but it killed roughly 60 per cent of people who caught it. We got lucky because, again, the disease fizzled out. These episodes, along with the emergence and reemergence of other diseases over the last twenty years such as the deadly bat-borne Nipah and Middle East respiratory viruses, and the mosquito-borne Zika virus, were the warnings for what would inevitably come.

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When I went back to work on Friday 3 January 2020, I emailed two of my most senior colleagues: Eliza Manningham-Buller, the Chair of the Wellcome Trust and former director general of the UK intelligence agency MI5, and Mike Ferguson, her deputy. I would not normally trouble them about a small, distant outbreak – but this one in China felt different. If it turned out to be different, the Wellcome Trust, where I have been director for eight years, would be called upon for its expertise and money. The charity has long worked in the field of infectious diseases, with researchers all over the world; it played a key role in the research response to the Ebola outbreaks of 2014 and 2018, including funding vaccine research and clinical trials.

Prefaced with the line ‘Just for info in confidence’, I told Eliza and Mike about my phone conversation with George Gao and included a link to a news item on the BBC website about the mystery viral pneumonia from Wuhan. Just before signing off, I speculated that China CDC would make an announcement within 48 hours. I assumed that’s what George had meant by his phone call. I reassured Eliza and Mike that ‘it is not SARS, although probably a known “relative”. Nothing for Wellcome to do at the moment.’

I turned out to be wrong. The cases of unexplained and untreatable pneumonia in Wuhan kept growing, matched later by reports of crowded hospital wards and overflowing mortuaries. Social media and online chat rooms in China hummed with rumours of a strange new illness spreading in Wuhan, including among hospital workers; reports began filtering in of police crackdowns on those trying to get information out over the heavily monitored internet.

By the second week of January, I was beginning to realise the scale of what was happening. I was also getting the uncomfortable feeling that some of the information needed by scientists all around the world to detect and fight this new disease was not being disclosed as fast as it could be. I did not know it then, but a fraught few weeks lay ahead.

In those weeks, I became exhausted and scared. I felt as if I was living a different person's life. During that period, I would do things I had never done before: acquire a burner phone, hold clandestine meetings, keep difficult secrets. I would have surreal conversations with my wife, Christiane, who persuaded me we should let the people closest to us know what was going on. I phoned my brother and best friend to give them my temporary number. In hushed conversations, I sketched out the possibility of a looming global health crisis that had the potential to be read as bioterrorism.

'If anything happens to me in the next few weeks,' I told them nervously, 'this is what you need to know.'

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The process of reporting a new disease to the wider world is quite informal and not at all glamorous. It often starts with a brief notice on ProMED-mail, an online repository collating short descriptions of outbreaks of animal and human diseases in different countries, as well as other news snippets relating to diseases, such as grant announcements. That is where I had picked up the information on the Wuhan cases that George Gao and I spoke about. The descriptions of outbreaks are clipped from official sources, such as health authorities, but also from social media and local newspapers. Every outbreak that becomes a global headline begins as a local rumour.

ProMED stands for 'Program for Monitoring Emerging Diseases' and is run by the International Society for Infectious Diseases, which boasts more than 80,000 members in 201 countries. It is not sustained by any government or the World Health Organization but by volunteers operating a non-profit initiative on a shoestring budget. It is also far more respected – and critical to global health – than the informal setup would imply. I first became aware of ProMED in 1999, while investigating a mysterious brain infection striking down pig farmers in Malaysia. That turned out to be the first known outbreak of Nipah virus, regarded ever since as one of the world's deadliest disease threats.

The ProMED alert that had caught my eye was dated 30 December 2019, next to a line reading simply: 'Undiagnosed pneumonia – China (HU):RFI'. 'HU' refers to Hubei, the central province in which the city of Wuhan is located: 'RFI' signals a request for further information. The first signs of SARS were cases of undiagnosed pneumonia.

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Nobody knew it then but that single line marked the debut of a new disease, one that would come to be called Covid-19 and cause the biggest upheaval to the global order since the Second World War. The line clicks through to an imperfect machine translation of a story relating to 'an urgent notice on treatment of pneumonia of unknown cause' originally posted that evening by the Medical Administration of Wuhan Municipal Health Committee, concerning four patients with an unknown form of pneumonia.

A report appended underneath that urgent notice adds worrying detail gleaned on 31 December: 27 people were in various hospitals in Wuhan with viral pneumonia or pulmonary (lung) infection. Two were recovering but seven were critical. Flu and bacterial diseases had been ruled out – but not SARS. Citizens were being urged not to panic.

All the patients apparently had links to the Wuhan South China Seafood Wholesale Market (also known as the Huanan Seafood Market). That market link would have worried scientists like me: crowded and cramped 'wet markets', named for the melting ice that keeps meat and seafood fresh, often sell wild and domestic animals alongside meat and fish. The messy overlap provides contact between species, a common feature in the emergence of new diseases because it opens avenues for microbial traffic. That exchange can be between different animal species and between animal species and humans. The report added: 'At present, related virus typing, isolation treatment, public opinion control, and terminal disinfection are underway.'

Public opinion control. Underneath the news reports, a ProMED moderator made an astute observation. Having been involved in publishing early information about SARS, the anonymous moderator wrote, 'the type of social media activity that is now surrounding this event is very reminiscent of the original "rumors" that accompanied the [SARS] outbreak.' Weibo, the Chinese social media channel, was also buzzing with speculation.

The moderator turned out to be Marjorie Pollack, an American epidemiologist who has worked in 50 countries for the US Centers for Disease Control and Prevention. She noted that the bubonic plague, which had cropped up the month before in Inner Mongolia, was sometimes accompanied by unusual pneumonia but assumed this had been already ruled out in Wuhan (plague is caused by *yersinia pestis*, a bacterium, while the Wuhan pneumonia bore the hallmarks of a viral infection). She appealed for more information, and for the results of any tests.

On 31 December, the WHO requested information from China on the Wuhan cluster of atypical pneumonias.

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On 3 January 2020, ProMED posted an update pulled from the *South China Morning Post*. The unexplained disease was spreading: 44 patients in Wuhan, up from 27; 11 seriously ill with breathing difficulties and lesions, or scarring, on both lungs. There was another unwelcome development: five people had shown up in Hong Kong with unexplained fever after visiting Wuhan. Yet the Chinese authorities had not yet found – or not yet chosen to disclose – the cause.

By 5 January 2020, the WHO, guided by the official information it was receiving from Wuhan, was reporting that there was no significant evidence of human-to-human transmission. Contact tracing was underway to find those linked to the Wuhan patients, many of whom had been stallholders at the seafood market. The persistent market link, the WHO reported, 'could indicate an exposure link to animals'.

That tight case definition resulted in an Escher's loop of misguided circular reasoning: testing only those people with a link to the market created the illusion that the market was the source of disease, because everyone testing positive had been there. In reality, the net should have been cast wider – and the continually growing casualties should have immediately prompted suspicions of human-to-human transmission rather than infections from a single source, such as a contaminated animal carcass.

The WHO also reported that no healthcare workers seemed to have come down with symptoms: illnesses among nurses and doctors act like a canary in the coalmine for new contagious diseases, because infection takes place before nurses, ambulance drivers and other healthcare staff know what they are dealing with.

But, to any outside observer familiar with China as a scientific superpower, second only to the US in research spending, the ignorance was peculiar. Why did nobody seem to know what Wuhan medics were dealing with? The authorities kept insisting that SARS, influenza and bacterial causes had been ruled out – and yet had not pronounced on what could be ruled in. It was baffling: samples would have been sent from those first patients to laboratories for urgent testing and analysis. There was even a top-level biosafety laboratory in Wuhan, a coincidence that would later fuel theories about the virus's origins. Why had that information, potentially crucial to global public health, not yet been released?

ProMED reported: 'The Chinese Center for Disease Control and Prevention is expected to make an announcement of its findings in the coming days, a person familiar with the matter said. The CDC couldn't be reached for comment late Tuesday [7 January 2020].' The report went on to remind readers that China had covered up SARS when it emerged in 2002, reporting it to the WHO only after it began spreading across and beyond southern China.

Just a week into the new year, the unknown disease was no longer wreaking havoc just in Wuhan, a city of 11 million people and a major travel hub in central China. Authorities in neighbouring Hong Kong and Singapore, having already experienced the unwanted gift of SARS nearly two decades earlier, were now monitoring their borders for passengers with fever. A lot of people were becoming anxious – and for good reason. A week is an unsettlingly long time in the world of infectious diseases.

By Friday 10 January it was clear that the Chinese authorities knew more than they were letting on. Colleagues at the World Health Organization discovered that two scientific papers about this new viral pneumonia were in the pipeline at *Nature* and the *New England Journal of Medicine*, two prestigious journals. Maria Van Kerkhove, an epidemiologist in the WHO's Health Emergencies Programme, alerted me.

It was time to send out a signal. I tweeted:

> If rumours of publications on the Wuhan Pneumonia situation are being prepared and submitted to @nature @NEJM are true & that critical health information is not being shared immediately with @WHO – something is very wrong

Within minutes, the tweets attracted a private message on Twitter and a phone call from the other side of the world. Something was, indeed, very wrong.

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Scientists track how viruses relate to each other by drawing family trees, in much the same way that people can trace their own origins back by following the trail of births, deaths and marriages. Instead of surnames and family records, viruses reveal their origins in their genetic sequences. Genetic overlap pinpoints the similarities between different viruses, signposting when they potentially share a common ancestor. Likenesses between human viruses and animal ones can also narrow down which animal might have transferred a virus across the species barrier to us.

Scientists can then construct a ‘phylogenetic tree’ that accords the newbie pathogen its rightful place in the viral hierarchy by establishing how closely related it is to other known viruses. This helps virologists to decide whether an emerging virus is a variation on a known virus or a fresh addition to a particular family of viruses. A tree for a virus can be drawn in different ways but often looks like a collection of fork prongs (or tines).

At the tip of each tine lies the name of a virus designed to showcase something of its origins. The pandemic virus that causes Covid-19 is now called SARS-CoV-2: severe acute respiratory syndrome coronavirus-2. The original

SARS virus to which it bears significant genetic resemblance used to be called SARS-CoV and has now been renamed SARS-CoV-1.

Eddie Holmes is a British-born virologist and professor at the University of Sydney who does exactly this sort of viral detective work. He is, in my book, the outstanding evolutionary biologist of his generation, with an extraordinary brain when it comes to pattern recognition.

Eddie belongs to a research consortium which includes the Shanghai Public Health Clinical Center and School of Public Health at Fudan University, Shanghai, where he holds an honorary professorship. Since 2012, Eddie has worked closely with Professor Yong-Zhen Zhang, a professor at Fudan University, on finding and identifying new animal viruses, and Wuhan is a familiar locale in their virus-hunting network.

‘We have this little routine,’ Eddie says of his work with Zhang trying to document the diversity and evolution of animal viruses. ‘His team collect samples – they can be spiders or fish or anything – and then I go over there once or twice a year and help analyse the data.’

They don’t normally study samples from humans but genomic sequencing, the method used to place viruses in their family trees, can also be used as a diagnostic, to help identify mystery viruses found in hospital patients. Over the past eight years, Eddie and Zhang, more used to collecting virus samples from cave-dwelling bats than from city dwellers, have built up contacts with Wuhan doctors. As Eddie says, rather honestly: ‘The animal stuff is great but everyone wants to find a new human virus. It was obvious that Zhang was going to be one of the first people to get hold of samples.’

On 3 January 2020, Zhang struck viral gold: a sample taken from a pneumonia patient hospitalised in Wuhan on 26

December 2019 arrived at his lab packed in dry ice in a metal box. By 2am on 5 January, after a 40-hour shift in the lab, Zhang and colleagues had worked out its genetic sequence. It was a coronavirus that looked suspiciously like SARS-CoV-1, the virus responsible for the 2002/3 outbreak. Coronaviruses are named for their similarity in appearance to a crown: under powerful microscopes, the virus particles look like tiny spheres covered in small spiky protrusions. Those spikes help the virus get into cells to infect people; most vaccines target the spikes to disrupt the process.

Eddie still remembers the phone call (Sydney is three hours ahead of Shanghai): 'We agreed that he should tell the Ministry of Health in China immediately. Zhang did it the same day.

'Zhang told them it was clearly very closely related to the first SARS virus and that it was very likely to be respiratory because of its relatedness. He also told the ministry that people should take precautions.'

That phrase – 'people should take precautions' – was a direct warning that this new virus, like its dangerous predecessor, might be able to spread from one person to another. Eddie says this should have been interpreted back then as a warning of human-to-human transmission. In the end, China did not confirm this publicly until 20 January, more than two weeks later.

While Zhang informed Beijing, some of the sequence was deposited on 5 January 2020 on GenBank, an online collection of publicly available gene sequences run by the National Institutes of Health in the US. But it takes a while for those deposited sequences to be checked, edited and put through the system in a way that others can use. There was an imperative to post the entire sequence more publicly. Anyone, anywhere, could then use that published information to develop a diagnostic test. The world would, at a stroke, have eyes on the virus.

There was, though, a major hitch: Zhang was told in no uncertain terms not to publish anything. The gagging order, Eddie understood, came from Beijing. The warnings to stay silent were real: medics had already been disciplined by the Chinese Communist Party (CCP) for discussing hospital cases online. One of the earliest whistleblowers, ophthalmologist Dr Li Wenliang, became a potent symbol of China's mismanagement of the emerging crisis: he was admonished for warning hospital colleagues of a dangerous new infection, became infected and died aged just 33. The Chinese government later apologised to his family, including his pregnant wife.

Eddie and Zhang hit on a loophole to get round the gagging order: the government ban on publishing information about the outbreak did not preclude them from writing and submitting a scientific paper. Holmes contacted the journal *Nature*; one of its editors, Clare Thomas, urged them to submit something as soon as possible. By 7 January 2020, Zhang's paper, with Eddie as one of the co-authors, reached *Nature*'s offices in London.

Things began moving quickly and chaotically. On 8 January, rumours began circulating that the new virus was a coronavirus, putting it in the same family as SARS. A day later, the Chinese authorities confirmed the fact. But, otherwise, and especially on the genome sequence of the virus, they were silent. Not only had Zhang contacted China's Ministry of Health with details of the new virus but Eddie was sure that, in doing so, Zhang had merely confirmed information that Beijing already knew. Eddie had screenshots of messages on WeChat, a social media platform in China, suggesting two private companies had already sequenced the virus in December 2019.

Eddie, disturbed at what was looking increasingly like a decision by China to hold back information on a new disease, saw my tweet about the two scientific papers about to come out. His name was on one of them. He rang me to tell me that he'd been trying to get the sequence released, with no luck.

After that call from Eddie, I realised that he and I were probably the only two people in the world outside China who knew there was this sequence in existence and what it was, with all the potential consequences. The information was stacking up: here was a mysterious new pneumonia and, with the sequence, we knew it was caused by a novel coronavirus closely related to SARS. Those are two big red flags.

But the really critical information, the kind that stops you sleeping at night, was still to come.

* * *

The news of a novel coronavirus outbreak in China at the start of 2020 chilled the blood of scientists, including me, who witnessed the appearance of severe acute respiratory syndrome (SARS) nearly two decades before. That disease, also associated with a fatal pneumonia, first emerged in the Guangdong province of southern China in 2002. It spread largely unchecked in southern China and then crossed borders. By August 2003, it had infected more than 8,000 people in 37 countries and killed 774. That was the virus that killed my friend Carlo in Vietnam.

Like so many of the viruses that feature in epidemiologists' anxiety dreams, SARS-CoV-1 is found naturally in bats – and the animals themselves seem untroubled by viruses that are so virulent in other species. The 2002/3 outbreak is thought to have been triggered by that virus passing from bats to humans via an intermediate species, with civet cats a probable culprit. These long-bodied, short-legged animals, closer in appearance to a mongoose than to a cat, are commonly sold for food and have been found to harbour viruses closely resembling SARS-CoV-1.

SARS is a painful memory in the collective Chinese consciousness – and in the annals of global public health – because the government spent the early months of the epidemic covering it up. In fact, the parallels between that original SARS outbreak, caused by the virus SARS-CoV-1, and the Covid-19 pandemic, caused by the closely related virus SARS-CoV-2, go beyond virus names. Both are likely to have started in November and, while reported up the chain of public health command, failed to properly attract the attention of Beijing until January.

It is an auspicious time of arrival for any malevolent microbe, given the proximity of the Chinese New Year. The week-long holiday is the backdrop to the world's largest annual migration, as around 450 million people criss-cross the country to visit friends and relatives. That mass movement is the perfect spreading opportunity for a virus. The anticipation of a major public holiday is a distraction for otherwise diligent health officials on the lookout for new diseases.

The top-down, hierarchical way in which the Chinese Communist Party runs the country, with a compulsion to control the message, also seems set up to frustrate early disclosure. With the original SARS, three days were reportedly lost due to the lack of suitably senior staff to open a document about the new illness marked 'Top Secret'. When health alerts eventually came, they were sent out during the Chinese New Year, when many hospital staff were absent. It was February 2003 before the World Health Organization was officially notified, by which time more than 300 people had fallen ill. Insistence in Beijing that the SARS outbreak was being contained was followed by an effective news blackout in the run-up to the National Party Congress in March 2003.

In April 2003, a surgeon in Beijing finally blew the whistle, claiming many cases in the capital had been covered up. The authorities in Beijing were slow to consent to WHO requests to investigate. The epidemic, which seeded large, deadly outbreaks in Hong Kong, Taiwan and Canada, was contained by August 2003 but the inglorious debut of SARS still serves as a benchmark for how not to handle a new disease. It took four months for China to report cases to the WHO, and another month before the coronavirus SARS-CoV-1 was unveiled as the pathogen responsible for the disease.

SARS was the costly catalyst for change in China: the country strengthened its disease surveillance network and put in place an online reporting system accessible by any hospital. It wasn't a half-hearted tweaking of the system but a radical rethink: the China CDC became a slick, professional, science-focused organisation, with fresh buildings, a new infrastructure and highly trained staff capable of gracing any world-class research institution – George Gao among them.

But the lessons from SARS still sting. Speed and openness are essential.

That is why Eddie contacted me. He needed to share the burden of the knowledge he had been building up in that first week in January: that the virus responsible for this mysterious pneumonia in Wuhan had been sequenced as far back as December 2019; that Zhang's consortium had a paper waiting to go; and that China knew the virus had been sequenced but had not yet released the information.

Eddie and I had a series of frantic calls between London and Sydney on the night of Thursday 9 January, which stretched into the early hours of Friday. We hatched a plan that Eddie would go back to his collaborators in China and I would go back to George Gao at China CDC. We would threaten to go public if they refused to disclose the information by Saturday morning GMT.

We decided to tell them, 'If you don't release the sequence in the next 24 hours we will release it the next day.' By 9.18pm London time, and 8.18am in Sydney, Eddie and I had committed to the high-stakes pact to force China's hand.

I felt terrible because I'd never done anything like that before – but issuing an ultimatum felt like the only way. News was filtering out about healthcare workers falling sick. Waiting for the wheels of China's bureaucracy to turn quickly enough to make a formal declaration just before Chinese New Year, which lay two weeks away, was too dangerous. It would have taken days and, frankly, we didn't have days. Once it was clear this was a SARS-related coronavirus spread by the respiratory route and that healthcare workers were succumbing, it was clear that things were going to deteriorate quickly.

The world had to have access to that sequence because the world needed to be able to diagnose it. It was going to appear in Beijing, in Hong Kong and Singapore in the hours or days that followed. It was going to spread everywhere.

Eddie remembers the pressure-cooker atmosphere of those days too. Zhang deserved public credit for leading the consortium's sequencing breakthrough – but Eddie also knew his colleague would also be at the sharp end of Beijing's displeasure for shattering the government's code of silence.

‘My big concern was not getting Zhang in trouble,’ Eddie says now. ‘I called him and said, “There’s a lot of pressure to release the sequence. I think we have to do it”. Zhang was on a plane going from Shanghai to Beijing, on the runway literally waiting to take off.’

Zhang asked his collaborator for a moment to think. It didn’t take long. Perhaps Zhang had already decided the world had waited long enough. Before the plane took to the skies, Zhang rang Eddie back with a simple message: ‘OK, let’s release it.’ Eddie phoned me immediately.

By the time Zhang’s plane touched down just over two hours later, the information was out.

* * *

The drama that preceded publication was followed by first comedy and then tragedy.

Comedy, because almost as soon as Eddie had promised to Zhang he would release the sequence, he realised he didn’t have it. Eddie had no need of the sequence itself in order to carry out his virological analysis for the *Nature* paper; his contribution just entailed sending suggestions of further work to colleagues in China. A colleague of Zhang’s in Shanghai quickly emailed the sequence over.

Without a moment to lose, Eddie rang Andrew Rambaut, an evolutionary biologist at the University of Edinburgh and a trusted contact. The clock was approaching midnight for Andrew but, as Eddie knew, his friend always worked late into the night. Andrew runs an open-source website, virological.org, collating information, including genome sequences, on viruses that might be of interest to other scientists – and agreed during the phone call from Eddie to publish the sequence.