Seven Year Coronavirus Trail from Bat Cave via Wuhan Lab

Description

?via The Times

In 2013, scientists investigating deaths in a disused mine found a coronavirus remarkably similar to that behind the pandemic. They took samples to their lab 1,000 miles away

In the monsoon season of August 2012 a small team of scientists travelled to southwest China to investigate a new and mysteriously lethal illness. After driving through terraced tea plantations, they reached their destination: an abandoned copper mine where — in white hazmat suits and respirator masks — they ventured into the darkness.

Instantly, they were struck by the stench. Overhead, bats roosted. Underfoot, rats and shrews scurried through thick layers of their droppings. It was a breeding ground for mutated micro-organisms and pathogens deadly to human beings. There was a reason to take extra care. Weeks earlier, six men who had entered the mine had been struck down by an illness that caused an uncontrollable pneumonia. Three of them died.

Today, as deaths from the Covid-19 pandemic exceed half a million and economies totter, the bats' repellent lair has taken on global significance.

Evidence seen by The Sunday Times suggests that a virus found in its depths — part of a faecal sample that was frozen and sent to a Chinese laboratory for analysis and storage — is the closest known match to the virus that causes Covid-19.

It came from one of the last droppings collected in the year-long quest, during which the six researchers sent hundreds of samples back to their home city of Wuhan. There, experts on bat viruses were trying to identify the source of the Sars — severe acute respiratory syndrome — pandemic 10 years earlier.

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The virus was a huge discovery. It was a "new strain" of a Sars-type coronavirus that, surprisingly, received only a passing mention in an academic paper. The six sick men were not referred to at all. What happened to the virus in the years between its discovery and the eruption of Covid-19? Why was its existence tucked away in obscure records, and its link to three deaths not mentioned? Nobody can deny the bravery of the scientists who risked their lives by harvesting the highly infectious virus. But did their courageous detective work lead inadvertently to a global disaster? ONE

Where flowers bloom all year

The first victims of a new virus

Kunming, the capital of Yunnan province in southwest China, is known as "the city of eternal spring" because its unique climate encourages flowers to bloom all year. The sprawling high-rise buildings of the First Affiliated Hospital tower over the ancient city.

On Tuesday April 24, 2012, a 45-year-old man with the surname of Guo was admitted to the hospital's intensive care unit suffering from severe pneumonia.

The next day a 42-year-old man with the surname Lv was taken to the hospital with the same life-threatening symptoms, and by Thursday three more cases — Zhou, 63, Liu, 46, and Li, 32 — had joined him in intensive care. A sixth man called Wu, 30, was taken into intensive care the following Wednesday.

All the men were linked. They had been given the task of clearing out piles of bat faeces in an abandoned copper mine in the hills south of the town of Tongguan in the Mojiang region. Some had worked for two weeks before falling ill, and others just a few days.

The illness confounded the doctors. The men had raging fevers of above 39C, coughs and aching limbs. All but one had severe difficulty in breathing.

After the first two men died, the remaining four underwent a barrage of tests for haemorrhagic fever, dengue fever, Japanese encephalitis and influenza, but they all came back negative. They were also tested for Sars, the outbreak that had erupted in southern China in 2002, but that also proved negative. The doctors sought the opinion of Professor Zhong Nanshan, a British-educated respiratory specialist and a former president of China's medical association who had spearheaded his country's efforts to combat Sars. Aware the men might be suffering from another Sars-related coronavirus, he advised the doctors to test them for antibodies.

The Wuhan Institute of Virology (WIV), a renowned centre of coronavirus expertise, was called in to test the four survivors. These produced a remarkable finding: while none had tested positive for Sars, all four had antibodies against another, unknown Sars-like coronavirus.

Furthermore, two patients who recovered and went home showed greater levels of antibodies than two still in hospital, one of whom later died.

Researchers in China have been unable to find any news reports of this new Sars-like coronavirus and the three deaths. There appears to have been a media blackout. It is, however, possible to piece together what happened in the Kunming hospital from a master's thesis by a young medic called Li Xu. His supervisor was Professor Qian Chuanyun, who worked in the emergency department that treated the men. Other vital details, including the results of the antibody tests, were found in a PhD paper by a student of the director of the Chinese Centre for Disease Control and Prevention.

Li's thesis was unable to say what exactly killed the three miners, but indicated that the most likely cause was a Sars-like coronavirus from a bat.

"This makes the research of the bats in the mine where the six miners worked and later suffered from severe pneumonia caused by unknown virus a significant research topic," Li concluded.

That research was already under way — led by the Wuhan virologist who became known as "Bat Woman" — and it adds to the mystery.

TWO

The bat heroine

The Bat Woman heralded as a hero in China

For historians of the Chinese Communist Party, Wuhan is where the 72-year-old Mao Tse-tung took a symbolic swim in the Yangtze River in 1966 before launching the Cultural Revolution. For generations born since that disastrous era, the modern industrial city is the crossroads of China's high-speed rail network and was the centre of the Covid-19 pandemic.

For science, however, Wuhan is the centre for research into the coronavirus in bats. Shi Zhengli, nicknamed "Bat Woman" by her colleagues, is heralded as a hero in China and in scientific communities across the world.

But the bats in Yunnan are 1,000 miles from her laboratory, and one of the most extraordinary coincidences of the Covid-19 pandemic is that ground zero happened to be in Wuhan, the world centre for the study and storage of the types of coronavirus the city's own scientists believe caused the

outbreak.

Coronaviruses are a group of pathogens that sometimes have the potential to leap species from animals to humans and appear to have a crown — or corona — of spikes when viewed under a microscope.

Before Covid-19, six types of coronavirus were known to infect humans but mostly they caused mild respiratory symptoms such as the common cold.

The first outbreak of Sars — now known as Sars-Cov-1 to distinguish it from Sars-Cov-2, the virus that causes Covid-19 — is one of the deadly exceptions. It emerged in Guangdong, southern China, in November 2002 and infected 8,096 people in 29 countries. It caused severe pneumonia in some and killed 774 people before petering out eight months later.

A race began to find out how a coronavirus had mutated into something so deadly and jumped from animals to humans. The initial prime suspects were masked palm civet cats, a delicacy in some parts of China. But suspicion shifted to bats, which had also been linked to other deadly viruses such as

rabies. Perhaps they were the primary source and civets were just intermediaries that they infected.



Shi and her team from the WIV began hunting among bat colonies in caves in southern China in 2004. In 2012 they were in the midst of a five-year research project centred on caves in remote mountains southwest of Kunming when the call came to investigate the incident in the copper mine about 200 miles away.

They were joined by local disease control experts when they descended into the mine that August with protective equipment and bat-catching nets.

Over the next year, the scientists took faecal samples from 276 bats. The samples were stored at minus 80C in a special solution and dispatched to the Wuhan institute, where molecular studies and analysis were conducted.

These showed that exactly half the bats carried coronaviruses and several were carrying more than one virus at a time — with the potential to cause a dangerous new mix of pathogens.

The results were reported in a scientific paper entitled "Coexistence of multiple coronaviruses in several bat colonies in an abandoned mineshaft

" co-authored by Shi and her fellow scientists in 2016.

Notably, the paper makes no mention of why the study had been carried out: the miners, their pneumonia and the deaths of three of them.

The paper does state, however, that of the 152 genetic sequences of coronavirus found in the six species of bats in the mineshaft, two were of the type that had caused Sars. One is classified as a "new strain" of Sars and labelled RaBtCoV/4991. It was found in a *Rhinolophus affinis*, commonly known as a horseshoe bat. The towering significance of RaBtCov/4991 would not be fully understood for seven years.

THREE

An ordinary coronavirus

The top security lab at the centre of Wuhan

A new facility was taking shape on the virology institute campus on the west side of the Yangtze in Wuhan. Built by a contractor for the People's Liberation Army under strict secrecy, a top-security laboratory for handling deadly human pathogens was unveiled in 2017.

There were 31 such laboratories in the world at the time but this was China's first. The new lab had been certified by the Chinese authorities as "biosafety level 4", or BSL-4, the highest. But it was raising eyebrows internationally.

Scientists and biosafety experts were concerned that the closed nature of the Chinese state and the emphasis on hierarchy would prove incompatible with running such a dangerous facility.

"Diversity of viewpoint, flat structures where everyone feels free to speak up and openness of information are important," Tim Trevan, a consultant in biosecurity, told the science magazine Nature when it opened.

Laboratory leaks are not uncommon. In the past, ebola and the fatal bat disease Marburg, which kills nine out of 10 people infected, have escaped from BSL-4 laboratories in the US. American health authorities recorded 749 laboratory safety breaches in the six years to 2015. Indeed, several people were infected by Sars in 2004 after an accident at China's National Institute of Virology in Beijing. The need for a secure facility in Wuhan was obvious, however. Shi and her team had already collected hundreds of samples of the coronavirus — including RaBtCov/4991 — from their work on bats across Yunnan province, and they were running controversial experiments to find out how they might mutate to become more infectious to humans.

This "gain-of-function" work is described in papers released by the WIV between 2015 and 2017, scientists say. Shi's team combined snippets of different coronaviruses to see if they could be made more transmissible in what they called "virus infectivity experiments".

It was controversial because it had the potential to turn bat coronaviruses into human pathogens capable of causing a pandemic. In 2014 the US government issued a ban on funding any endeavour to make a virus more contagious.

Shi's team argued that gain-of-function work increased its understanding of how an ordinary coronavirus might one day transform into a killer such as Sars.

Others disagreed. "The debate is whether in fact you learn more by helping to develop vaccines or even drugs by replicating a more virulent virus than currently exists, versus not doing that," explained Deenan Pillay, professor of virology at University College London. "And I think the consensus became that the risk was too much."

In January 2018 the US embassy in Beijing took the unusual step of sending scientists with diplomatic status to Wuhan to find out what was going on in the institute's new biosafety laboratories. They met Shi and members of her team.

Details of the diplomats' findings have been found in US diplomatic cables that were leaked to The

Washington Post and others. "Most importantly," states a cable from January 19, 2018, "the researchers also showed that various Sars-like coronaviruses can interact with ACE2, the human receptor identified for Sars-coronavirus. This finding strongly suggests that Sars-like coronaviruses from bats can be transmitted to humans to cause Sars-like diseases."

The Americans were evidently worried about safety. "During interactions with scientists at the WIV laboratory, they noted the new lab has a serious shortage of appropriately trained technicians and investigators needed to safely operate this high-containment laboratory," the cable added. Shi was in a conference in Shanghai on Monday December 30, 2019, when she received a call to say there was a new coronavirus on the loose — and it had surfaced in Wuhan, of all places. Since her work had established that such viruses were most likely to originate in south China, she found the news puzzling and extremely worrying. "I wondered if [the local health authority] got it wrong," she told the Scientific American magazine in a rare interview this year. "I had never expected this kind of thing to happen in Wuhan, in central China."

One of her initial thoughts, as she prepared to return immediately to analyse the virus, was "Could they [the new coronaviruses] have come from our lab?". It was a natural anxiety, although she said she was later able to dismiss it after examining the lab's records.

FOUR

Patient Zero

When did Covid-19 really start?

The precise point at which Covid-19 erupted in Wuhan may never be known. Various theories have been discredited.

A study by Harvard University claimed the virus may have started last August. It relied on satellite images in which the car parks of selected Wuhan hospitals looked busier. However, the study's detractors have pointed to discrepancies in the evidence.

There is also a theory — propagated by the Chinese media — that the virus may have been introduced into the country by foreign athletes competing in the Military World Games in Wuhan last October. They included the French former world champion pentathlete Élodie Clouvel and the Italian Olympic gold medallist fencer Matteo Tagliariol, who were laid low by fever during the Games.

Few of the athletes have been tested to find out whether they carry antibodies to Covid-19, apart from the Swedish team. Melina Westerberg, a Swedish pentathlete, has revealed that while many of her teammates were sick during the Games, they tested negative. "It was just a coincidence," she said. It is possible that the virus did start patchily at around the time of the Military World Games. Yu Chuanhua, an epidemiology professor at Wuhan University, has told Chinese media that one man was admitted to hospital on September 29 with Covid-19-like symptoms but it is impossible now to show whether he had the virus because he died. There were two more suspected early carriers of the virus from November 14 and 21 in the city's 47,000-strong database of cases, but they are unconfirmed. Probably the first confirmed case was a 70-year-old man with Alzheimer's disease, whose family had told researchers from Wuhan Jinyintan Hospital that his symptoms had begun on December 1. From that point it accelerated to about 60 identifiable cases by December 20, according to government research data reported in the South China Morning Post. However, it would not be until a week later that Dr Zhang Jixian, of the Hospital of Integrated Traditional Chinese and Western Medicine in Hubei province, became the first person to report a suspected outbreak to the provincial government. By then it had already spread as far as Europe, probably via regular flights from Wuhan. The virus may have been in Italy as early as December 18. The country's National Institute of Health reported finding traces of Covid-19 in sewage water collected in Milan and Turin on that date.

It was certainly in France, as a man called Amirouche Hammar was admitted to Jean-Verdier hospital in Paris on December 27. He had unknown respiratory pneumonia and was coughing blood. His samples later revealed Covid-19. His wife, who had a slight cough, worked at a supermarket used by shoppers leaving Charles de Gaulle airport, where there were direct flights from Wuhan.

Early cases

First Covid-19 cases recorded in Wuhan that were linked to the Huanan seafood market and not linked, by the day that symptoms were first reported

Dec152229Jan0510152025303540MarketclosedJan 1

Chart: The Times and The Sunday Times • Source: The New England Journal of Medicine

In Wuhan itself, the first cluster of cases included traders and shoppers at the <u>Huanan seafood market</u>, a maze of small trading stores opening on to crowded alleys in the centre of the city. Despite its name, the market also sold meat and vegetables, and there was an exotic wildlife section in the west of the market.

On January 1 the Huanan market was closed and scientists found 33 coronavirus samples, nearly all in the area of the market where wild animals were sold.

It seemed like an open and shut case. When the results were released later that month, the Chinese state news agency Xinhua reported: "The results suggest that the novel coronavirus outbreak is highly relevant to the trading of wild animals."

However, an early study published in The Lancet made clear that of the 41 patients who contracted Covid-19 in Wuhan only 27 had been "exposed" to the market. A third had no connection to the market, including the study's "patient zero", who fell ill on December 1.

Months later George Gao, the director of the Chinese Centre for Disease Control and Prevention, revealed that all the samples taken from animals at the market had tested negative for the virus and that those found had been from sewage or other environmental sources. The Chinese health authorities are now working on the theory that the market helped spread the disease but was not where it originated.

FIVE

Mapping the virus

China warns world of deadly new strain

On December 31, the day Shi returned to the WIV to begin work identifying the new coronavirus, the Chinese authorities decided it was time to tell the world there was potentially a problem.

The World Health Organisation (WHO) was notified that a number of people had been struck down with pneumonia but the cause was not stated. On the same day, the Wuhan health authority put out a bland public statement reporting 27 cases of flu-like infection and urged people to seek medical attention if they fell ill. Neither statement indicated that the new illness could be transmitted between humans or that the likely source was already known: a coronavirus.

By the second week in January, desperate scenes were unfolding at Wuhan hospitals. Hopelessly ill-prepared and ill-equipped staff were forced to make life-and-death calls about who they could treat. Within a few days, the lack of beds, equipment and staff made the decisions for them.

Shi's team managed to identify five cases of the coronavirus from samples taken from patients at

Wuhan Jinyintan Hospital using a technique to amplify the virus's genetic material. The samples were sent to another lab, which completed the whole genomic sequence.

However, the sequence would not be passed to the WHO until January 12 and China would not admit there had been human-to-human transmission until January 20, despite sitting on evidence the virus had been passed to medics.

One of Shi's other urgent tasks was to check through her laboratory's records to see if any errors, particularly with disposal of hazardous materials, could have caused a leak from the premises. She spoke of her relief to discover that the sequences for the new virus were not an exact match with the samples her team had brought back from the bat caves. "That really took a load off my mind," she told the Scientific American, "I had not slept a wink for days."

SIX

RaTG13

From bat cave to lab

She then set about writing a paper describing the new coronavirus to the world for the first time. Published in Nature on February 3 and entitled "A pneumonia outbreak associated with a new coronavirus of probable bat origin", the document was groundbreaking.

It set out a full genomic description of the Covid-19 virus and revealed that the WIV had in storage the closest known relative of the virus, which it had taken from a bat. The sample was named RaTG13. According to the paper, it is a 96.2% match to the Covid-19 virus and they share a common lineage distinct from other Sars-type coronaviruses. The paper concludes that this close likeness "provides evidence" that Covid-19 "may have originated in bats".

In other words, RaTG13 was the biggest lead available as to the origin of Covid-19. It was therefore surprising that the paper gave only scant detail about the history of the virus sample, stating merely that it was taken from a *Rhinolophus affinis* bat in Yunnan province in 2013 — hence the "Ra" and the 13

Inquiries have established, however, that RaTG13 is almost certainly the coronavirus discovered in the abandoned mine in 2013, which had been named RaBtCoV/4991 in the institute's earlier scientific paper. For some reason, Shi and her team appear to have renamed it.

The clearest evidence is in a database of bat viruses published by the Chinese Academy of Sciences — the parent body of the WIV — which lists RaTG13 and the mine sample as the same entity. It says it was discovered on July 24, 2013, as part of a collection of coronaviruses that were described in the 2016 paper on the abandoned mine.

In fact, researchers in India and Austria have compared the partial genome of the mine sample that was published in the 2016 paper and found it is a 100% match with the same sequence for RaTG13. The same partial sequence for the mine sample is a 98.7% match with the Covid-19 virus.

Peter Daszak, a close collaborator with the Wuhan institute, who has worked with Shi's team hunting down viruses for 15 years, has confirmed to The Sunday Times that RaTG13 was the sample found in the mine. He said there was no significance in the renaming. "The conspiracy folks are saying there's something suspicious about the change in name, but the world has changed in six years — the coding system has changed," he said.

He recalled: "It was just one of the 16,000 bats we sampled. It was a faecal sample, we put it in a tube, put it in liquid nitrogen, took it back to the lab. We sequenced a short fragment."

In 2013 the Wuhan team had run the sample through a polymerase chain reaction process to amplify the amount of genetic material so it could be studied, Daszak said. But it did no more work on it until the Covid-19 outbreak because it had not been a close match to Sars.

Other scientists find the initial indifference about a new strain of the coronavirus hard to understand.

Nikolai Petrovsky, professor of medicine at Flinders University in Adelaide, South Australia, said it was "simply not credible" that the WIV would have failed to carry out any further analysis on RaBtCoV/4991, especially as it had been linked to the deaths of three miners.

"If you really thought you had a novel virus that had caused an outbreak that killed humans then there is nothing you wouldn't do — given that was their whole reason for being [there] — to get to the bottom of that, even if that meant exhausting the sample and then going back to get more," he said.

"I would expect people to be as clear as they can be about the history of the isolates of their sequencing," said Professor Wendy Barclay, head of Imperial College London's infectious disease department and a member of the UK government's Sage advisory committee. "Most of us would have reported the entire history of the isolate, [back] to where all that came from, at the time."

According to Daszak, the mine sample had been stored in Wuhan for six years. Its scientists "went back to that sample in 2020, in early January or maybe even at the end of last year, I don't know. They tried to get full genome sequencing, which is important to find out the whole diversity of the viral genome."

However, after sequencing the full genome for RaTG13 the lab's sample of the virus disintegrated, he said. "I think they tried to culture it but they were unable to, so that sample, I think, has gone." In recent weeks, academics are said to have written to Nature asking for the WIV to write an erratum clarifying the sample's provenance, but the Chinese lab has maintained a stony silence. A spokesman for Nature said: "Concerns relating to this paper have been brought to Nature's attention and are being considered at the moment. We cannot comment further at this time."

SEVEN

Ski holidays

The contagion spread through Europe

The director of the WIV, Wang Yanyi, gave an interview in May in which she described suggestions that Covid-19 might have leaked from the lab as "pure fabrication". She said that the institute managed to sequence the genome of RaTG13 but had not been able to return it to a live virus. "Thus, there is no possibility of us leaking RaTG13," she said.

Shi's interview with the Scientific American mentions the discovery of a coronavirus that 96% matches the Covid-19 virus, and has a reference to the miners dying in a cave she investigated. However, the two things are not linked and Shi downplays the significance of the miners' deaths by claiming they succumbed to a fungus.

Experts consulted by this newspaper thought it was significant the men had tested positive for antibodies against Sars. Professor Martin Hibberd, a professor of emerging infectious diseases at the London School of Hygiene & Tropical Medicine, said the antibodies provided "a good clue" that the cause of death was "a proper coronavirus", which "most likely" was Sars-related.

"[RaTG13] is so similar to all the other Sars coronaviruses and so I'd imagine all of that family can cause similar disease, so it makes good sense to me that if the miners caught it they would end up with something that looks similar."

On January 23 Wuhan became the first city in the world to go into lockdown and it would later suffer nearly 4,000 deaths, according to official figures that some people believe are too low.

Britain's first official cases — a Chinese student studying in York and a relative — would not emerge for another week, but it is highly likely the virus was already in the country. There were 901 flights from China to the UK between December 1, when the first known patient fell ill, and January 24. Of those, 23 flights brought thousands of passengers directly from Wuhan to Heathrow.

There is also evidence that Britons were bringing back the virus from Europe. Professor Tim Spector, an epidemiologist at King's College London, who runs the Covid Symptom Study app, says he was

contacted by up to 500 people who had returned to the UK between Christmas and January with symptoms.

Many were returning from ski resorts, notably in Austria. In April, 42% of residents in the town of Ischgl were found to have antibodies. "I was interested in the Austrian surveys done in Tyrol because I was quite struck by the stories of all the people that came back from Austrian ski holidays in January, predominantly, feeling ill. It was very convincing because a lot of the stories were the same from different people," he said.

EIGHT

The investigation

How did this happen?

The origin of Covid-19 is one of the most pressing questions facing humanity. Scientists worldwide are trying to understand how it evolved, which could help stop such a crisis happening again.

The suggestion that well-intentioned scientists may have introduced Covid-19 to their own city is vehemently denied by the WIV, and its work on the origin of the virus has become an x-rated topic in China. Its leadership has taken strict control of new studies and information about where the virus may have come from.

A directive from the education ministry's science and technology department in the spring stipulated that such work had to be read by a taskforce directly under the state council — comprising China's president, Xi Jinping, and top ministers — before it can be published.

The secrecy has only increased as the origin of Covid-19 has become politicised as a weapon of aggressive foreign policy. President Donald Trump has described the virus as a "kung flu" and has delighted in claiming it is a Chinese disease. Scientists are dismayed and fear China will retreat further into its shell.

Professor Richard Ebright, of Rutgers University's Waksman Institute of Microbiology in New Jersey, believes there is now less than a 50:50 chance China will allow a transparent investigation into the origin of the pandemic. "That's unfortunate," he said. "And that largely reflects the poor handling of the matter by the US president, who chose to push this in a way that made it unlikely that there could be an open investigation."

Over the next few days, WHO scientists will be allowed to fly into China to begin an investigation into the origins of the virus after two months of negotiations. Many experts such as Daszak believe the source of the virus will be found in a bat in the south of China.

"It didn't emerge in the market, it emerged somewhere else," said Daszak. He said the "best guess right now" is that the virus started within a "cluster" on the Chinese border that includes the area where RaTG13 was found and an area just south of the mineshaft, where another bat pathogen with a 93% likeness to Covid-19 was discovered recently.

As for how the virus travelled to Wuhan, Daszak said: "Fair assumption is that it spilt into animals in southern China and was then shipped in, via infected people, or animals associated with trade, to Wuhan."

But how could such an infectious virus avoid causing a single noticeable outbreak during the 1,000-mile journey from Yunnan to the city?

Hibberd said it was feasible the virus could have travelled in an animal such as a pangolin, which passed it to a human wildlife trader when it was being transported for sale in the market. "Maybe a young guy moves a pangolin and sold it on and may have had a mild infection but didn't have any disease," he said. "It's not impossible for that scenario to happen."

On the other hand, Hibberd believes it is possible the virus could have been brought back by one of the scientists, who were frequent travellers between the caves and Wuhan. "If you imagine these researchers who probably did this are students — who are probably quite young — it's entirely possible that a researcher might become infected through the study of bats."

The WIV was not the only body of scientists from the city delving into virus-laden caves. On December 10 last year a Chinese state media outlet published an extraordinary video lionising the bravery of a researcher called Tian Junhua, who is said to have caught 10,000 bats in studies for Wuhan's disease control centre.

Tian admitted that he knew little about bats when he first started visiting the caves eight years ago, and once had to isolate himself for 14 days after being showered with bat urine while wearing inadequate protection. On occasions bat blood spilt onto his hands but he says he has never been infected. The young researcher aroused suspicion because one of the offices of the disease control centre is about 300 yards from the Huanan seafood market. He has refused to talk to reporters, but his friends have firmly denied that he was "patient zero".

The final and trickiest question for the WHO inspectors is whether the virus might have <u>escaped from a laboratory</u> in Wuhan. Is it possible, for example, that RaTG13 or a similar virus turned into Covid-19 and then leaked into the population after infecting one of the scientists at the Wuhan institute? This seriously divides the experts. The Australian virologist Edward Holmes has estimated that RaTG13 would take up to 50 years to evolve the extra 4% that would make it a 100% match with the Covid-19 virus. Hibberd is slightly less conservative and believes it might take less than 20 years to morph naturally into the virus driving the current pandemic.

But others say such arguments are based on the assumption the virus develops at a constant rate, along lines that have been monitored over the past six months. "That is not a valid assumption," said Ebright. "When a virus changes hosts and adapts to a new host the rate of evolutionary change is much higher. And so it is possible that RaTG13, particularly if it entered humans prior to November 2019, may have undergone adaptation in humans at a rate that would allow it to give rise to Sars-Cov-2. I think that is a distinct possibility."

Ebright believes an even more controversial theory should not be ruled out. "It also, of course, is a distinct possibility that work done in the laboratory on RaTG13 may have resulted in artificial inlaboratory adaptation that erased those three to five decades of evolutionary distance." It is a view Hibberd does not believe is possible. "Sars-Cov-2 and RaTG13 are not the same virus and I don't think you can easily manipulate one into the other. It seems exceptionally difficult," he said. Ebright alleges, however, that the type of work required to create Covid-19 from RaTG13 was "identical" to work the laboratory had done in the past. "The very same techniques, the very same experimental strategies using RaTG13 as the starting point, would yield a virus essentially identical to Sars-Cov-2."

The Sunday Times put a series of questions to the WIV. They included why it had failed for months to acknowledge the closest match to the Covid-19 virus was found in a mine where people had died from a coronavirus-like illness. The questions were met with silence.