Where did COVID come from? Five mysteries that remain

In the wake of the World Health Organization's investigation, there are still key questions about when, where and how the pandemic began.

WHO investigators visit sites in China as part of their probe into the pandemic's origins.Credit: Hector Retemal/AFP/Getty

Following a month-long fact-finding mission in China, a World Health Organization (WHO) team investigating

the origins of the COVID-19 pandemic concluded that the virus probably originated in bats and passed to people through an intermediate animal. But fundamental questions remain about when, where and how SARS-CoV-2 first infected people.

As the international WHO team finalizes a report of its findings, which is expected next week, *Nature* speaks to four of the investigators about what they still want to know.

Was the virus circulating in Wuhan before the first known cases?

To trace the virus's origin, it's crucial to pin down exactly when the first cases occurred in people. The WHO team established that the first person known to have COVID-19 was an office worker in Wuhan with no recent travel history, who began showing symptoms on 8 December 2019, says Peter Ben Embarek, a food-

safety scientist at the WHO in Geneva, Switzerland, who led the investigation. But the virus was probably spreading in the city before that, because it was well-established by later that month, he says.

Yet evidence of earlier spread has proved elusive. Researchers in China conducted an extensive survey of patient reports from hospitals in Wuhan made between October and December 2019, and identified fewer than 100 people who had symptoms of COVID-19. They then tested the blood of 67 of those people for antibodies generated by past infection with SARS-CoV-2, but found none. This suggests there wasn't a large cluster of infections before December, or an unusual spike in deaths in the surrounding province of Hubei.

But Ben Embarek says the analysis should be repeated using less restrictive symptom criteria, to make sure that researchers spot all potential COVID-19 cases.

Scientists in China should also search for evidence of past infection in some 200,000 archived samples currently held at the Wuhan Blood Center and in other regions across China, says team member Dominic Dwyer, a medical virologist at New South Wales Health Pathology in Sydney, Australia. This would show whether the virus was spreading in the general population in China — not just among people who went to health facilities — before December 2019.

Some scientists not involved in the WHO investigation have already looked at blood-bank samples taken up to a year before the pandemic, in Guangzhou, southern China. (Close relatives of SARS-CoV-2 have been found in bats and pangolins in southern China.) Some of the samples tested positive for antibodies against SARS-CoV-2, but Ian Lipkin, an infectious-diseases researcher at Columbia University in New York City, who worked on the analysis, says the test was not specific enough to say for sure that the antibodies weren't caused by infection with other viruses. "There is a lot of laboratory work that needs to be done that

hasn't been done," says Lipkin, who also wants to know whether there are autopsy samples from before December 2019 that could be studied for traces of viral genetic material.

Was the virus spreading in people outside China before December 2019?

Answering this question is also key to establishing the timeline of the first COVID-19 cases. Previously, researchers in Europe have reported[1,2,3] finding antibodies against SARS-CoV-2 in samples taken at blood banks from November 2019 onwards.

Ben Embarek says this doesn't necessarily suggest the virus originated in Europe, but supports the idea that it was spreading in Wuhan before the first known cases. "Wuhan at that time was a very well-connected international city with direct flights to the entire planet on a daily basis. So if it was circulating in Wuhan, it

could easily have been brought to other parts of the world through travellers, and circulating again, undetected, in different regions," he says.

Still, he recommends that the blood samples from Europe be retested to confirm that they indicate cases of COVID-19. Some of them, from Italy and France, are already being reanalysed, he says.

What was the role of the Huanan market?

The intermediate animal that passed the virus from bats to people has not been identified, but researchers think it might be a wild species that is sold as food in 'wet markets', which typically sell live animals. Early in the pandemic, investigators homed in on the Huanan Seafood Market in Wuhan, because it sold fresh and frozen animals and many of the earliest infections were in people who had visited it. But the lead went cold when other early cases were found that were not

associated with the market. Viral material was identified in drains and sewage at the market, but none was found on any animal carcasses.

Still, the market is the only place where a large number of the people infected at the start of the outbreak were exposed to meat and animals. It's important to establish how the virus got into the market and whether it was on an animal, says WHO team member Hung Nguyen-Viet, an environment and food-safety researcher at the International Livestock Research Institute in Nairobi.

Nguyen-Viet says the team identified ten stalls selling wildlife, either wild or farmed, that could have carried the virus into the market from farms in southern China. Some wild animals sold for meat, such as rabbits and ferret-badgers, are susceptible to SARS-CoV-2 or the related virus that causes severe acute respiratory syndrome (SARS).

WHO team member Peter Daszak, president of the non-profit research organization Ecohealth Alliance in New

York City, says the farms should be investigated to see whether there were infections in the animals or among workers. He also wants to know what animals were sold in other Wuhan markets. When the team interviewed the first person known to have COVID-19, he mentioned that his parents had visited a local community wet market, says Daszak.

Did frozen wild-animal meat have a role in the early spread of the virus?

The WHO team concluded that it's most likely the virus jumped from live animals to people, but Ben Embarek says it is possible the virus entered the Huanan market through infected frozen wild animals from farms in southern China, and then sparked an outbreak. Daszak wonders whether frozen ferret-badgers sold at the market could have carried the virus. "These were carcasses skinned at the market, not just cubes of meat in a plastic packet," he says.

Although researchers in China have also isolated viral RNA from the packaging of imported frozen fish[4], Ben Embarek says the WHO team concluded that these goods were not likely to be the route of the virus's first arrival in Wuhan.

Lipkin says there is no evidence that the virus entered the market through infected frozen wild animals. It could have just as easily been brought in by infected people who handled wild animals, he says.

Was the virus circulating in animals in China before the pandemic?

To establish which animal passed the virus to people, researchers need to find evidence of the virus in that species. Researchers in China tested some 30,000 wild,

farmed and domestic animals in 2019 and 2020 but found no evidence of active or past SARS-CoV-2 infection, except in some cats in Wuhan in March 2020[5].

However, Ben Embarek says these surveys were not representative of China's overall animal population, and that many more animals need to be tested for traces of infection, particularly on wildlife farms. "The amount of testing that's been done is not sufficient to say, in any way, that wildlife farms were not carrying the virus," says Daszak.

The explosive way in which the outbreak took off in Wuhan in December suggests that the virus was probably introduced once, through the wildlife trade, says Daszak. He says future testing should focus on farmed wild animals.

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