



WHO investigators visit sites in China as part of their probe into the pandemic's origins.

WHERE DID COVID COME FROM? FIVE MYSTERIES THAT REMAIN

In the wake of a World Health Organization investigation, scientists still have questions.

By Smriti Mallapaty

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 team finalizes a report on its findings, *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, China, 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 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, 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 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," 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 that the virus originated in Europe, but that it does support the idea that the virus 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 are already being reanalysed, he says.

What was the role of the Huanan Seafood 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 reported 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.

HECTOR RETEMAL/AFP/GETTY

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.

WHO team member Peter Daszak, president of the non-profit research organization Ecohealth Alliance in New York City, says that the farms should be investigated to see whether there were infections in the animals or among workers. 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 that the virus entered the Huanan market through infected frozen wild animals from farms in southern China, and then sparked an outbreak.

Although researchers in China have isolated viral RNA from the packaging of imported frozen fish⁴, 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 had 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 2020⁵.

However, Ben Embarek says that 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.

1. Carrat, F. et al. *Eur. J. Epidemiol.* <https://doi.org/10.1007/s10654-020-00716-2> (2021).

2. Amendola, A. et al. *Emerg. Infect. Dis.* **27**, 648–650 (2021).

3. Apolone, G. et al. *Tumori J.* <https://doi.org/10.1177/0300891620974755> (2020).

4. Liu, P. et al. *Biosaf. Health* **2**, 199–201 (2020).

5. Zhang, Q. et al. *Emerg. Microbes. Infect.* **9**, 2013–2019 (2020).

Q&A



Deducing which pandemic policies work best

Since the start of the COVID-19 pandemic, thousands of scientists and volunteers have been tracking the interventions that governments have adopted to curb viral spread — from closing restaurants to mandating face masks. They hope to deduce which policies are most effective. At a conference this month, scientists involved in 50 tracking databases discussed their efforts. Peter Klimek, a mathematical physicist at the Complexity Science Hub (CSH) Vienna and the Medical University of Vienna, who is involved in the CSH's tracking project, explains the challenge.

How much work has gone into these trackers?

In our tracker, more than 40 volunteers and scientists have been involved in assigning codes to more than 11,000 measures in 57 countries. Other efforts, such as the CoronaNet consortium and the government response tracker run by the University of Oxford, UK, each have hundreds of volunteers and researchers. Some tracking efforts have received funding, but most are struggling owing to a lack of money, and some have had to stop. It's also a challenge to keep volunteers motivated.

How have the trackers been used?

We advise the Austrian government on policy measures to contain the spread of coronavirus and avoid health-system overload. When we're asked questions, such as why some countries have much lower case numbers than others, the first places we look are the databases tracking government interventions. We still don't know what is the best way to plug the data from the tracking systems into mathematical models. But the trackers are a unique treasure trove that we can use to make epidemiological modelling a data-driven science and to prepare for the next pandemic.

What have they told us so far?

When many countries applied various control measures simultaneously, we knew very little about the effects of government interventions. When more data became available, we found that curfews, cancellations of small gatherings, and closures of schools, shops and restaurants

were among the most effective policies (N. Haug et al. *Nature Human Behav.* **4**, 1303–1312; 2020).

But there is less agreement, when analysing different trackers, on how to rank these measures. For example, it is not certain that highly restrictive measures are automatically more effective than a smart mix of comparatively modest restrictions implemented with better timing.

Why is it hard to estimate the effects of interventions?

It is difficult to untangle the effects of any given measure from those of other policy interventions. There are many statistical approaches to disentangling relationships in complex systems, but none of them is perfect. And sociocultural factors can make social distancing more effective in one country than in another.

The effects of interventions also change over time. The situation has become more complicated as government interventions have become more diverse, and as people adhere less willingly to restrictions.

Why not combine the trackers?

Each tracker has its own perspectives. Some do integrate data from different databases, including one maintained by the World Health Organization. But this comes at the expense of some of the granularity that the original databases might have had. From the perspective of data quality and reproducibility of results, merging trackers into a super-database isn't a good idea.

How might this sort of work change in the future?

There is growing societal and political pressure to understand hypothetical scenarios: how not having implemented a certain measure might have changed the course of the pandemic. For example, was it really necessary to close schools? Or will the social and economic costs turn out to have outweighed the health-related benefits? Without reliable tracker data, there will be no solid evidence to answer such questions.

Interview by Quirin Schiermeier

This interview has been edited for length and clarity.