

HEALTH

Arizona scientist finds 'strong evidence' on how pandemic began, reviving debate on virus origins

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A prominent Arizona scientist's assertion that a wet market in China — and not a lab leak — is the likely ground zero of the COVID-19 pandemic has reignited a long-running international debate.

Michael Worobey's research, published on Nov. 18 in the journal *Science*, shows that a lab leak "is almost off the table," as the origin of the pandemic, he said this week. Rather, he believes it occurred after a natural jump from animal to human, according to his research.

His investigation, conducted over several months with the help of translators, points to a female seafood vendor at the Huanan wet market near Wuhan as the earliest known case of COVID-19. It was not the 41-year-old accountant from Wuhan that China and the World Health Organization had previously identified as the first known COVID-19 case, he found.

The origins of the virus that causes COVID-19 in humans has been a source of controversy from the start. Officials pointed to the animals at the market, but another hypothesis, that the virus had existed inside a Chinese research lab and then released — accidentally or intentionally — has persisted.

Aside from the political implications of the source, scientists including Worobey have called for a more transparent investigation, saying that understanding the pandemic's origin is the key to mitigating future outbreaks.

The new research found that Chinese disease surveillance did not identify an earlier case that "provides strong evidence of a live-animal market origin of the pandemic," Worobey's article states.

Worobey was always open to the possibility of a lab leak as the genesis of the first human COVID-19 infection and was one of 18 scientists who signed an open letter published on May 14 in the journal *Science*, calling for a transparent, data-driven investigation into the origins of COVID-19.

Knowing how COVID-19 emerged is critical for informing global strategies to reduce the risk of future outbreaks, the scientists wrote.

"I did very seriously consider the lab leak idea," Worobey said in an interview with *The Arizona Republic* this week. "But as I followed the evidence, everything points away from that and decisively to a wet market origin."

Worobey, an infectious disease expert who is head of the University of Arizona's Department of Ecology and Evolutionary Biology, has been the subject of a flurry of media attention and social media discussions since the article was published, relaunching the public debate over how the SARS-CoV-2 virus first infected humans.

Some of the reaction has been critical, and skeptics of Worobey's theory have called for further investigation.

Research into the origins of the pandemic is ongoing, Worobey emphasized.

"There is more work to do, and I am working on additional analyses now," he said.

It's unlikely the seafood vendor was 'patient zero' of the pandemic

Findings in his *Science* article include "compelling evidence" that community transmission started at the Huanan market near Wuhan, said Worobey, who is well-known in the science community for epidemiological detective work, has led groundbreaking research into the history of the HIV/AIDS outbreak.

"Although there was quite a bit of hand-wringing on Twitter of lab leak proponents, there was nothing brought up that is substantial," he said, referring to feedback on the article. "And so I really think it is pointing to this particular market as the likely site of the origin."

The female seafood vendor identified in the paper, Wei Guixian, became ill on Dec. 10 and was likely infected via respiratory transmission from an animal host, Worobey said. His original article said Dec. 11.

"The seafood vendor got sick on Dec 10 not 11," Worobey wrote in an email this week.

"This will be corrected in the print version of the paper. I only pinned this down after the early release version was posted."

He noted that his research does not confirm that Guixian was 'patient zero' of the pandemic — that is, the very first case of COVID-19 ever in a human — but rather that she is the first known case researchers can identify, he said.

Since only about 7% of those infected with the novel coronavirus end up in the hospital as the vendor did, it's unlikely she was the very first case, he said, although she may have been among the very first.

"The index case was most likely one of the 93% who never required hospitalization and indeed could have been any of hundreds of workers who had even brief contact with infected live mammals," the article states.

In addition, Worobey noticed a discrepancy related to a crucial detail about the timing of the "earliest" known COVID-19 case outlined in a joint report completed by China and the World Health Organization.

Based on an interview with that patient, a 41-year-old with no connections to the wet market, Worobey realized that his symptoms didn't set in until December 16, almost a full week later than researchers initially thought. Worobey found out that the man's Dec. 8 illness was a dental problem related to baby teeth retained into adulthood.

"This is corroborated by hospital records and a scientific paper," Worobey writes in his study. "This indicates that he was infected through community transmission after the virus had begun spreading from Huanan Market."

A raccoon dog could have transmitted the virus to humans

While Worobey is not certain in what kind of animal host the novel coronavirus originated, raccoon dogs are at the top of his list, he said, because caged raccoon dogs were sold at Huanan wet market and they can transmit the virus very efficiently.

Raccoon dogs, which are small mammals that sport the characteristic eye mask fur pattern of raccoons but are found in the same family as dogs and other canines, are a species of concern for scientists studying zoonotic diseases, according to a journal article in

Parasitology Research from the University of Veterinary Medicine in Vienna.

Raccoon dogs are highly susceptible to coronaviruses and may have been an intermediate source of the SARS outbreak in 2004. Based on that context, Worobey believes it likely that history may have repeated itself with SARS-CoV-2.

The animal to human transmission is "a lot more complex" than classifying it as an example of human encroachment fostering zoonotic disease, Worobey said.

"One thing that might have played a role is the government encouraging farming of some of these species as a way for poor areas to dig themselves out of poverty," he said. "It's not simply a case that we're cutting down rainforests and this pandemic happened."

Not all scientists are convinced that Worobey's paper proves the wet market is where the pandemic began.

"This analysis is interesting and worth doing, but it has all of these limitations that are not being clearly explained in the paper," said Alina Chan, a postdoctoral researcher at The Broad Institute of MIT and Harvard, who also signed the May 14 letter calling for an investigation into the pandemic's origins. "I think that what he's (Worobey) doing is only one piece of a huge puzzle."

Chan, who has consistently called for further investigation into a lab leak, said there are three main reasons to investigate the origins of the novel coronavirus: to create an informed strategy to prevent future pandemics; to set a precedent to hold labs and researchers accountable; and to provide a sense of closure to the families and loved ones of the more than 5 million people worldwide who have died of COVID-19 so far.

A lab leak origin is plausible, Chan has long maintained. Among other indicators the first COVID-19 cases were identified in the Wuhan area and scientists at China's Wuhan Institute of Virology study novel coronaviruses.

Worobey himself actively engaged in Twitter reaction to his paper, including by posting translations of patient records and patient interviews and writing a Twitter thread explaining his research the day it was published.

"You can't explain away the preponderance of early cases linked to Huanan Market — as so many people, from Chinese authorities and scientists, to believers in a lab origin, have done. Most of cases really were linked to the market," he wrote in the thread.

He added that his article does not cover "every important detail, not by a long shot," and actively engaged in questions and answers from Twitter followers. One follower asked whether discovering that the outbreak started in late September or early October would alter his analysis.

"Modeling I have done with colleagues suggests an index (first known) case as early as Oct could be possible. But Sept cases would alter my analysis, yes," Worobey replied.

China's system for reporting unexplained pneumonia was a 'complete failure'

Some critics have dismissed theories that the Huanan market was where the pandemic began, arguing that it was the only place epidemiologists were looking for cases.

But Worobey says his study shows the market actually was where the pandemic started. And he said the response he's had since it published appears to have convinced people of that central point — that, "most of the early cases were linked to this one small market, which is the size of a Home Depot in a city the size of New York City."

To gain a clearer understanding of the earliest cases of COVID-19 in Wuhan, Worobey set out to document a timeline of the events that took place there between December 2019 and January 2020. Like many researchers, he wanted to know whether the cluster of cases reported at the Huanan market reflected the outbreak's origins, or whether something else, like reporting protocols, might explain them.

To find the answer, Worobey evaluated the system doctors in China use to report pneumonia cases that don't have a clear origin. That system is known as the Viral Pneumonia of Unknown Etiology mechanism (VPUE). Chinese health officials instituted VPUE in 2004 after the SARS outbreak in 2003, in hopes of creating an early detection measure for health officials to sound the alarms if another unknown virus seemed to be surfacing.

Under VPUE protocols, if a patient presents with unexplainable pneumonia symptoms, doctors should screen them for exposure to a wet market. Some researchers studying the origins of COVID-19 believed that based on this protocol, official reporting of unknown viral pneumonia cases would be skewed toward wet markets, while cases not related to wet markets would not be recorded.

What Worobey found is that the VPUE system wasn't being used in December 2019.

"No one was reporting the cases to that system until January. It was a complete failure of a billion-dollar system meant to protect China from a second SARS," he said. "What is interesting is that people at the China CDC where that system is based have published very, very high profile papers where they claimed that the system identified the virus, but that is false."

One of the lessons to be learned from the pandemic is how China's VPUE system "tragically failed," he said.

"We need to learn from that. The whole world actually should have an early warning system like China's, but obviously, it needs to be working properly for that to benefit anyone," he said.

The bigger picture goal to Worobey's sleuthing is figuring out how the deadly COVID-19 pandemic started "so that we can neutralize that threat properly," he said.

"If it really did happen through a raccoon dog at a market, but the world believes it happened through a lab that had an accidental escape and all your focus is on lab safety as the way of preventing pandemics, inevitably the actual route through wildlife is not going to be taken as seriously and responded to properly," he said.

"When a plane crashes, investigators spend months and even years trying to piece together every fragment and every bit of information to work out why that happened. And that's what I'm trying to do here — to figure out why the plane crashed so that we can avoid the same thing happening again."

It would still be helpful if Chinese officials would be transparent, Worobey said.

"At this point, I have little to no doubt that it didn't happen through a lab leak, and therefore anything that they could reveal on their end would help to sort of take the heat down in this debate a bit," he said.

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