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Live bats being confiscated at a market in Surakarta on the Indonesian island of Java in March 2020.

COVID's origins: what we do and don't know

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Researchers summarize key insights from the world's first comprehensive investigation into how a pandemic started.

We are 23 of the 27 original members of the Scientific Advisory Group for the Origins of Novel Pathogens (SAGO) for the World Health Organization (WHO). After nearly 3.5 years of deliberations, we concluded our independent assessment of the origin of the coronavirus SARS-CoV-2, and provided our report[1] in June 2025 to the WHO director-general.

In the 78-page document, we determined that most of the peer-reviewed scientific evidence supports the hypothesis that SARS-CoV-2 has a zoonotic origin, meaning that it came from an animal. But until requests for additional information are met or more data become available, there can be no certainty about when, where and how SARS-CoV-2 entered the human population.

Although the term of the first SAGO group ended in October last year, meaning we are no longer members, the WHO has proposed a second term for SAGO and issued a call for new participants. Our 2025 report[1] provides recommendations for subsequent investigations seeking to establish the origin of the COVID-19 pandemic. In the meantime, with the politicization and speculation around the origin of the pandemic showing no signs of abating, 23 of us mark the close of SAGO's first chapter by clarifying our position on the origin of SARS-CoV-2 and the science behind it in a more accessible way.

Of the four original members of SAGO who are not co-authors of this article, one resigned

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A bird market in Hong Kong in 2025.

before the 2025 report was finalized. Three others dissented from our decision to evaluate the possibility that SARS-CoV-2 had leaked from a laboratory on the basis of there being no evidence for this (see hypotheses three and four below). We are grateful to all four for their contributions to our investigation. One of us (M.G.G.), whose name is on the 2025 report, requests that her dissent regarding the evaluation of the lab-leak hypotheses be noted.

We stress that we are solely responsible for the views expressed in this article, and that such views do not necessarily represent the views, decisions or policies of the WHO, or of any institutions that we are affiliated with.

Mission-driven

The WHO's director-general, Tedros Adhanom Ghebreyesus, established SAGO in November 2021 and tasked it with designing a guiding framework to steer two things: an ongoing effort to try to determine the origins of SARS-CoV-2, and investigations of how emerging and re-emerging pathogens originate more broadly[2].

The 27 independent scientific experts from 27 countries who made up SAGO investigated all reasonable possibilities – not with the aim of blaming any one country for the emergence of SARS-CoV-2, but to determine what happened so that the world is better able to prevent epidemics and pandemics in the future.

To investigate the origin of SARS-CoV-2 in the human population, we assessed reports of early cases and clinical studies. We investigated potential sources of infection, including animal reservoirs, intermediate hosts, insect vectors and environmental sources. We also assessed the genomics and evolutionary biology of the virus, as well as the possibility of the virus having escaped through a lab or research-associated incident. These key 'checkpoints' are listed in the global framework document that we published in 2024 (ref. 3).

Our deliberations on the origins of SARS-CoV-2 have been based on the available scientific evidence. We used the work of international teams[4] that in 2020 and 2021 had visited Wuhan, China, where the first evidence-backed cases of the virus circulating in humans were discovered[5]. We used published scientific studies relevant to all the areas we were investigating; preprints and presentations by scientists who had worked on relevant research, either in China or elsewhere; and discussions involving international experts and SAGO members held between November 2021 and June 2025. We also consulted reviews conducted by various scientific bodies, including a 2022 Lancet Commission[6]. And we reviewed publicly available intelligence reports from oversight committees and government agencies, as summarized in our 2025 publication[1].

Four scientifically credible hypotheses had been proposed before November 2021 by the Joint WHO–China Study, an effort to rapidly inform China and the world on next steps in the response to the outbreak. Here, we summarize our conclusions following our investigations into the plausibility of each.

Hypothesis one: animals infected with SARS-CoV-2 passed the virus to humans

Most of the peer-reviewed scientific evidence supports this hypothesis.

Although they are too distantly related to SARS-CoV-2 to have been its direct progenitors, closely related ancestral strains have been found in horseshoe bats (*Rhinolophus* spp.) in southeast Asia. A *Betacoronavirus* called RaTG13, which shares 96.1% of its genetic code with SARS-CoV-2, was identified in 2013 in China[7]. (*Betacoronavirus* is the genus to which SARS-CoV-2 belongs.) Another strain called BANAL-52, which shares 96.8% of its genetic code with SARS-CoV-2, was identified in 2020 in Laos[8]. This suggests that similar strains circulating in bats in China or southeast Asia might have spilled over to intermediate animal hosts or directly to humans.

We also know that the Huanan Seafood Market in Wuhan had a significant role in the early transmission and initial spread of the virus.

More than 60% of the known earliest human cases in December 2019 involved people who worked at the market, made purchases there, lived near it or had some other epidemiological link with it[9]. (At least 175 people were diagnosed with the disease, either through lab testing or on the basis of clinical symptoms before 1 January 2020.)

Two distinct genetic lineages of SARS-CoV-2 were identified in samples from early cases associated with the Huanan market, as well as from the environmental sampling of stalls and run-off water in drains at the market in January 2020. This supports the idea that the virus had already been evolving in animals before it reached the market[10].

Metagenomic sequencing of environmental samples collected at the market has indicated that several wildlife species had been there before it was cleaned and sterilized on 1 January 2020 by the Chinese authorities in response to the outbreak. These include raccoon dogs (*Nyctereutes procyonoides*), hoary bamboo rats (*Rhizomys pruinosus*) and palm civets (*Paguma larvata*), all of which are known to be susceptible to the early strains of SARS-CoV-2 (refs 11 and 12). These animals could have been the intermediate hosts that brought the virus to the market, leading to the early cases in humans[11,12] – although it remains unclear whether the virus first infected humans at Huanan, or whether the spillover event occurred earlier, with the virus subsequently being carried to the market by infected humans or animals.

Adding to all this, there is no verified evidence of the existence of human or animal cases of SARS-CoV-2 infection anywhere else before December 2019. There were retrospective reports of one or two possible cases occurring in November 2019 in Italy and France, and of the virus being detected in a wastewater sample (also in November that year) in Brazil. But in all instances, the positive test results could not be confirmed by independent labs.

Hypothesis two: SARS-CoV-2 was introduced into China's animal markets from overseas through imported goods

The 2021 WHO–China Joint Study and SAGO's 2022 report both determined that further data would be required to support this idea[4,5].

In April last year, the Chinese government endorsed this route as the most likely source of SARS-CoV-2. But almost six years on from the start of the pandemic, we conclude that the available scientific evidence does not support this hypothesis[1].

> **"Huanan Seafood Market in Wuhan had a significant role in the early transmission."**

SARS-CoV-2 was detected on frozen goods, but only several months into the pandemic when the virus was already widespread in humans. By this point, infected people could have contaminated surfaces. Also, no further evidence has become available to suggest that the transmission of SARS-CoV-2 to humans from frozen products occurred at Huanan Seafood Market, at any other market in Wuhan or elsewhere at the start of the pandemic.

Hypothesis three: SARS-CoV-2 originated from an accidental lab-related event

Much of the information needed to assess this hypothesis has not been made available to the WHO or SAGO.

Raccoon dogs (*Nyctereutes procyonoides*) are susceptible to early strains of SARS-CoV-2.

GETTY

Repeated requests have been made to the Chinese government by the WHO to release the health records of research-lab staff, biosafety and biosecurity protocols, and audits or independent inspections conducted to verify the safety procedures of labs in Wuhan. These include those of the Chinese Center for Disease Control and Prevention in Wuhan and the Wuhan Institute of Virology, a leading research centre for bat coronaviruses. In our view, the government has not provided the necessary information that we have requested since the launch of SAGO in November 2021 to investigate a potential biosafety breach. The National Health Commission of China states that the country has shared all relevant data and information, and proposes that investigations be undertaken instead in labs in other countries where coronavirus research has been conducted[13].

Most of the scientific reviews we assessed support the zoonotic-origins hypothesis and find no conclusive evidence for a lab leak. Most of the published government-agency and intelligence reports that we assessed (which are listed in our 2025 publication[1]) assign levels of confidence, such as 'low' or 'moderate', to the lab-leak or zoonotic-origins hypotheses. But such reports deliver different conclusions, seemingly on the basis of political rather than scientific arguments.

In short, published intelligence reports, which focus mainly on biosafety and biosecurity policies and practices at the Wuhan Institute of Virology, are speculative. None provides concrete evidence of a breach.

Together, these reports highlight the continued need for a thorough, unbiased investigation into the origins of SARS-CoV-2 to enhance global health security. SAGO and the WHO have requested additional intelligence reports, including those that were classified or unpublished at the time, which several countries have produced in recent months – including China, Germany and the United States. This information has not yet been provided to SAGO or to the public.

Hypothesis four: SARS-CoV-2 originated from the deliberate manipulation of a virus in a lab

We analysed reports on the genome structure of SARS-CoV-2, as well as publications addressing the likelihood that it had been manipulated through reverse genetics. This involves making alterations to a virus's known genes or regulatory elements to investigate how targeted mutations change its properties. Such changes might be introduced to make a virus less pathogenic, for instance, or easier to study.

We did not find evidence to suggest that SARS-CoV-2 resulting from experimental manipulation was a more likely scenario than it emerging from naturally occurring mutations or recombination events. (Recombination

A nurse and patient at a temporary COVID-19 ward outside a hospital in Los Angeles, California, in 2021.

FRANCINE ORR/*LOS ANGELES TIMES* VIA GETTY

involves the exchange of genetic material between genetically distinct, but usually closely related, viruses that infect the same host cell.)

Members of *Sarbecovirus*, the viral subgenus of the *Betacoronavirus* genus to which SARS-CoV-2, SARS-CoV-1 and other SARS-related coronaviruses (mainly from bats) belong, have mosaic genomes. Pieces of the viruses' genomes originate from distinct evolutionary lineages owing to multiple recombination events in bats, or in other hosts[14].

Three bat viruses from Laos, described in 2022 (BANAL-52, BANAL-103 and BANAL-236), were found to enter human cells through a cell-surface receptor called ACE2 (ref. 8). In each of those viruses, the receptor-binding domains are very similar to that of SARS-CoV-2, with a difference of only one amino acid in BANAL-52 and BANAL-103. This suggests that before SARS-CoV-2 emerged in humans, it was already able to replicate in human cells using human ACE2 receptors.

A polybasic furin cleavage motif in SARS-CoV-2 called RRAR is not found in other sarbecoviruses. SARS-CoV-2 might have been able to obtain this motif – making it easier for the virus to infect human cells – by recombining with other coronaviruses, unrelated viruses or even with host genes. Furin-cleavage elements are commonly found in the spike proteins of members of *Betacoronavirus* subgenera, such as *Embecovirus*, *Hibecovirus* and *Merbecovirus*, including the human coronaviruses HKU1, OC43 and MERS-CoV (ref. 1). (These elements are not genetic homologues and might have been acquired independently.) In short, the mere presence of the furin cleavage element in SARS-CoV-2 does not confirm a lab origin, and published literature does not provide any other convincing evidence for a non-natural origin based on genetic engineering.

Challenging widely circulating theories

During our work, we were presented with several reports from civil movements and scientists working with scholars from unrelated fields of expertise. One theory that has been widely promoted in parts of the popular press and on social media focuses on a grant proposal known as DEFUSE. This was submitted to the US Department of Defense in 2018 by EcoHealth Alliance, in collaboration with researchers at the University of North Carolina at Chapel Hill and at the Wuhan Institute of Virology. (EcoHealth Alliance was a US-based non-governmental organization that was researching the emergence of infectious diseases at the time.)

Some have argued that, in trying to design a vaccine to reduce the load of coronaviruses in bats, researchers in the United States used reverse genetics to create SARS-CoV-2, which then escaped from a lab in China. Another widely circulating theory is that the virus could have escaped from animal experiments conducted in US labs. In the end, we decided to address these theories in our report to highlight some of the misconceptions, misinterpretations and speculations on which they are based.

The DEFUSE grant proposal mentions a vaccine technology based on recombinant chimeric live coronavirus vectors, which contain parts of different *Sarbecovirus* genomes. It also mentions recombinant expression of synthetic genes encoding chimeric spike proteins. These are proteins (not viruses) that consist of parts of the spike protein of a bat coronavirus, SHC014-CoV, parts of another previously known bat coronavirus, HKU3, as well as parts of SARS-CoV-1.

The SHC014-CoV sequence was provided by a researcher at the Wuhan Institute of Virology, and a research team at the University of North Carolina at Chapel Hill conducted binding assays to determine whether SHC014-CoV is capable of infecting human cells with ACE2 receptors[15]. But the genome elements making up the recombinant chimeric live coronavirus do not belong to the clade to which SARS-CoV-2 belongs (a clade is a group of genetically similar viruses). Indeed, the terms recombinant and chimeric have different meanings depending on whether they are being used for live viruses or mere proteins.

Although some of the researchers submitting the DEFUSE grant application held patents on recombinant chimeric live coronavirus vectors, they did not propose to vaccinate bats using this technology. In their grant application – which was never actually funded – they proposed using only recombinant proteins (or subunit antigens) to vaccinate bats. These cannot replicate or spread.

Thus, contrary to the theories put forward, there was never any intention to use spreading, coronavirus-derived vaccine vectors on bats. Even if the DEFUSE grant application had been approved, and even if the researchers had used the recombinant chimeric live virus technology in human cell lines or lab animals, it is scientifically implausible for SARS-CoV-2 to have been derived from the genome elements in the chimeric vaccine backbone or proposed spike protein.

Other grant proposals submitted to the US National Institutes of Health and implicated in theories about a lab origin for SARS-CoV-2 involved vaccinating bats with a vaccine consisting of modified vaccinia Ankara and vesicular stomatitis virus vectors. This vaccine technology uses safe, well-characterized, non-replicating vaccine vectors that present only a single protein of the pathogen in question to stimulate an immune response. Lastly, animal experiments involving SARS-CoV-2 were conducted in various species and countries only after the virus had been discovered in 2020 (see table 2 at go.nature.com/3nvqhrj).

Outstanding questions

Determining how a disease originated gets harder with time. We reiterate our request for any researchers, scientists or governments with information on the origins of SARS-CoV-2 to make that information available to the WHO and the next iteration of SAGO. We also stress that formal scientific evaluation of findings requires peer-reviewed publication.

Upstream sources of the animals that supplied the Huanan Seafood Market in late 2019, including potentially illegal trade routes, captured wildlife or breeding farms for fur or food, warrant further investigation. No animal testing positive for SARS-CoV-2 has ever been reported in China. Yet it is unlikely that none was infected given the number of susceptible species that were in markets in the Wuhan region during the pandemic – and given that hundreds of infections were reported in species, such as ferrets, tigers, domestic cats and white-tailed deer, in the rest of the world from 2020 to 2023 (see go.nature.com/3nvqhrj).

Genomic and other forms of surveillance in humans and animals in east and southeast Asia should be sustained. Such surveillance might detect the continued circulation in animal reservoirs of strains that had infected humans early in the pandemic, or emerging variants of concern, especially in communities living near bat caves. And independent international investigations of any evidence arising from labs in China or from labs in other parts of the world where researchers worked on coronaviruses closely related to SARS-CoV-2 before December 2019 should be carried out. Also, improved biosafety measures for scientists working with zoonotic coronaviruses and other viruses should be encouraged internationally.

Overall, perhaps the most important message to emerge from SAGO's first term is that only rigorous scientific research, not conjecture or political opinion, will help to solve the mystery of where a virus estimated to have killed more than 20 million people by the end of 2022, and which cost the global economy up to US$16 trillion, came from. If the world truly wants answers, it must deliver the information and data that make rigorous scientific research possible.

> **"No animal testing positive for SARS-CoV-2 has ever been reported in China."**

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1. Scientific Advisory Group for the Origins of Novel Pathogens. *Independent Assessment of the Origins of SARS-CoV-2* (WHO, 2025).
2. World Health Organization. *Terms of Reference for the Scientific Advisory Group for the Origins of Novel Pathogens (SAGO)* (WHO, 2021).
3. Scientific Advisory Group for the Origins of Novel Pathogens. *WHO Global Framework to Define and Guide Studies into the Origins of Emerging and Re-Emerging Pathogens with Epidemic and Pandemic Potential* (WHO, 2024).
4. World Health Organization. *WHO-Convened Global Study of Origins of SARS-CoV-2: China Part* (WHO, 2021).
5. Scientific Advisory Group for the Origins of Novel Pathogens. *Preliminary Report of the SAGO* (WHO, 2022).
6. Sachs, J. D. *et al. Lancet* **400**, 1224–1280 (2022).
7. Zhou, H. *et al. Curr. Biol.* **30**, 2196–2203 (2020).
8. Temmam, S. *et al. Nature* **604**, 330–336 (2022).
9. Worobey, M. *et al. Science* **377**, 951–959 (2022).
10. Pekar, J. E. *et al. Virus Evol.* **11**, veaf008 (2025).
11. Liu, W. J. *et al. Nature* **631**, 402–408 (2024).
12. Crits-Christoph, A. *et al.* Preprint at Zenodo https://doi.org/10.5281/zenodo.7754299 (2023).
13. State Council Information Office of the People's Republic of China. *Covid-19 Prevention, Control and Origins Tracing: China's Actions and Stance* (SCIO, 2025).
14. Patiño-Galindo, J. Á. *et al. Genome Med.* **13**, 124 (2021).
15. Menachery, V. D. *et al. Nature Med.* **21**, 1508–1513 (2015).

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