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The Origins of Covid-19 — Why It Matters (and Why It Doesn't)

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The Origins of Covid-19 — Why It Matters (and Why It Doesn't)

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When health emergencies arise, scientists seek to discover the cause — such as how a pathogen emerged and spread — because this knowledge can enhance our understanding of risks and strategies for prevention, preparedness, and mitigation. Yet well into the fourth year of the Covid-19 pandemic, intense political and scientific debates about its origins continue. The two major hypotheses are a natural zoonotic spillover, most likely occurring at the Huanan Seafood Wholesale Market, and a laboratory leak from the Wuhan Institute of Virology (WIV). It is worth examining the efforts to discover SARS-CoV-2's origins, the political obstacles, and what the evidence tells us. This evidence can help clarify the virus's evolutionary path, but regardless of its origins, there are steps the global community can take to reduce future pandemic threats.

The origins story dates back to December 31, 2019, when the World Health Organization (WHO) learned of a cluster of cases of pneumonia of unknown cause in Wuhan (see timeline). Wuhan authorities closed the Huanan market the next day, rendering live animals unavailable for testing. China publicly shared the SARS-CoV-2 genetic sequence on January 12, 2020. It was not until weeks after the WHO declared Covid-19 a Public Health Emergency of International Concern on January 30 that a WHO–China Joint Mission visited Beijing and Wuhan (February 16 to 24).

The joint WHO–China technical report published in March 2021 rated a zoonotic spillover as a "likely to very likely" source of the virus, cold food-chain products as "possible," and a laboratory incident as "extremely unlikely."[1] The WHO director-general immediately repudiated the report's findings, believing it was premature to rule out a possible laboratory incident. An open letter in *Science* on May 14, 2021, credited the laboratory theory, calling for open access to laboratory records and

science-based studies.[2] On October 13, 2021, the WHO director-general established a Scientific Advisory Group for the Origins of Novel Pathogens (SAGO). China officially rejected the WHO's plan for a second phase of investigation of origins. The SAGO's preliminary report warned that China was withholding key data.

Recently, a team of international experts announced that they had identified data on SARS-CoV-2–positive environmental samples collected from the Huanan market in January 2020, , which China withheld from the public domain for 3 years. Chinese scientists had uploaded the data to GISAID (the Global Initiative for Sharing All Influenza Data) but then removed them. In response to WHO pressure, China restored those data to GISAID.

Determining the origins of SARS-CoV-2 should be strictly a scientific matter, but it has become embroiled in politics. In March 2020, the Chinese Ministry of Foreign Affairs alleged, without evidence, that U.S. Army personnel had introduced SARS-CoV-2 during a visit to Wuhan, prompting President Donald Trump to claim that the virus originated at the WIV. Accusing the director-general of siding with China, Trump notified the United Nations that the United States intended to withdraw from the WHO. Although President Joe Biden later reversed that decision, the origins controversy has continued. On May 26, 2021, Biden ordered U.S. intelligence agencies to review the competing origins hypotheses. The Office of the Director of National Intelligence released a "Declassified Assessment on COVID-19 Origins," finding that the evidence to support either of the two plausible theories was inconclusive and acknowledging that China's cooperation was necessary for reaching any conclusive assessment.[3]

Origins politics heated up early this year. On January 25, 2023, the Office of the Inspector General of the U.S. Department of Health and Human Services concluded that the National Institute of Allergy and Infectious Diseases had failed to adequately oversee a grant to the EcoHealth Alliance for research into bat viruses at the WIV.[4] A month later, the Department of Energy, which oversees a network of 17 U.S. laboratories, concluded with "low confidence" that SARS-CoV-2 most likely arose

from a laboratory incident. The Federal Bureau of Investigation said it favored the laboratory theory with “moderate” confidence. Four other agencies, along with a national intelligence panel, still judge that SARS-CoV-2 emerged from natural zoonotic spillover, while two remain undecided. All U.S. intelligence agencies rejected the allegation that participants in a clandestine Chinese biologic weapons program intentionally developed SARS-CoV-2. Yet a report issued in mid-December 2022 by Republican members of the House of Representatives still credited that theory. On March 21, 2023, Biden signed a bill declassifying documents about Covid-19’s origins, and Congress commenced hearings.

Of the three possibilities — natural, accidental, or deliberate — the most scientific evidence yet identified supports natural emergence. More than half of the earliest Covid-19 cases were connected to the Huanan market, and epidemiologic mapping revealed that the concentration of cases was centered there. In January 2020, Chinese officials cleared the market without testing live animals, but positive environmental samples, including those from an animal cage and a hair-and-feather–removal machine, indicated the presence of both SARS-COV-2 and Covid-susceptible animals.[5] Recently released findings included raccoon dog DNA, pointing to a possible SARS-CoV-2 progenitor. Samples from early cases in humans also contained two different SARS-CoV-2 lineages. Although only one lineage spread globally, the existence of multiple lineages suggests that a SARS-CoV-2 epidemic in animals may have led to multiple spillover events.

Proponents of the accidental laboratory leak theory stress the geographic location of the WIV, in the city where the pandemic began. . They point the presence of bat coronavirus RaTG13 strain at the lab, arguing that genetic manipulations such as gain-of-function (GOF) research may have produced SARS-CoV-2. Most scientists refute this theory because there is considerable evolutionary distance between the two viruses. However, the possibility that the lab held a different progenitor strain to SARS-CoV-2 that led to a laboratory leak cannot be unequivocally ruled out.

China's obfuscation may mean that we will never have certainty about the origins of the greatest pandemic in more than a century. After all the world has suffered in loss of life, economic hardship, and exacerbated health disparities, there is intrinsic value in knowing the cause. An objectively determined body of scientific facts cannot fully defuse the political rhetoric surrounding the origins investigation, but the search must continue. The newly released genetic data may reveal whether specific animals were infected and offer information about where they came from, opening new possibilities to investigate, which may also improve attribution techniques for investigating future outbreaks. Irrespective of Covid's origins, future outbreaks could result from deliberate, accidental, or natural causes, and improving our ability to understand and prove theories will be critical. We propose three important steps for fortifying pandemic preparedness.

First, it is vital to prevent spillovers using a One Health strategy linking animal, human, and environmental health. Some 60% of outbreaks of diseases previously unseen in humans arise from natural zoonoses. Human and animal populations could be separated more effectively with stricter regulation of wet markets and enforcement of laws prohibiting wildlife trade. Land-management efforts such as halting deforestation would benefit the environment while creating a buffer between wildlife and humans. Widespread use of sustainable and humane farming practices would eliminate overcrowding of domesticated animals and curtail prophylactic antimicrobial use — with added benefits in preventing antimicrobial resistance.

Second, it is important to fortify laboratory safety to reduce the risks of unintentional release of a dangerous pathogen. Regulatory requirements should include site-specific and activity-specific risk assessments to identify and mitigate risks; core protocols for infection prevention and control; and training for proper use of, and access to, personal protective equipment. International standards exist for bio-risk management, which should be broadly adopted.

Finally, GOF research designed to elucidate the transmissibility or pathogenicity traits of pathogens should be appropriately overseen to reduce risks while allowing important research and vaccine development to continue. Such research may result in the creation of microbes with enhanced pandemic potential, which could be released unintentionally or intentionally. However, there is no international agreement about which research activities are problematic or how to reduce risks.. On January 27, 2023, the U.S. National Science Advisory Board for Biosecurity issued a more rigorous framework for oversight of research, which prominent virologists criticized as overbroad and inhibitory to US vaccine development. As GOF research is conducted in laboratories globally, an international framework is needed.

Since the pandemic's earliest days, controversy has swirled about how it began. Origins investigations are scientific endeavors, but we need to plan ahead so that scientists get rapid access to key geographic sites, open scientific exchange, and full transparency. Though such investigations proceed more slowly than the news cycle, these steps are the keys to unlocking the mystery surrounding Covid-19 and preparing the world for the future outbreaks that are certain to occur.

Disclosure forms provided by the authors are available at NEJM.org.

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[timeline legend]

Key Events in the Effort to Determine the Origins of the Covid-19 Pandemic.

D-G denotes director-general, DOE Department of Energy, FAO Food and Agriculture Organization of the United Nations, FBI Federal Bureau of Investigation, HHS Department of Health and Human Services, NIAID National Institute of Allergy and Infectious Diseases, OIE Office of the Inspector General, PHEIC Public Health Emergency of International Concern, SAGO Scientific Advisory Group for the Origins of Novel Pathogens, WHO World Health Organization, and WSJ *Wall Street Journal*.