SARS-CoV-2's origin should be investigated worldwide for pandemic prevention

The origin of SARS-CoV-2 has received intensive global attention since its spread was first reported to the international community in early January, 2020. Multiple studies[1–9] conducted collaboratively by scientists around the world have found that animal-to-human cross-species spillover is the most likely source of SARS-CoV-2, whereas laboratory leakage is extremely unlikely. However, the research and global health communities have yet to reach a clear conclusion as to the specific time, place, and cross-species transmission route through which SARS-CoV-2 entered the human population.[1–9]

Viruses could be made in a laboratory; however, there is no scientific evidence to support the idea that SARS-CoV-2 is artificial, and there are also no data to support the notion that any laboratory had handled SARS-CoV-2 or its proximal ancestor before the COVID-19 pandemic.[7,10,11] Although the bat coronavirus RaTG13, first reported by Wuhan Institute of Virology (WIV), Chinese Academy of Sciences, shares the highest genome-wide sequence identity (96·2%) with SARS-CoV-2 of all known coronaviruses, it still has more than 1000 nucleotide differences, spread evenly across the genome.[2] Wide consensus has been reached by the scientific community[11] that such a virus cannot be the direct source of SARS-CoV-2, or even a template for synthesising SARS-CoV-2. The bat coronaviruses isolated or experimented with by WIV scientists, such as strains WIV1 and WIV16, are SARS-like coronaviruses or alpha coronaviruses. Their sequences differ even further from SARS-CoV-2 than RaTG13, and there is no evidence that they could evolve to SARS-CoV-2.[12–17] Furthermore, no one presented with respiratory illness similar to COVID-19 in WIV prior to December, 2019, which was corroborated by institution-wide SARS-CoV-2-specific serological testing.[6] These findings suggest that the outbreak did not start from a laboratory incident at WIV.

Since the SARS outbreak in 2003, China has developed rigorous administration and supervision systems to regulate activities in high-level biosafety laboratories, and enacted a series of laws and decrees in this regard.[18,19] These laws, decrees, and regulations have built a strict and complete whole-chain administration, covering aspects including laboratory admission, personnel access, research programme review, experimental operation supervision, facilities and equipment operation, handling of disposals, and health surveillance of laboratory personnel. Each laboratory will be subjected to strict internal audit and unannounced inspections by multiple government authorities every year, making artificial manufacture of a human-made virus or laboratory leakage extremely unlikely. After inspection of the WIV biosafety laboratory, the WHO–China joint expert group also concluded that the introduction of SARS-CoV-2 through a laboratory incident was "extremely unlikely".[6] Therefore, without evidence, a laboratory origin should not be a priority at present for investigating the origin of SARS-CoV-2. Instead, as mentioned in the phase 1 joint report[6] of the WHO-convened global study of origins of SARS-CoV-2, internal audit is a better alternative for all high-level biosafety laboratories worldwide to further exclude the "laboratory incident" hypothesis.

Historically, the emergence of infectious diseases in humans has most often been caused by interspecies barrier breakthrough of animal-origin pathogens.[20–23] A natural origin of SARS-CoV-2 is by far the most likely scenario. Pinpointing the precise natural origin of the virus would also help to reject alternative hypotheses. Characterisation of the codon preferences of SARS-CoV-2 and its genome's structure indicate that the circulating virus is highly similar to strains carried by wild animals.[24,25] The virus's evolutionary history in animals and its fast adaptive mutation within the infected human population also suggest that SARS-CoV-2 is more likely to have come from nature than other potential sources.[26–28] A variety of evidence indicates that horseshoe bat species found in Cambodia, Thailand, Japan, and the southwest border areas of China, as well as Malayan pangolins captured in anti-smuggling actions, carry coronaviruses similar to SARS-CoV-2.[5,29–33] Although the animal viruses that have been identified are not immediate precursors of SARS-CoV-2, their existence suggests that global investigations into the evolutionary characteristics of the animal origin for SARS-CoV-2 are warranted. Such investigations would include testing wild animal hosts of coronaviruses at the nucleic acid and serum levels to positively identify the natural origin of the cross-species spillover. Various studies[34–41] have already reported that several species of mammals (including mink, civets, cats, pangolins, rabbits, ferrets, foxes, deer, etc) are capable of being infected by SARS-CoV-2. It is entirely possible that SARS-CoV-2-related viruses could cross the species barrier between humans and animals repeatedly in many parts of the world. In fact, it is almost certain that such animal-to-human transmissions are happening repeatedly. There are many unsuccessful jumps before a virus takes to humans. Therefore, tracing such sporadic zoonoses and the virus's potential intermediate hosts among an even greater range of animal species in the real world is also of great importance.

Based on research findings to date, SARS-CoV-2 could have a complex origin, making investigation of its origins a hard task. Several studies from multiple countries have found

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that the virus might have been present in humans before the end of December, 2019, when the first outbreak was detected in Wuhan. For example, an evolutionary dynamics analysis indicated that the virus may have been spreading before the end of December.[6,42] In addition, a number of reports from many parts of the world have revealed the possible existence of COVID-19 cases and environmental positive samples prior to the end of December, 2019. Population-based nucleic acid and serology tests, as well as sewage tests, provide evidence of SARS-CoV-2's presence in Italy during September to December, 2019.[43-46] Similarly, nucleic acid and serology tests provide evidence of the virus's presence in France during December, 2019,[47,48] and nucleic acid tests of sewage provide evidence of its presence in Brazil in November, 2019.[49] Furthermore, recent serology test results indicate the possible existence of SARS-CoV-2 infection in a number of states across the USA in December, 2019, much earlier than the first case confirmed in the USA through nucleic acid testing.[50,51] Although some findings have yet to be confirmed by nucleic acid sequencing, some methods used are not standardised, and serological tests might be affected by cross-reactivity of antibodies, this evidence deserves further investigation before it can be formally ruled out.

Additional research has suggested that SARS-CoV-2 may be transmitted via cold chains. Viral nucleic acids were detected and live virus was isolated from frozen foods and their outer packaging in several regions of China, including Beijing and Qingdao, that had COVID-19 outbreaks in 2020. These findings suggest that cold chains may have played an important role in the spread of the virus.[52-57] Studies on the viability and infectivity of the virus at different temperatures on different objects indicate that the virus can remain infectious on foods and other surfaces for a long time at low temperature, and cold-chain workers could become infected by contacting contaminated products, sparking new chains of transmission.[58,59] These results suggest that SARS-CoV-2 could plausibly spread across regions through cold-chain transmission and raise questions as to whether the location in which the virus was first reported was necessarily the site of its origin.

In light of the complexity and unresolved questions surrounding SARS-CoV-2's origin revealed by the WHO-China joint report that focused on Wuhan and China, there is a pressing need for extensive international cooperation in integrating multiple testing techniques to examine early cases and potential positive samples that pre-date the first known outbreak. In addition to combining genome sequencing, data from clinical and epidemiological studies, and results from environmental testing, we recommend that the next phase of investigation into the virus's origin should be carried out synchronously in multiple locations, not just in China. It should include: (1) collection of samples from wild animals, testing and analyses on sarbecoviruses and related serum antibodies, and targeted searching for viruses that have the same origin as SARS-CoV-2 in areas with insufficient samples or that have never been sampled, especially areas with specific species known to carry SARS-CoV-2-related viruses; (2) based on China's experience in investigating upstream and downstream supply chains of wildlife markets, a global retrospective survey of cross-region wildlife markets and upstream and downstream supply chains should be conducted to collect samples, as well as possible preserved early animal and environmental samples, to detect viruses or related serum antibodies; (3) based on the aforementioned possible early case clues, retrospective studies should be carried out worldwide, including the search and re-identification of suspicious cases and deaths, and laboratory re-testing of early patient swabs, tissues, and blood bank samples that may have been retained; (4) through integration of global molecular epidemiological data of high quality viral genome information, phylogenetic analysis and ancestral time analysis should be conducted to construct the evolutionary history of viral lineages, and estimate initial virus quantity and dynamic propagation speed, based on combined epidemiological and geographical information; and (5) to further evaluate the potential role of cold chains in the introduction and transmission of SARS-CoV-2, retrospective sampling and testing should be performed to trace the origin of cold-chain imports, and the viability and infectivity of SARS-CoV-2 at different temperatures should be further analysed.

SARS-CoV-2 is a common enemy of humankind. Like other infectious diseases, it respects no national boundaries. In the face of a pandemic without modern precedent, humankind must work together. This is a humanitarian issue, the gravity and sanctity of which has been respected even during wartime. To cope with the challenge, Chinese scientists and medical workers have always kept an open and cooperative attitude, working vigorously with the international scientific community in all aspects and offering unreserved accurate data even during China's toughest period of fighting against the virus.

Notably, after the initial outbreak of COVID-19, Chinese research institutions, including the Chinese Center for Disease Control and Prevention, Chinese Academy of Medical Sciences, and Chinese Academy of Sciences, conducted parallel detection of case samples, identified SARS-CoV-2 as the causative agent of the pandemic together, and immediately shared the whole genome sequence of the virus with the rest of the world; through these efforts, Chinese researchers contributed critical

references for the development of diagnostic reagents, vaccines, and drugs.[2,8,60–63] Chinese scientists, along with fellow researchers from other countries, also issued an early warning of a potential pandemic to the international community.[64–67] Moreover, Chinese scientists have conducted a series of research projects to investigate the origin of SARS-CoV-2 since the COVID-19 outbreak, and have made much progress in understanding epidemiology, infection mechanisms, and animal host searching.[30,34,35,68,69]

There is yet insufficient evidence to determine whether the natural origin of SARS-CoV-2 was in China or elsewhere. Because Wuhan was the first place where the outbreak of COVID-19 was identified, a WHO-convened study group, together with Chinese experts, has conducted an extensive investigation in Wuhan in the past year; however, no creditable evidence has been found so far to support the idea that initial animal-to-human adaptation occurred in Wuhan. Since whether animal-to-human adaptation took place in or outside Wuhan remains unclear, it is reasonable to propose that the next phase of investigation of SARS-CoV-2's origin should not entirely focus on China; instead a worldwide search at different geographical locations should be carried out to identify where and when the first animal-to-human transmission occurred.

The concept of international health, which focuses on issues outside of one's own country, has evolved into that of global health, which tackles health issues that transcend national boundaries.[70] We should view the search for SARS-CoV-2's origin as a collective attempt to better prevent and cope with future potential pandemics. Finding evidence of SARS-CoV-2's origins through scientific inquiry is essential to such efforts. Prior experience with tracing the origin of emerging viruses—eg, HIV—indicates that the task may be very difficult and time consuming, and the location where an epidemic is first reported is not necessarily the place where it originated.[71,72] Moreover, investigations into the origins of SARS-CoV-2 should be carried out by scientists on the basis of science alone, without interference or coercion from political forces. The strongest weapons we can wield to prevent and control future pandemics are unity and cooperation, which not only conform to the common interests of humankind but also serve as the foundation for the community of human health. Chinese scientists are willing, as always, to work with scientists of the world to explore the scientific complexities of the virus's origin objectively in the principles of openness and cooperation. Any hypothesis that lacks scientific evidence may lead to separation within the scientific community and among different population groups. Such speculation is not conducive to the unity and cooperation needed in the global fight against COVID-19 and other pathogens and is contrary to the spirit of science and humanitarianism.

QJ served as a member of the academic committee of the State Key Laboratory of Virology (SKLV) between 2005 and 2016. SKLV is co-sponsored by Wuhan University and Wuhan Institute of Virology (WIV), Chinese Academy of Sciences (CAS). He now has no connection with SKLV. GW, WT, and WX are part-time researchers of Center for Biosafety Mega-Science, CAS. DG has given several public lectures or talks at WIV, and has published three joint papers with the scientists of WIV. He is a member of the editorial board of the academic journal Virologica Sinica sponsored by WIV, Chinese Society of Microbiology, and Springer. KL is the director of SKLV. He is also an associate editor of Virologica Sinica. He is an employee of Wuhan University and paid solely by Wuhan University. JW was an associate editor of Virologica Sinica between 2017–2019. He is a member of the editorial board of this journal now. ZW, JL, ML, LF, ZQ, LR, WY, and CW declare no competing interests.

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