Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The origins of viruses: discovery takes time, international resources, and cooperation

Revealing the origins of SARS-CoV-2 is a prerequisite for cutting off the virus from the root and preventing future spillover of the virus. This work is of great significance in infection disease prevention and control in the face of Disease X.[1] Although scientists around the world are searching very hard, the origins of SARS-CoV-2 remain elusive. In fact, for many infectious pathogens, although their origins have been traced back decades, the debate around the origins remains alive.

HIV is a good first example. The first official report about AIDS was made on June 5, 1981, by the US Centers for Disease Control and Prevention. 5 years later, Nahmias and colleagues[2] discovered a human serum sample collected in Léopoldville (now Kinshasa, Democratic Republic of the Congo) in early 1959 that suggested exposure to HIV. Phylogenetic analysis subsequently suggested that an HIV ancestor had been introduced to Africa before 1959,[3] and a relatively recent report, from 2008, revealed that the HIV-1 M group originated in about 1908 (CI 1884–1924) and has been circulating in the population for about 100 years.[4]

In 2004, human coronavirus HKU1 (HCoV-HKU1) was identified from a patient with pneumonia who returned to Hong Kong from Shenzhen, China.[5] However, since then, HCoV-HKU1 positive signals have been detected across the globe and spanning decades: in specimens from Australian children that were collected in 2004,[6] in respiratory specimens collected in Connecticut, USA, in 2001–02,[7] in Finnish children in 1996–98,[8] and in nasopharyngeal swab samples from children in Brazil that were frozen in 1995.[9]

The virus that causes severe fever with thrombocytopenia syndrome, SFTSV, was discovered in Henan province, China, in 2009.[10] This discovery prompted SFTSV testing of samples obtained from patients in Jiangsu province, China, who had similar clinical manifestations in 2007 but whose aetiology was elusive, with positive results.[11] Other researchers tested serum samples from six patients with fever and thrombocytopenia in Yixing County, Jiangsu province, China, in 1996. And on the basis of epidemiological, clinical, and retrospective serological studies, the pathogen in this small cluster was confirmed to be SFTSV.[12]

MERS-CoV was first reported in a Saudi Arabian man, aged 60 years, who died in 2012.[13] The transmission route of this virus from animals to humans is not well understood, but dromedary camels are considered the major intermediate host of MERS-CoV,[14] and bats are thought to be reservoir hosts. The discovery of antibodies in serum samples collected in 2003 indicates that MERS-CoV, or a closely related virus, had been prevalent in dromedary camels in the region long before the first MERS case was identified in humans. Alagaili and colleagues[15] have proved that MERS-CoV had been circulating in camels since at least 1992 and can be phylogenically classified into clades related to human disease outbreaks. In 2014, researchers tested 189 stored dromedary camel serum samples collected in Egypt in 1997 and in Sudan and Somalia in 1983–84. 81% of the samples had neutralising antibodies against MERS-CoV, suggesting long-term virus circulation in these animals.[16]

As these cases show, tracing the origins of a virus requires long-term and extensive sample accumulation, which can take several years or decades. The geographical origins of a virus might not rely on an initial sick patient, and in some cases the index patient might never be found. Real-time RT-PCR and high-throughput sequencing technologies will help clarify the origins of emerging viruses, and in-depth research needs to be carried out from epidemiology, genomics, aetiology, and serology to lay the foundation for research on intermediate animal hosts, virus sources, and the transition of a virus into the human population. Patients with similar symptoms before the pandemic should therefore be re-evaluated,[17] and stored samples from a broad geographical area should be re-tested. Blood and tissue banks are important resources for retrospective serological or genomics studies, especially by looking into the epidemiology of the disease in countries or regions where evidence of the virus has appeared in blood samples or environmental samples before the outbreak. Comprehensive genomic studies in animal species that are susceptible to the virus are necessary to identify the natural or intermediate hosts. Finally, the experience of on-going progress with HIV, HCoV-HKU1, SFTSV, and MERS-CoV origin studies shows that open-mindedness and close international cooperation are pivotal for tracing the origins of any viruses. Stay away from politicisation of the origins of the COVID-19 causative agents, and work together globally for science.

We declare no competing interests. YT and WL contributed equally to this Correspondence.

*Yigang Tong, Wenli Liu, Peipei Liu, William J Liu, Qihui Wang, *George F Gao*
gaof@im.ac.cn

Beijing Advanced Innovation Center for Soft Matter Science and Engineering, College of Life Science and Technology, Beijing University of Chemical Technology, Beijing, China (YT, WL); National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China (PL, WJL, GFG); CAS Key Laboratory of Pathogen Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing, China (QW, GFG)

1 Gao GF. From "A"IV to "Z"IKV: attacks from emerging and re-emerging pathogens. *Cell* 2018; **172:** 1157–59.
2 Nahmias AJ, Weiss J, Yao X, et al. Evidence for human infection with an HTLV-III/LAV-like virus in central Africa, 1959. *Lancet* 1986; **327:** 1279.
3 Zhu T, Korber B, Nahmias A, et al. An African HIV-1 sequence from 1959 and implications for the origin of the epidemic. *Nature* 1998; **391:** 594–97.

Cala Image/Science Photo Library

Published **Online**
September 30, 2021
https://doi.org/10.1016/S0140-6736(21)02180-2

4 Worobey M, Gemmel M, Teuwen DE, et al. Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960. *Nature* 2008; **455:** 661–64.

5 Woo P, Lau S, Chu CM, et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. *J Virol* 2005; **79:** 884–95.

6 Sloots TP, McErlean P, Speicher DJ, et al. Evidence of human coronavirus HKU1 and human bocavirus in Australian children. *J Clin Virol* 2006; **35:** 99–102.

7 Esper F, Weibel C, Ferguson D, et al. Coronavirus HKU1 infection in the United States. *Emerg Infect Dis* 2006; **12:** 775–79.

8 Ruohola A, Waris M, Allander T, et al. Viral etiology of common cold in children, Finland. *Emerg Infect Dis* 2009; **15:** 344–46.

9 Goes LG, Durigon EL, Campos AA, et al. Coronavirus HKU1 in children, Brazil, 1995. *Emerg Infect Dis* 2011; **17:** 1147.

10 Yu XJ, Liang MF, Zhang SY, et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. *N Engl J Med* 2011; **364:** 1523–32.

11 Bao CJ, Guo XL, Qi X, et al. A family cluster of infections by a newly recognized bunyavirus in eastern China, 2007: further evidence of person-to-person transmission. *Clin Infect Dis* 2011; **53:** 1208–14.

12 Hu JL, Shi C, Li ZF, et al. A cluster of cases of severe fever with thrombocytopenia syndrome bunyavirus infection in China, 1996: a retrospective serological study. *PLoS Negl Trop Dis* 2018; **12:** e0006603.

13 Zaki AM, Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012; **367:** 1814–20.

14 Azhar EI, El-Kafrawy SA, Farraj SA, et al. Evidence for camel-to-human transmission of MERS coronavirus. *N Engl J Med* 2014; **371:** 1359–60.

15 Alagaili AN, Briese T, Mishra N, et al. Middle East respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia. *mBio* 2014; **5:** e00884-14.

16 Müller MA, Corman VM, Jores J, et al. MERS coronavirus neutralizing antibodies in camels, eastern Africa, 1983–1997. *Emerg Infect Dis* 2014; **20:** 2093–95.

17 The Lancet Infectious Diseases. "In an ocean of ashes, islands of order": WHO's SARS-CoV-2 origin report. *Lancet Infect Dis* 2021; **21:** 579.

Published **Online** September 17, 2021 https://doi.org/10.1016/S0140-6736(21)02019-5

An appeal for an objective, open, and transparent scientific debate about the origin of SARS-CoV-2

On July 5, 2021, a Correspondence was published in *The Lancet* called "Science, not speculation, is essential to determine how SARS-CoV-2 reached humans".[1] The letter recapitulates the arguments of an earlier letter (published in February, 2020) by the same authors,[2] which claimed overwhelming support for the hypothesis that the novel coronavirus causing the COVID-19 pandemic originated in wildlife. The authors associated any alternative view with conspiracy theories by stating: "We stand together to strongly condemn conspiracy theories suggesting that COVID-19 does not have a natural origin". The statement has imparted a silencing effect on the wider scientific debate, including among science journalists.[3] The 2021 letter did not repeat the proposition that scientists open to alternative hypotheses were conspiracy theorists, but did state: "We believe the strongest clue from new, credible, and peer-reviewed evidence in the scientific literature is that the virus evolved in nature, while suggestions of a laboratory leak source of the pandemic remain without scientifically validated evidence that directly supports it in peer-reviewed scientific journals". In fact, this argument could literally be reversed. As will be shown below, there is no direct support for the natural origin of SARS-CoV-2, and a laboratory-related accident is plausible.

There is so far no scientifically validated evidence that directly supports a natural origin. Among the references cited in the two letters by Calisher and colleagues,[1,2] all but one simply show that SARS-CoV-2 is phylogenetically related to other betacoronaviruses. The fact that the causative agent of COVID-19 descends from a natural virus is widely accepted, but this does not explain how it came to infect humans. The question of the proximal origin of SARS-CoV-2—ie, the final virus and host before passage to humans—was expressly addressed in only one highly cited opinion piece, which supports the natural origin hypothesis,[4] but suffers from a logical fallacy:[5] it opposes two hypotheses—laboratory engineering versus zoonosis—wrongly implying that there are no other possible scenarios. The article then provides arguments against the laboratory engineering hypothesis, which are not conclusive for the following reasons. First, it assumes that the optimisation of the receptor binding domain for human ACE2 requires prior knowledge of the adaptive mutations, whereas selection in cell culture or animal models would lead to the same effect. Second, the absence of traces of reverse-engineering systems does not preclude genome editing, which is performed with so-called seamless techniques.[6,7] Finally, the absence of a previously known backbone is not a proof, since researchers can work for several years on viruses before publishing their full genome (this was the case for RaTG13, the closest known virus, which was collected in 2013 and published in 2020).[8] Based on these indirect and questionable arguments, the authors conclude in favour of a natural proximal origin. In the last part of the article, they briefly evoke selection during passage (ie, experiments aiming to test the capacity of a virus to infect cell cultures or model animals) and acknowledge the documented cases of laboratory escapes of SARS-CoV, but they dismiss this scenario, based on the argument that the strong similarity between receptor binding domains of SARS-CoV-2 and pangolins provides a more parsimonious explanation of the specific mutations. However, the pangolin hypothesis has since been abandoned,[9–12] so the whole reasoning should be re-evaluated.

Although considerable evidence supports the natural origins of other outbreaks (eg, Nipah, MERS, and the 2002–04 SARS outbreak) direct evidence for a natural origin for SARS-CoV-2 is missing. After 19 months of investigations, the