

The Cause of Severe Acute Respiratory Syndrome: What Did We Learn from It?

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Featured Article: Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003;361:1319–25.³

Severe acute respiratory syndrome (SARS) was the first major global public health crisis of the 21st century. In March 2003, we reported to the World Health Organization (WHO) the discovery of a novel coronavirus (CoV) responsible for this newly emerged disease. SARS first emerged in Guangdong, China in November 2002, leading to major outbreaks in the provincial capital, Guangzhou, in January. We first heard about these outbreaks in mid-February 2003. Hong Kong set up enhanced surveillance for all patients with severe pneumonia of unknown etiology in Hong Kong, especially those with a travel history to Guangdong. Our investigation for known respiratory pathogens proved negative. We then started to look more broadly for unusual viruses, including attempting virus culture using a range of cell lines not normally used for respiratory viruses, broad-range PCR/RT-PCR, random primer RT-PCR methods, as well as electron microscopy of a lung biopsy from a suspected patient. By March 17, 2003, we began to see subtle changes in FRhk 4 monkey kidney cells inoculated with specimens from 2 suspected patients. By electron microscopy, we could see virus particles within these cells. We then used fixed infected cells to demonstrate antibody responses in paired sera from a number of suspected SARS patients, but not in controls. Using random RT-PCR, we were able to identify the virus as a novel coronavirus. The initial short RNA sequence of 646 nucleotides obtained from the random RT-PCR rapidly allowed the development of RT-PCR assays for detecting SARS patients (1). All these findings were shared in real-time via daily teleconferences organized by the WHO to link up laboratories working on this

outbreak. Two other laboratories within the network (Centers for Disease Control and Prevention, US, and Bernhard Nocht Institute for Tropical Medicine, Hamburg) reported similar findings from other SARS patients but others were still arguing for other etiologies (e.g., human metapneumovirus). Sharing of data within the WHO network allowed a rapid consensus that the novel coronavirus was indeed the cause of SARS.

The discovery that a severe respiratory disease caused by a coronavirus was a surprise, because previously known human CoVs (OC43 and 229E) were primarily associated with mild upper respiratory infections. Virological and epidemiological features of SARS (namely, low virus load and low transmissibility in the first few days of illness and rarity of asymptomatic infections) allowed case detection and isolation, thereby breaking the transmission chain to contain the outbreak. Unfortunately, it was apparently early on that SARS-CoV-2 was very different, transmitting more like influenza, which ultimately made the same measures for SARS insufficient to contain COVID-19 (2).

The discovery of a SARS-CoV raised the question about its origins because serology of blood donor sera collected prior to the outbreak indicated this virus was new to humans. The epidemiology of the earliest cases in Guangdong in late 2002 highlighted that occupational exposure to wild game animal markets was a common factor. We subsequently detected SARS-CoV in Himalayan palm civets and other small mammals found in these animal markets, suggesting this was the interface where the species jump to humans occurred (3). The closure of these markets in Guangdong very likely prevented the re-emergence of SARS from this source after the global outbreak was contained. Further work, however, suggested that civets in the wild had no evidence of virus infection. Testing of a range of wild animal species in Hong Kong revealed coronaviruses in insectivorous bats, the first time coronaviruses had been detected in bats (4), though the initial bat coronavirus was not similar to SARS-CoV. *Rhinolophus* bats were eventually identified as the natural reservoir of a group of SARS-CoV-like bat coronaviruses (5). As it turned out, SARS-CoV-2 did re-emerge from this reservoir. Extensive studies of coronaviruses in bats has led to the realization that other human coronaviruses (e.g., 229E and NL63) might also emerge from bats in the past,

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highlighting the pandemic potential of CoVs (6). The emergence of Middle East Respiratory Syndrome (MERS) in 2012, caused by another coronavirus, heightened the global public health concern arising from zoonotic coronaviruses.

SARS demonstrated that an infectious disease emerging anywhere can have a major global impact. This led to the implementation of the International Health Regulations in 2015, which obliged countries to develop capacity to detect, report, and respond to unusual infectious disease outbreaks. Under this policy, SARS and 3 other infectious diseases were classified as diseases of serious public concern. In addition, in 2016 the WHO identified highly pathogenic coronaviruses relevant to humans (i.e., SARS and MERS) as one of the 8 categorical priority diseases for research and development of countermeasures (7).

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article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

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References

1. Poon LL, Wong OK, Chan KH, Luk W, Yuen KY, Peiris JS, Guan Y. Rapid diagnosis of a coronavirus associated with severe acute respiratory syndrome (SARS). *Clin Chem* 2003; 49:953-5.
2. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med* 2020;382:1177-9.
3. Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX, Cheung CL, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science* 2003;302:276-8.
4. Poon LL, Chu DK, Chan KH, Wong OK, Ellis TM, Leung YH, et al. Identification of a novel coronavirus in bats. *J Virol* 2005;79:2001-9.
5. Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH, et al. Bats are natural reservoirs of SARS-like coronaviruses. *Science* 2005;310:676-9.
6. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol* 2019;17:181-92.
7. World Health Organization. An R&D blueprint for action to prevent epidemics. https://www.who.int/blueprint/about/r_d_blueprint_plan_of_action.pdf?ua=1 (Accessed July 2020).