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REVIEWS

Spotlight

Unveiling the Origin and Transmission of 2019-nCoV

Yifei Xu[1,*]

A novel coronavirus has caused thousands of human infections in China since December 2019, raising a global public health concern. Recent studies (Huang *et al.*, Chan *et al.*, and Zhou *et al.*) have provided timely insights into its origin and ability to spread among humans, informing infection prevention and control practices.

The novelist Paulo Coelho once wrote that 'Everything that happens twice will surely happen a third time'. While our memory of the fatal severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) has not faded, a third, novel coronavirus (2019-nCoV) is coming into the spotlight. 2019-nCoV was first detected in Wuhan, China, in December 2019, and quickly spread across the country (Figure 1A). As of 8 February 2020, >34 800 confirmed 2019-nCoV cases and 724 deaths have been reported in China and 24 other countries [1]. WHO declared 2019-nCoV a public health emergency of international concern on 30 January 2020. Several recent studies have provided critical and timely insights into the origin and human-to-human transmission of this virus [2–4].

A group of Chinese scientists investigated the epidemiological data of the first 41 2019-nCoV patients admitted to a hospital in Wuhan before 2 January 2020 [2]. Twenty-seven (66%) of the patients had a direct contact history with the local Huanan seafood market where live and slaughtered wild animals were sold for food consumption. The Huanan market and its wild animals were suspected of being the source of human infection by 2019-nCoV. Zhou *et al.* retrieved five complete genomes from samples collected from 2019-nCoV patients and, through genome analysis, they found that the virus is a betacoronavirus that shares a sequence identity of 96% with a coronavirus found in bats [4]. The spike gene of coronavirus has been shown to play a critical role in interspecies transmission: Zhou and colleagues found that 2019-nCoV can use ACE2 as a cell entry receptor. In this way, 2019-nCOV resembles SARS-CoV [5,6].

SARS-CoV and MERS-CoV originated from bats, both jumping species to infect humans through different intermediate hosts [7] (Figure 1B). It is suspected that palm civets sold in live animal markets were the intermediate host for SARS-CoV [7,8]. MERS-CoV was transmitted through dromedary camels [7,8]. Identification of the intermediate host for a novel virus is not a trivial investigation, and it is not yet clear whether 2019-nCoV infected humans via direct transmission from a bat or through intermediate hosts.

Chan *et al.* conducted an epidemiological and genomic investigation of a household cluster of six patients in Shenzhen, a major city located 1000 km from Wuhan; this provided evidence for human-to-human transmission and intercity spread of 2019-nCoV [3]. Among the six patients, five were found to be infected with 2019-nCoV after visiting Wuhan, and the remaining patient, who had not recently traveled to Wuhan, acquired the infection through close contact with family members in Shenzhen. None of the family members had been in contact with the Huanan market, or with wild animals, but two of them had been to a hospital in Wuhan during their visit, suggesting that these patients had acquired the infection in the Wuhan hospital and had brought the virus back to Shenzhen, subsequently transmitting it to the family member.

Although the Huanan market in Wuhan was highly relevant to the emergence and spread of 2019-nCoV, and the virus has been detected in environmental samples from the market, the origin of this virus has not been determined conclusively. Analysis of available 2019-nCoV genomes has shown very limited genetic diversity, indicating that these genomes share a very recent common ancestor. Examination of the epidemiological data in [2] found that the first known patient, and the other 13 out of the 41 initial patients, had no contact history with the Huanan wet market. Moreover, the first patient shared no epidemiological link with any patient in the cohort. Thus, it is possible that there was more than one source of infection. For example, a homogeneous virus may have existed in the supply chain of wild animals, and in Huanan and other markets in the city. Regardless of its initial source, it is likely that 2019-nCoV was introduced into a small cluster of humans from a cluster of infected animals and, from there, the virus acquired the capacity for human-to-human transmission, spreading in the city before the cluster of patients from the Huanan market was identified.

Clinical data have shown that the date of symptom onset of the first known patient was 1 December 2019 [2]. Given the known incubation period – between 1 and 14 days – the interspecies transmission could have occurred as late as November 2019. Because none of the family members of the first known patient have developed fever, or any common respiratory symptoms, it is reasonable to speculate as to whether more than one introduction of 2019-nCoV occurred, with the hypothesis that some strains cannot transmit between humans while others have acquired the capacity for human-to-human transmission, causing the current outbreak.

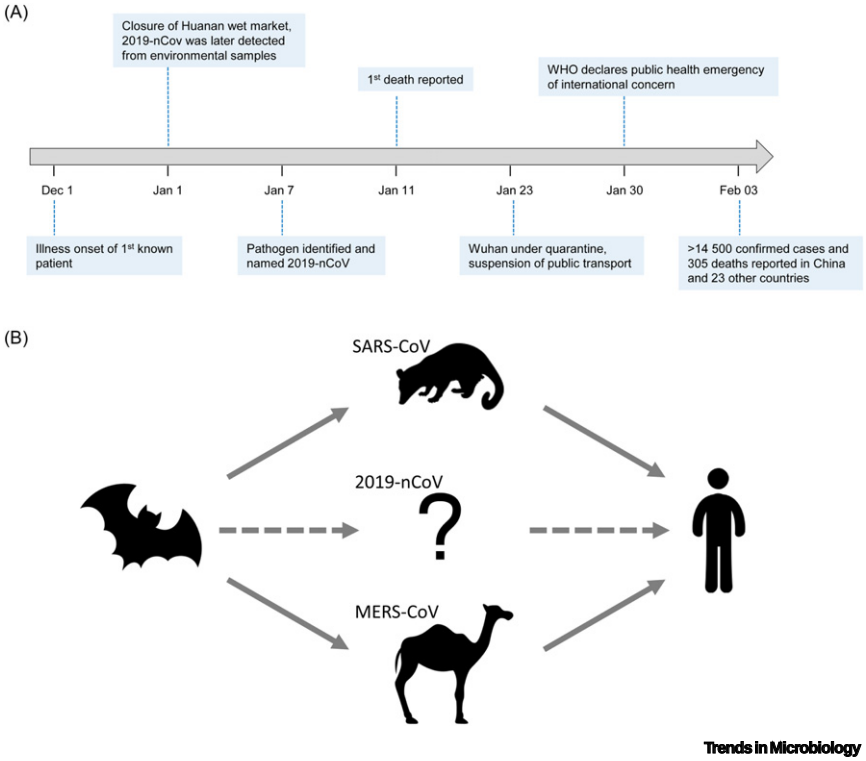

Figure 1. The Possible Interspecies Transmission Route and Timeline of 2019-nCoV. (A) Timeline of major events in the 2019-nCoV outbreak. (B) Potential interspecies transmission routes of SARS-CoV, MERS-CoV, and 2019-nCoV. The question mark and broken line denote unknown intermediate host and suspected transmission.

The origin of 2019-nCoV merits in-depth investigations, with a few key questions that also need to be addressed thoroughly. (i) What is the molecular mechanism underlying the interspecies transmission of 2019-nCoV? How is this mechanism similar to, or distinct from, that associated with the emergence of SARS-CoV and MERS-CoV? (ii) What is the role played by point mutation and recombination in the evolution of 2019-nCoV? Since coronaviruses can experience rapid mutation and frequent recombination, will these activities generate novel strains with heightened transmissibility and pathogenicity? (iii) How prevalent is the virus in its natural host, and does it possess the ability to infect other animals? This question is relevant because coronavirus originating in the bat has been found to cross the species barrier and infect pigs [9], which are hypothesized to serve as the 'mixing vessels' for the generation of genetically novel viruses. The introduction of 2019-nCoV into livestock animals could pose a potential threat to both agriculture and public health.

Following the emergence of SARS-CoV and MERS-CoV, 2019-nCoV represents a third major emergence of a novel coronavirus. It is now time to learn from the lessons of these two previous outbreaks to prevent the spread of further disease from 2019-nCoV.

[1]Nuffield Department of Medicine, University of Oxford, Oxford, UK

*Correspondence:
yifei.xu@ndm.ox.ac.uk (Y. Xu).

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Spotlight

Tracing the Origin of Invasive Fungal Infections

Nicolas Papon,[1,*] Marie-Elisabeth Bougnoux,[2,3] and Christophe d'Enfert[2]

Invasive fungal infections are a major cause of mortality in immunocompromised patients. By using high-resolution sequencing, Zhai *et al.* provide insight into translocation of *Candida* strains from the gut mycobiota to the bloodstream of transplanted patients. Microbiota-driven diagnostic methods could rapidly emerge for preventing deadly fungal infections.

Globally, the incidence of fungal infections in human health represents a worldwide burden evidenced by the worrisome prevalence values of roughly 1 billion cases of superficial mycosis, 20 million cases of allergic fungal disease, and more than 1 million cases of invasive fungal infections