



Review

From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses

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ABSTRACT

This article introduces a series of invited papers in *Antiviral Research* marking the 10th anniversary of the outbreak of severe acute respiratory syndrome (SARS), caused by a novel coronavirus that emerged in southern China in late 2002. Until that time, coronaviruses had not been recognized as agents causing severe disease in humans, hence, the emergence of the SARS-CoV came as a complete surprise. Research during the past ten years has revealed the existence of a diverse pool of coronaviruses circulating among various bat species and other animals, suggesting that further introductions of highly pathogenic coronaviruses into the human population are not merely probable, but inevitable. The recent emergence of another coronavirus causing severe disease, Middle East respiratory syndrome (MERS), in humans, has made it clear that coronaviruses pose a major threat to human health, and that more research is urgently needed to elucidate their replication mechanisms, identify potential drug targets, and develop effective countermeasures. In this series, experts in many different aspects of coronavirus replication and disease will provide authoritative, up-to-date reviews of the following topics:

- clinical management and infection control of SARS;
- reservoir hosts of coronaviruses;
- receptor recognition and cross-species transmission of SARS-CoV;
- SARS-CoV evasion of innate immune responses;
- structures and functions of individual coronavirus proteins;
- anti-coronavirus drug discovery and development; and
- the public health legacy of the SARS outbreak.

Each article will be identified in the last line of its abstract as belonging to the series “From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses.”

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1. Introduction

“Those who cannot remember the past are condemned to repeat it”
– George Santayana.

Ten years ago, a novel coronavirus causing pneumonia in humans emerged in Guangdong, China. The first known patient was a 45-year old man in the city of Foshan, who developed fever and respiratory symptoms on November 16, 2002, transmitting infection to his wife and three other family members. The second index case was a restaurant chef in Shenzhen who became ill on 10 December, returned to his home in Heyuan and transmitted infection to health care workers (HCWs) in the local hospital, including the physician who accompanied him in an ambulance to Guangzhou provincial hospital. This scenario of the emergence of clusters of cases of severe respiratory disease among family members and hospital workers, each cluster apparently going extinct after a few rounds of secondary or tertiary transmission, was played out repeatedly in subsequent weeks in a number of municipalities in Guangdong province. The index cases of many of these early case clusters were food handlers or chefs working in restaurants where a variety of exotic and game animals were

slaughtered on the premises (Xu et al., 2004a). During subsequent weeks, the outbreak became self-sustaining, with large clusters of transmission in hospitals spilling back into the community (Table 1).

The first “super-spreading” event, which became a hallmark of the epidemiology of this disease, occurred with the hospitalization of a 44-year old man in Guangzhou on 30 January, 2003. He was to transmit infection to 19 relatives and more than 50 hospital staff. On 21 February, one of the doctors infected as part of this extended hospital outbreak traveled to Hong Kong, where he stayed one night in a hotel and was hospitalised the next day. During his stay, he transmitted infection to 16 other hotel guests and one visitor, who traveled on to their destinations, seeding outbreaks of this disease in Vietnam, Singapore, Toronto and in Hong Kong. On 12 March, following the outbreaks in mainland China, Hong Kong and Vietnam, the World Health Organization (WHO) issued a global alert about an unusual pneumonia which appeared to cause outbreaks of disease in hospitals. This led to the recognition and reporting of additional case clusters in Toronto and Singapore, prompting the WHO to issue an Emergency Travel Advisory on 15 March, providing an early case definition and naming the dis-

Table 1

SARS and its aftermath: a chronology of events over the past ten years. Partly based on WHO Western Pacific Region (2006).

Date	Key events
16 November 2002	A 45-year-old man in Foshan city, Guangdong province, China develops an atypical pneumonia and infects four relatives. This is the first identified case of SARS from epidemiological investigations.
10 December 2002	A 35-year-old restaurant worker in Shenzhen develops pneumonia and 8 health care workers in contact with him become ill.
8 January 2003	A 26-year-old man working in the game animal trade in Guangxi Province (adjacent province to Guangdong) develops pneumonia and infects family members.
January 2003	Pneumonia outbreaks in Guangzhou (capital city of Guangdong Province).
23 January 2003	Guangdong Health Bureau circulates document giving case definition and control measures to health bureaus and hospitals in the province.
30 January 2003	A patient hospitalized in Guangzhou transmits infection to more than 50 hospital staff and 19 relatives, the first of many “super-spreading” events.
11 February 2003	WHO receives reports of an outbreak of respiratory disease in Guangdong, 305 cases and 5 deaths. One-third of cases are health care workers infected while caring for patients with similar illness.
21 February 2003	A doctor from Guangdong caring for patients with atypical pneumonia checks in at Hotel M in Hong Kong to attend a wedding. He had been ill since 15 February, but now deteriorates further and is hospitalized on 22 February. He infects 16 other guests and one visitor at this hotel, some of whom travel on to Vietnam, Singapore and Toronto where they initiate local clusters of transmission.
26 February 2003	A Hotel M contact is admitted to a private hospital in Hanoi and is the source of an outbreak there. Seven health care workers ill by 5 March.
4 March 2003	A Hotel M contact admitted to Prince of Wales Hospital, Hong Kong. He had been ill since 24 February, but his illness is not severe and not recognized as a possible case of the new “atypical pneumonia”. By 7 March, health care workers at this hospital report a respiratory illness. Overall, he infects 50 health care workers, 17 medical students, 30 other patients and 42 visitors to the ward and 4 family members.
5 March 2003	A Hotel M contact dies in Toronto. Five family members affected.
12 March 2003	WHO issues global alert.
14 March 2003	Singapore and Toronto report clusters of atypical pneumonia. In retrospect, both groups have an epidemiological link to Hotel M. One of the doctors who had treated patients in Singapore has gone to New York and develops symptoms while traveling. He is quarantined as his flight lands in Frankfurt, Germany. He has infected two family members travelling with him and one crew member.
15 March 2003	The WHO has received reports of over 150 cases of this new disease, now named Severe Acute Respiratory Syndrome (SARS). Travel advisory issued.
17 March 2003	A WHO multi-center laboratory network is established for the study of SARS causation and diagnosis.
21–27 March 2003	A novel coronavirus is identified in patients with SARS.
14 April 2003	Mapping of the full genome of SARS-CoV is completed.
16 April 2003	WHO announces that SARS-CoV is the causative agent of SARS.
23 May 2003	A virus related to SARS-CoV is detected in animals in Guangdong.
5 July 2003	Absence of further transmission in Taiwan signals the end of the SARS outbreak in humans.
September 2003 – February 2004	Laboratory-acquired SARS cases reported in Singapore, Taiwan and Beijing. The case in Beijing leads to limited community transmission in Beijing and Anhui.
December 2003 – January 2004	Transient re-emergence of SARS infecting humans from animal markets.
23 May 2005	The International Health Regulations are adopted by the Fifty-eighth World Health Assembly on 23 May 2005. They enter into force on 15 June 2007.
September 2012	A novel coronavirus causing respiratory disease is isolated in Saudi Arabia. Earlier cases in Jordan (April 2012) were retrospectively diagnosed. The aetiological agent is a novel human β -coronavirus, subsequently named the Middle East respiratory syndrome (MERS) coronavirus.
1 April – 23 May 2013	Outbreak of over 20 cases of MERS reported in hospitals in Al-Ahsa, in eastern Saudi Arabia.
As of 7 September 2013	114 confirmed cases of MERS have been reported to WHO, leading to 54 deaths. Index cases have occurred in Jordan, Saudi Arabia, Qatar and the United Arab Emirates. Imported cases, sometimes with limited secondary transmission, have been reported from France, Germany, Italy, Tunisia and the United Kingdom.

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