REVIEW

# Severe acute respiratory syndrome: lessons and uncertainties

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## ABSTRACT

**The outbreak of severe acute respiratory syndrome (SARS) has produced scientific and epidemiological discoveries with unprecedented speed, and this information has been spread instantaneously to the global health community through the internet. Within a few weeks, the coronavirus associated with SARS (SARS-CoV) was identified and sequenced. The source of the outbreak and the exact modes of transmission are still subjects of research. Important lessons can be learned from the SARS outbreak about both the scientific and the public health approach to emerging pathogens.**

In November 2002, over 300 cases of highly contagious and severe atypical pneumonia of unknown cause had occurred in the Guangdong province in southern China. Many cases were rapidly fatal.[1] This outbreak went unnoticed until February 2003, when a physician from Guangdong became ill while staying at a hotel in Hong Kong. Twelve guests became infected, including at least seven who stayed in rooms on the same floor. These hotel guests subsequently became the index patients who spread the infection to Singapore, Vietnam, Canada and a variety of other countries. As of 9 June 2003, severe acute respiratory syndrome (SARS) has been diagnosed in more than 8400 patients in 32 countries, with a death rate of 9.3%.[2]
Starting on 13 March, 2003, the World Health Organization (WHO) coordinated an international investigation that has produced scientific and epidemiological discoveries with unprecedented speed. What is just as impressive as the speed of scientific discoveries is the instantaneous spread of information. Satellite broadcasts, webcasts and videoconferencing as well as rapid publications on the internet by the major scientific journals have supported the dissemination of emerging information to the entire global health community.
In the early 1980s, it took competing laboratories two years to identify HIV as the cause of AIDS. In 2003, an international network of 13 laboratories in ten countries was created, sharing knowledge and collaborating in an unprecedented fashion, using daily teleconferences and a secure website for sharing research data in real-time. This effort lead to identification of the coronavirus associated with SARS (now named SARS-CoV) within two weeks, and the sequencing of its entire genome in two more weeks.[3,4] Sequences were compared with those of previously characterised coronavirus strains and within days it was clear that this virus was distinct from all known human pathogens. SARS-CoV has been found in patients with SARS, using a variety of methods including tissue culture, electron microscopy, microarray technology, and polymerase chain reaction (PCR), by teams in Europe and the US.[5,6] In addition, serum was tested for antibodies to SARS-CoV, and seroconversion was documented in patients with SARS. Importantly, Osterhaus and colleagues in Rotterdam have satisfied Koch's postulates by demonstrating that monkeys develop SARS only after injection of the SARS-CoV, but not by other candidate viruses.[7]

The source of the outbreak is still a subject of speculation and research. Coronaviruses cause disease in many animals, including pigs, cattle, chickens, cats and dogs. Genetic changes occur frequently and the virus has been associated with upper respiratory infections in humans. Regions like the Chinese province of Guangdong, with its subtropical climate and a population of 75 million living in close proximity to animals, may be the world's melting pot for recombinant animal viruses crossing species to humans. Future research, such as serological tests of wild and domestic animals and birds may identify the natural host. Likely candidates are the masked palm civet (*Paguma larvata*), the raccoon dog (*Nyctereutes procyonoides*), and the Chinese ferret badger (*Melogale moschata*). An important question is whether SARS-CoV lost its ability to infect its original host when it jumped to humans. The lack of an animal reservoir would increase the chance of containing the outbreak.

The unusually rapid transmission suggests that not only large droplets, requiring intimate or face-to-face contact with a patient or inoculation of mucous membranes, transmit the virus but that other routes of transmission may be possible. Airborne transmission through droplet nuclei could account for the extensive spread within buildings that has been observed in Hong Kong. Obviously, this mode of transmission would make containment of the outbreak more challenging. Alternatively, viral contamination of sewers or water supply systems, leading to faecal-oral transmission, has been suggested as source of the increased spread in a Hong Kong apartment complex. The detection of SARS-CoV in faecal as well as in respiratory specimens has confirmed that this virus, like many animal coronaviruses, may indeed be spread both by faecal contamination and by respiratory droplets. This dual tropism is another challenge for the management of the outbreak. Furthermore, fomite transmission could be relevant, since coronaviruses can survive on contaminated objects in the environment. It has been suggested that a few persons may be especially infectious ('super spreaders') and that most others are less likely transmit the virus, but this concept is still speculative.
Experiments with other coronaviruses have demonstrated several worrisome properties, including persistent infection, lack of protective immunity and immune enhancement, i.e. antiviral antibodies contributing to disease progression. Either these problems or co-infection with a yet unidentified virus may explain the relatively high mortality rates among SARS patients.

The infection of a large proportion of exposed medical and nursing personnel has caused considerable anxiety. While caring for the index patient in Hong Kong, 69 healthcare workers and 16 medical students, all with unremarkable medical histories, developed SARS, in turn leading to 26 tertiary cases which included family members of the infected healthcare workers.[8,9] Likewise, brief contacts by both the family physician and visitors were sufficient to transmit the infection from the index patient in Toronto.[10] Moreover, another patient was infected and died from SARS, after having been observed in the emergency department on a gurney separated by a cotton curtain from the index patient, without any direct contact. While recent research in the field of infection control is primarily directed at other topics, the SARS epidemic clearly points out the importance of basic infection control measurements.

It is still unclear whether the epidemic will disappear, level off and develop a seasonal pattern of limited upsurges in the future, or become a pandemic. If SARS transmission evolves to mimic that of influenza, containment may well be impossible without vaccination.
As has happened repeatedly in the past with other diseases for which a rapid and accurate diagnostic test is not (yet) available, national and local health authorities have been using the surveillance definition of proven and probable SARS as a basis for guidelines for recognition and isolation of possible clinical cases. However, case definitions that have been designed for surveillance aim at a high level of specificity, whereas optimal clinical care for the individual patient and prevention of secondary cases require highly sensitive case criteria. For example, whereas surveillance criteria may require the presence of fever and a pulmonary infiltrate, many patients proven to be infected with SARS in both the Hong Kong and Toronto populations did not have frank pulmonary infiltrates or had hypothermia or a normal temperature rather than fever.[8-10]

Treatment of patients with SARS is basically supportive, since no specific therapeutic agent is available. In this issue of the Journal, Van Vonderen *et al.* have reviewed the available data on treatment with the antiviral drug ribavirin or corticosteroids in severely ill patients.[11] A rationale for the use of corticosteroids derives from the similarity of the pulmonary signs to those seen in bronchiolitis obliterans with organising pneumonia (BOOP). While it appears that there is no rationale in prescribing ribavirin, the use of corticosteroids in severe cases is still a matter of debate.[11]

The emergence of SARS has represented a major challenge. Speed of scientific discovery and speed of communication are hallmarks of the response to SARS and reflect impressive achievements in science, epidemiology and international collaboration. The investigation of the SARS outbreak may serve as a template for laboratory and epidemiological response to future infectious-disease pandemics.
However, we do not know where we are currently on the epidemic curve. It is still unclear whether the epidemic will level off or will continue to move faster than our scientific and control capacities. The outcome cannot be predicted.

## SARS ON THE WWW

- LCI: public health site including important protocols for healthcare institutions in the Netherlands (in Dutch), www.infectieziekten.info
- World Health Organization: WHO's information on SARS and other health information of international significance, www.who.int/en/
- The Center for Disease Control's site on SARS: info on SARS from this federal government agency (diagnosis, travel, treatment, etc.), www.cdc.gov/ncidod/sars
- Health Canada (healthcare professionals section): guidelines and all basic information, www.hc-sc.gc.ca/pphb-dgspsp/sars-sras/index.html
- Hong Kong: Hong Kong Special Administrative Region Health Department, www.info.gov.hk/info/sars/eindex.htm
- PubMed: special SARS link to all recent literature at once, www.ncbi.nlm.nih.gov.library.csuhayward.edu/entrez/query.fcgi
- SARS Reference: medical textbook with comprehensive and up-to-date overview of SARS, www.sarsreference.com/index.htm

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