



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

# Severe Acute Respiratory Syndrome

## Historical, Epidemiologic, and Clinical Features



David S.C. Hui, MBBS, MD(UNSW), FRACP, FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)<sup>a,\*</sup>,

Alimuddin Zumla, MBChB, MSc, PhD, MD, FRCP(Lond), FRCP(Edin), FRCPath(UK), FAAS<sup>b</sup>

### KEYWORDS

• SARS • Coronavirus • Epidemic • Epidemiology • Clinical • Prevention

### KEY POINTS

- Severe acute respiratory syndrome (SARS) is highly infectious zoonotic respiratory disease of humans with significant morbidity and mortality. The specific animal host reservoir remains unknown although horseshoe bats are reservoirs of coronaviruses.
- SARS is caused by SARS-coronavirus (SARS-CoV), which first emerged in China and gained global notoriety in 2002 to 2003 causing a travel-related global outbreak with 8098 cases and 774 deaths. Nosocomial transmission of SARS-CoV was common.
- The main mode of transmission of SARS-CoV is person-to-person spread through inhalation of respiratory droplets. Feco-oral transmission via contaminated fomite on surfaces has been recorded.
- Fever and respiratory symptoms, such as influenza predominate, and diarrhea is common. About 25% of cases can rapidly progress and require intensive care.
- Treatment involves supportive care with appropriate fluid and electrolyte balance, oxygenation, and organ support. Convalescent plasma, protease inhibitors, and interferon might confer beneficial effects.
- Prevention requires strict infection control procedures, with respiratory and contact precautions for routine care, but upgrade to airborne precaution is needed for managing aerosol-generating procedures.

---

Disclosure: D.S. Hui and A. Zumla have an interest in global public health, emerging and re-emerging infections, particularly respiratory tract infections. Both authors have research interests in coronaviruses.

<sup>a</sup> Department of Medicine and Therapeutics, Stanley Ho Center for Emerging Infectious Diseases, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong; <sup>b</sup> Center for Clinical Microbiology, University College London, Royal Free Campus 2nd Floor, Rowland Hill Street, London NW3 2PF, United Kingdom

\* Corresponding author.

E-mail address: [dschui@cuhk.edu.hk](mailto:dschui@cuhk.edu.hk)

Infect Dis Clin N Am 33 (2019) 869–889

<https://doi.org/10.1016/j.idc.2019.07.001>

0891-5520/19/© 2019 Elsevier Inc. All rights reserved.

[id.theclinics.com](http://id.theclinics.com)

## INTRODUCTION

Over the past 2 decades 2 previously unknown coronaviruses (CoVs), the severe acute respiratory syndrome CoV (SARS-CoV) and the Middle East respiratory syndrome CoV (MERS-CoV) have focused medical, scientific, and media attention because of their lethal nature and epidemic potential. In November 2002, the first case of SARS occurred in Foshan, China,<sup>1</sup> and in June 2012, the first case of MERS died at a hospital in Jeddah, Saudi Arabia. Both zoonotic diseases remain on the World Health Organization (WHO) list of blueprint priority diseases because they remain global threats to global public health security.<sup>2</sup> This review focuses on the historical, epidemiologic, and clinical features of SARS.

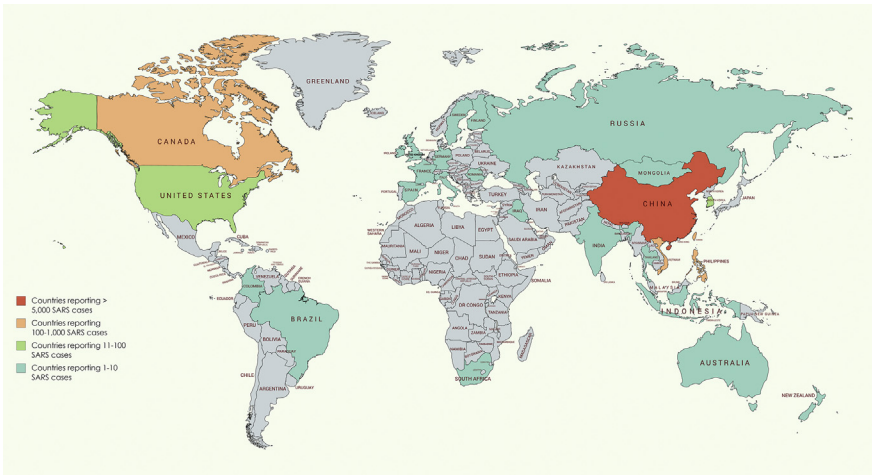
## HISTORICAL

Before 2003, only 2 CoVs, human CoV 229E (HCoV-229E) and HCoV-OC43, were known to cause human disease. These manifest with mild symptoms like the common cold in adults and with more severe disease in infants, the elderly, and the immunosuppressed. In November 2002, unusual cases of “atypical pneumonia” of unknown cause occurred in Foshan City, Guangdong province, in China, where many health care workers became infected.<sup>1</sup> The infection was brought to Hong Kong on February 21, 2003, by a physician who had looked after similar cases of atypical pneumonia in mainland China, leading to subsequent outbreaks of severe pneumonia in Hong Kong and labeled by WHO as “severe acute respiratory syndrome” on March 15, 2003.<sup>3–5</sup> Several months elapsed and several hundred cases of SARS were observed before SARS-CoV was identified. A novel  $\beta$  CoV (SARS-CoV) of lineage B was confirmed as the cause of the atypical pneumonia cases on March 22, 2003.<sup>4</sup> The SARS-CoV epidemic spread to 29 countries and regions, and it was evident that the global public health, medical, and scientific communities were not adequately prepared for the emergence of SARS. Chains of human-to-human transmission occurred in Toronto in Canada, Hong Kong Special Administrative Region of China, Chinese Taipei, Singapore, and Hanoi, Viet Nam. The history of the SARS epidemic was short and WHO declared the end of the SARS epidemic in July 2003. There were a total of 8096 SARS cases (which included 774 deaths)<sup>4</sup> reported from 29 countries and regions.<sup>5</sup> **Fig. 1** shows the geographic map of distribution of SARS cases.

During the epidemic, SARS caused major disruptions to international air travel, and had a major impact on the health services and business in affected countries.<sup>6</sup> Since July 2003, there were 4 occasions when SARS has reappeared, 3 of these were attributed to breaches in laboratory biosafety in Singapore, Taipei, and Beijing, where 7 cases were associated with 1 chain of transmission and with hospital spread. The fourth incident in Guangdong province, China, resulted in 4 sporadic community-acquired cases over a 66-week period from December 2003 to January 2004. Three cases had been exposed to animals or environmental sources. There was no further community transmission.

## VIROLOGY

Coronaviruses (order *Nidovirales*, family *Coronaviridae*, subfamily *Coronavirinae*) are a group of enveloped, positive-sense, single-stranded, highly diverse RNA viruses that are further divided into 4 genera:  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ .<sup>7</sup> CoVs may cause diseases of varying severity in different systems in humans and other animal species. In March 2003, a novel group 2b  $\beta$  CoV was confirmed as the causative agent responsible for



**Fig. 1.** Global distribution of SARS.

SARS-CoV infection.<sup>4,8,9</sup> The genome sequence of the SARS-CoV did not bear close relationship to any of the previously identified CoVs.<sup>10,11</sup>

SARS-CoV genome consists of 5′ methylated caps and 3′ polyadenylated tails. The partially overlapping 5′ terminal open reading frame 1a/b (ORF1a/b) is within the 5′ two-thirds of the CoV genome and encodes the large replicase polyprotein 1a (pp1a) and pp1ab. These polyproteins are cleaved by 3C-like serine protease and papain-like cysteine protease to produce nonstructural proteins, such as RNA polymerase and helicase, which are important enzymes involved in the transcription and replication of CoVs. The 3′ one-third of the CoV genome encodes the structural proteins (spike [S], envelope [E], membrane [M], and nucleocapsid [N]), which are important for virus-cell receptor binding and assembly of virion, and other accessory proteins and nonstructural proteins that may have immunomodulatory effects.<sup>7</sup>

## HOST RESERVOIR

Data from a retrospective serology study done in Guangzhou in southern China, suggested that the SARS-CoV might have transmitted from animal species to humans in the wet market, because a high sero-prevalence (16.7%) was found among asymptomatic wild animal salesmen.<sup>12</sup> A highly similar variant of SARS-CoV was detected in palm civets at an animal market located in Shenzhen.<sup>13</sup> Masked palm civets were then assumed to be accountable for the transmission of SARS-CoV to humans because 30% of wild animal handlers were found to have positive serology against SARS-CoV infection compared with 1% of controls in Guangdong province.<sup>13</sup> In addition, up to 39% of SARS-CoV cases that arose in the early stage of the outbreak were associated with a history of exposure to animal markets.<sup>14</sup> This assumption was further enhanced by an epidemiology linkage in 3 of the 4 patients to indirect or direct contact with palm civets during the sporadic outbreaks of SARS-CoV infection that occurred in Guangzhou in December 2003 and January 2004.<sup>15,16</sup>

Subsequently, however, Chinese horseshoe bats were found to carry SARS-like CoVs in 2005,<sup>17,18</sup> with a high degree of nucleotide sequence similarity (88%–92%) to human or civet cat isolates, suggesting that bats could well have been the natural source of an early ancestor of SARS-CoV. It remains uncertain as to whether an intermediate mammalian host is involved before human transmission.

## **PATHOGENESIS**

The pathogenesis of SARS is complex, and not fully defined because multiple factors govern the wide-ranging clinical manifestations from mild to severe disease.<sup>19</sup> Apart from the respiratory tract, SARS-CoV can infect several organs and cell types during the course of the disease, including intestinal mucosal cells, renal tubular epithelial cells, neurons, and cells of the lymphoid and reticuloendothelial system.<sup>19</sup>

### ***Entry into Host Cells and Pathology***

---

SARS-CoV invades humans through the respiratory tract as the entry site,<sup>20</sup> and infection occurs in 3 steps: receptor binding, conformational changes in S glycoprotein, and cathepsin L proteolysis within endosomes.<sup>21</sup> Entry of SARS-CoV is mediated by angiotensin-converting enzyme 2 (ACE2), a metallopeptidase that is expressed on many human organ tissues, as the host functional receptor.<sup>22</sup> ACE2 is present abundantly in the epithelia of human lungs and small intestine,<sup>23</sup> but the presence of ACE2 may not be the sole requirement for SARS-CoV tropism. One example is that, despite the abundant expression of ACE2 in vascular endothelial cells and intestinal smooth muscle cells, SARS-CoV was not detected in these cells, whereas it was found in colonic enterocytes and hepatocytes without ACE2 expression.<sup>23,24</sup>

### ***Histology***

---

Several autopsies of patients with SARS showed the predominant pathologic finding as diffuse alveolar damage (DAD). Lung histopathology in patients with SARS included DAD, loss of cilia, squamous metaplasia, denudation of bronchial epithelia, giant-cell infiltrate, with a marked increase in macrophages in the alveoli and the interstitium. ACE2 may contribute to the development of DAD. SARS-CoV infections and the S glycoprotein of the SARS-CoV could reduce ACE2 expression. In the mouse model, injection of SARS-CoV S glycoprotein worsened acute lung injury (ALI) in vivo that could be reduced by blocking the renin-angiotensin pathway.<sup>25</sup> In addition, overexpression of SARS-CoV proteins such as 3a and 7a, which were expressed in the lungs and intestinal tissues of patients with SARS, could induce apoptosis in vitro.<sup>26,27</sup>

Splenic atrophy of the white pulp, hemophagocytosis, hyaline membranes, and secondary bacterial pneumonia were observed.<sup>28,29</sup> Lesions resembling cryptogenic organizing pneumonia (COP) in subpleural regions were also seen.<sup>30</sup> Extensive expression of SARS-CoV antigen in type I pneumocytes in cynomolgus macaques experimentally infected with SARS-CoV was noted at day 4, suggesting that type I pneumocytes might be the early primary target for SARS-CoV infection.<sup>31</sup> Diarrhea was present in up to 70% of SARS cases.<sup>24,32</sup> In specimens obtained by colonoscopy or postmortem examination, active viral replication was noted within the small and large intestine with minimal architectural disruption. SARS-CoV infection was confirmed by viral culture of these specimens, while SARS-CoV RNA was detected in the stool specimens for almost 10 weeks after illness onset.<sup>24</sup> The presence of diarrhea and mortality were associated with a higher nasopharyngeal SARS-CoV viral load on day 10 after illness onset.<sup>33</sup>

### ***Immune Responses and Immunopathology***

---

While innate and acquired immune responses enable containment of virus and mild disease, cytokine dysregulation, viral cytopathic effects, downregulation of lung ACE 2, abnormal immune responses, and autoimmune mechanisms may lead to more severe disease and death, disease progression in SARS may be related to activation of T-helper (Th1) cell-mediated immunity and hyperinnate inflammatory

response.<sup>28,32</sup> Marked increases in the Th1 and inflammatory cytokines (interferon- $\gamma$  [IFN- $\gamma$ ], interleukin-1 [IL-1], IL-6, and IL-12) were noted for more than 2 weeks after illness onset in a study of 20 adults with SARS-CoV infection, together with marked increases in chemokines such as Th1 chemokine IFN- $\gamma$ -inducible protein-10 (IP-10), neutrophil chemokine IL-8, and monocyte chemoattractant protein-1 (MCP-1).<sup>34</sup> In mice infected with SARS-CoV, T cells played an important role in SARS-CoV clearance, whereas a reduced T-cell response contributed to severe disease.<sup>35</sup> In another study of mice infected with SARS-CoV, robust virus replication accompanied by delayed type I IFN (IFN-I) response was observed orchestrating inflammatory responses and lung immunopathology with reduced survival, while early administration of IFN-I ameliorated immunopathology. This delayed IFN-I signaling was thought to promote the accumulation of pathogenic inflammatory monocyte-macrophages, leading to elevated lung cytokine/chemokine levels, vascular leakage, and impaired virus-specific T-cell responses, whereas genetic ablation of the IFN- $\alpha\beta$  receptor or inflammatory monocyte-macrophage depletion protected mice from fatal infection, without affecting viral load.<sup>36</sup>

In addition, Toll-like receptors (TLR) signaling through the TIR domain-containing adapter-inducing INF- $\beta$  (TRIF) adaptor protein might play a role in protecting mice from lethal SARS-CoV disease based on a study of the innate responses in mice.<sup>37</sup> TLR3(-/-), TLR4(-/-), and TRIF-related adapted molecule [TRAM](-/-) mice were more prone to SARS-CoV infection than wild-type mice, although there was only transient weight loss without mortality. In contrast, mice deficient in the TLR3/TLR4 adaptor TRIF were highly susceptible to SARS-CoV infection, with marked weight loss, more pathologic conditions of the lung, higher viral titers, impaired lung function, and mortality. In TRIF(-/-) mice infected with SARS-CoV, distinct changes in inflammation occurred including excess infiltration of neutrophils and inflammatory cells that correlated with increased pathologic conditions of other known causes of acute respiratory distress syndrome (ARDS). Aberrant proinflammatory cytokines, chemokines, and INF-stimulated gene signaling programs were observed following infection of TRIF(-/-) mice that resembled those seen in human patients with poor clinical outcome following SARS-CoV infection. These findings suggest the importance of TLR adaptor signaling in generating a balanced protective innate immune response to highly pathogenic CoV infections.<sup>37</sup> In addition, SARS-CoV M protein may function as a cytosolic pathogen-associated molecular pattern to stimulate IFN- $\beta$  production by activating a TLR-related TRAF3-independent signaling cascade.<sup>38</sup>

A case-control study conducted in Chinese patients with SARS-CoV infection and healthy controls has shown that genetic variants of IL-12 receptor B1 (IL12RB1) predispose to SARS-CoV infection.<sup>39</sup> Another case-control study has shown that mannose-binding lectin (MBL), a key molecule in innate immunity that functions as an ante-antibody before specific antibody response, contributes to the first-line host defense against SARS-CoV, and that MBL deficiency is a predisposing factor to SARS-CoV infection.<sup>40</sup>

In macaques infected with SARS-CoV, there is evidence that anti-spike immunoglobulin G (IgG) causes severe ALI by altering macrophage inflammation-resolving response in infected lungs. In acutely infected macaques, there was functional polarization of alveolar macrophages, demonstrating wound-healing and proinflammatory characteristics simultaneously. However, the presence of S-IgG before clearance of virus aborted wound-healing responses and promoted production of IL-8 and MCP1, with recruitment of proinflammatory monocytes/macrophages. Interestingly, the sera of patients who had succumbed to SARS-CoV infection enhanced SARS-CoV-induced MCP1 and IL-8 production by human monocyte-derived

wound-healing macrophages, whereas blockade of the Fc- $\gamma$  receptor reduced such effects. The findings reveal a mechanism responsible for virus-mediated ALI and define a pathologic consequence of viral-specific antibody response, in addition to providing some insight on a potential target for treatment of SARS-CoV.<sup>41</sup>

## EPIDEMIOLOGY AND DISEASE TRANSMISSION

### *Discovery and Spread*

---

In a chest hospital in Guangzhou city, a retrospective study of 55 patients hospitalized with atypical pneumonia between January 24 and February 18, 2003, showed a positive culture of SARS-CoV in the nasopharyngeal aspirates of 3 patients, and positive serology to SARS-CoV in 48 patients (87%). The genetic sequence of the virus isolated from patients in Guangdong was found subsequently to be prototypical of the SARS-CoV found in affected areas around the world.<sup>42</sup>

The index case for the major SARS-CoV outbreak in Hong Kong was a 64-year-old male renal physician, who traveled from the Guangdong province on February 21, 2003, to Hong Kong.<sup>2,4</sup> SARS-CoV was transmitted to at least 16 patrons of Hotel M where he stayed on the 9th floor. The renal physician subsequently died of severe pneumonia a few days later at a hospital near the hotel.<sup>28</sup> Within a few weeks, catalyzed by the speed of international air travel, the infected hotel patrons spread SARS-CoV to 29 countries/regions.<sup>4,43</sup> The main mode of spread of SARS-CoV seems to be through close contact with an infected person and transmitted via respiratory droplets or contact with fomite.<sup>44</sup>

### *Transmission in Hospitals*

---

A super-spreading event at the Prince of Wales Hospital (PWH) in Hong Kong highlighted the nosocomial transmission potential of SARS-CoV infection. A 26-year-old man (and visitor who had stayed on the 9th floor of Hotel M), who was admitted to a general medical ward 8A of the hospital with fever and pneumonia on March 4, 2003,<sup>45,46</sup> led to 138 subjects (including previously healthy health care workers) contracting the disease within a 2-week period after exposure. An overcrowded medical ward environment, inadequate air changes in the hospital ward, and the administration of nebulized salbutamol to the index patient via a jet nebulizer, for its mucociliary clearance effects, seem to have contributed to this super-spreading event.<sup>45,46</sup> SARS-CoV was detected in respiratory tract secretions, urine, feces, and tears of some patients with SARS-CoV infection.<sup>44,47</sup> Computational fluid dynamics analysis in conjunction with investigation of the temporal-spatial pattern of spread of SARS-CoV infection among in-patients on the affected medical ward 8A, implicated airborne transmission.<sup>48</sup> A multiagent modeling analysis of 1744 scenarios was used to examine the contribution by different modes of transmission in the ward 8A outbreak and found that SARS-CoV most likely had spread via the combined long-range airborne and fomite routes, while fomites played a nonnegligible role in the transmission.<sup>49</sup>

In Toronto, SARS-CoV was found on polymerase chain reaction (PCR) testing of environmental air samples taken from a hospital room occupied by a patient with SARS-CoV infection, as well as from conventional surface swabs taken from a bed table, a patient's television remote control, and a medication refrigerator door at a nurses' station.<sup>50</sup> The possibility of airborne transmission as indicated by the data emphasizes that it is imperative to take appropriate respiratory protection in addition to strict surface hygiene practices. **Box 1** shows the key timeline of spread of SARS-CoV infection from China to Singapore, Taiwan, Vietnam, and Canada via

**Box 1****Important timeline of spread of severe acute respiratory syndrome coronavirus infection from China to Canada, Vietnam, Taiwan, Vietnam, and Singapore via Hong Kong<sup>51</sup>**

November 16, 2002

- First known case of atypical pneumonia in Foshan City, Guangdong province, China, but cause not identified until much later.

February 11, 2003

- WHO received reports from the Chinese Ministry of Health of an outbreak of acute respiratory syndrome with 300 cases and 5 deaths in Guangdong province.

February 21, 2003

- A 64-year-old medical doctor from Zhongshan University in Guangzhou (Guangdong province) arrived in Hong Kong to attend a wedding and was a guest on the ninth floor of Hotel M (room 911).

February 22, 2003

- The Guangdong doctor was admitted to the intensive care unit at the Kwong Wah Hospital in Hong Kong with respiratory failure (he had previously treated patients with atypical pneumonia in Guangdong). He warned medical staff that he might have contracted a "very virulent disease," with onset of symptoms on February 15, 2003.

February 26, 2003

- A 48-year-old Chinese-American businessman was admitted to the French Hospital in Hanoi with a 3-day history of fever and respiratory symptoms. He traveled to Hong Kong on February 17, departed for Hanoi on February 23, and fell ill there. Shortly before his departure from Hong Kong, he had stayed on the ninth floor of the Hotel M, in a room across the hall from the Guangdong doctor.

March 1, 2003

- A 26-year-old woman was admitted to a hospital in Singapore with respiratory symptoms. A resident of Singapore, she was a guest on the ninth floor of the Hotel M in Hong Kong from February 21 to 25.

March 4, 2003

- The Guangdong doctor died of atypical pneumonia at Kwong Wah Hospital in Hong Kong.

March 5, 2003

- In Hanoi, the Chinese-American businessman, in a stable but critical condition, was air medevaced to the Princess Margaret Hospital in Hong Kong. Seven health care workers who had cared for him in Hanoi became ill.
- A 78-year-old Toronto woman, who had checked out of the Hotel M in Hong Kong on February 23, died at Toronto's Scarborough Grace Hospital. Five members of her family were infected and admitted to the hospital. Her son, aged 43, fell ill on February 27, 2003, and was subsequently admitted to a community hospital on March 7, 2003, leading to a major nosocomial outbreak. Subsequent chains of disease transmissions resulted in numerous hospital outbreaks that involved 257 people.

March 7, 2003

- Health care workers at Hong Kong's Prince of Wales Hospital started to complain of respiratory tract infection, progressing to pneumonia. All had an identifiable link with ward 8A.

March 8, 2003

- In Taiwan, the source of SARS-CoV infection was a 54-year-old merchant who returned to Taipei via Hong Kong after visiting Guangdong on February 5, 2003. By February 25, 2003, he had developed fever, myalgia, and dry cough but was not hospitalized until March 8, 2003.

March 12, 2003

- WHO issued a global alert about cases of severe atypical pneumonia following mounting reports of spread among staff at hospitals in Hong Kong and Hanoi.



- At the French Hospital in Hanoi, 26 staff had symptoms. Of these, 25 had either pneumonia or acute respiratory syndrome, and 5 were in critical condition. The hospital was closed to new admissions.
- Hong Kong health authorities formally reported an outbreak of an unidentified flu-like illness among hospital staff at the Prince of Wales Hospital. As of midnight March 11, 50 health care workers had been screened; 23 were found to have febrile illness, and 8 showed early chest radiographic signs of pneumonia. A 26-year-old man, who had visited an acquaintance staying on the ninth floor of the Hotel M from February 15 to 23, was shown to be the source of this hospital outbreak following subsequent epidemiologic investigation.

March 13, 2003

- The Ministry of Health in Singapore reported 3 cases of atypical pneumonia in young women who had recently returned to Singapore after traveling to Hong Kong. All had stayed on the ninth floor of the Hotel M in late February.

March 15, 2003

- WHO issued a travel advisory as evidence mounted that SARS was spreading by air travel along international routes. WHO named the mysterious illness after its symptoms: severe acute respiratory syndrome (SARS) and declared it “a worldwide health threat.”

March 26, 2003

- The arrival of an infected resident of the Amoy Gardens in Hong Kong to Taiwan on March 26, 2003, led to an escalation of SARS-CoV cases in Taiwan from mid-April 2003. Subsequent phylogenetic analysis of both Taiwan and Hong Kong outbreaks revealed the same strain of virus.

April 28, 2003

- In Hanoi, there was a reported total of 63 cases of SARS-CoV infection before the outbreak was declared to be over on April 28, 2003

May 5, 2003

- The SARS-CoV outbreak in Singapore was characterized by rapid nosocomial transmission involving a large number of health care workers (97 out of 238 probable SARS cases [41%]) and several super-spreading events. Transmission of SARS was finally brought to an end, with no new cases after May 5, 2003.

May 14, 2003

- Toronto was initially removed from the WHO list of areas with recent local SARS transmission and there was a province-wide scaling back of SARS control measures, such as fever surveillance and monitoring of respiratory symptoms in existing in-patients and visitors. However, 1 month after the SARS-CoV outbreak was thought to have ended, another surge of cases arose in a Toronto rehabilitation hospital involving health care workers, visitors, and patients who had been exposed to hospitalized patients with undiagnosed SARS-CoV infection.

July 2, 2003

- Toronto was finally free from local transmission.

5 July, 2003

- It was finally announced by WHO that the transmission chain of SARS-CoV in Taiwan was broken, bringing an end to the SARS-CoV epidemic.

From WHO. Update 95-SARS: Chronology of a serial killer. Accessed 10 Jan 2016. Available at: [http://www.who.int/csr/don/2003\\_07\\_04/en](http://www.who.int/csr/don/2003_07_04/en); with permission.

Hong Kong.<sup>51</sup> **Box 2** summarizes the risk factors for nosocomial transmission and super-spreading events of SARS-CoV infection.<sup>52,53</sup>

### **Community Transmission**

Opportunistic airborne transmission seems to have been responsible for a major community outbreak of SARS-CoV infection involving more than 300 people in Hong Kong, in a private residential complex, the Amoy Gardens.<sup>54,55</sup> The spread of

**Box 2****Risk factors of nosocomial transmission of severe acute respiratory syndrome coronavirus infection**

- a. Independent risk factors of super-spreading nosocomial outbreaks of SARS<sup>52</sup>:
- Performance of resuscitation (OR = 3.81; 95% CI, 1.04–13.87; *P* = .04).
  - Staff working while experiencing symptoms (OR = 10.55; 95% CI, 2.28–48.87; *P* = .003)
  - Patients with SARS requiring oxygen therapy at least 6 L/min (OR = 4.30; 95% CI, 1.00–18.43; *P* = .05)
  - Patients with SARS requiring noninvasive positive pressure ventilation (OR = 11.82; 95% CI, 1.97–70.80; *P* = .007)
  - Minimum distance between beds <1 m (OR = 6.98; 95% CI, 1.68–28.75; *P* = .008)
  - Washing or changing facilities for staff (OR = 0.12; 95% CI, 0.02–0.97; *P* = .05)
- b. Respiratory procedures associated with increased risk of transmission to health care workers.<sup>53</sup>
- Procedures reported to present an increased risk of transmission included (n, pooled OR [95% CI]):
- Tracheal intubation (n = 4 cohorts; 6.6 [2.3, 18.9], and n = 4 case-controls; 6.6 [4.1, 10.6]);
  - Noninvasive ventilation (n = 2 cohorts; OR = 3.1 [1.4, 6.8]);
  - Tracheotomy (n = 1 case-control; 4.2 [1.5, 11.5]);
  - Manual ventilation before intubation (n = 1 cohort; OR = 2.8 [1.3, 6.4]).

*Adapted from* Yu IT, Xie ZH, Tsoi KK, et al. Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? *Clin Infect Dis* 2007;44:1017–1025; and Tran K, Cimon K, Severn M, et al. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One* 2012;7:e35797.

SARS-CoV and creation of infectious aerosols that moved upward through the warm airshaft of the apartment building may have been because of dried up U-bend drainage on a bathroom floor and backflow of contaminated sewage (from a SARS patient with renal failure and diarrhea), in combination with negative pressure generated by the toilet exhaust fans. It was suggested via computational fluid dynamics modeling that long-range airborne transmission (>200 m) to nearby buildings was possibly caused by wind flow dispersion.<sup>56</sup>

### **Other Routes of Transmission**

The main mode of SARS-CoV transmission is via respiratory droplets, although the potential of transmission by opportunistic airborne routes via aerosol-generating procedures in health care facilities,<sup>44,50</sup> and environmental factors, as in the case of Amoy Gardens, is known.<sup>54–56</sup> Other transmission routes leading to the spread of SARS-CoV included feco-oral (presence of virus in stool, and diarrhea as a symptom)<sup>54–56</sup> and fomite on surfaces (virus found on surfaces in hospitals treating patients with SARS-CoV).<sup>56</sup> The SARS-CoV that spread worldwide was due to a single virus strain.<sup>57</sup>

### **CLINICAL MANIFESTATIONS**

A wide range of clinical manifestations are seen in patients with SARS from mild, moderate, to severe and rapidly progressive and fulminant disease.

#### **Incubation Period**

The estimated mean incubation period of SARS-CoV infection was 4.6 days (95% CI, 3.8–5.8 days)<sup>58</sup> and 95% of illness onset occurred within 10 days.<sup>59</sup> The mean time from symptom onset to hospitalization was between 2 and 8 days, but was shorter

toward the later phase of the epidemic. The mean time from symptom onset to need for invasive mechanical ventilation (IMV) and to death was 11 and 23.7 days, respectively.<sup>60</sup>

### Symptoms

The major clinical features of SARS are fever, rigors, chills, myalgia, dry cough, malaise, dyspnea, and headache. Sore throat, sputum production, rhinorrhea, nausea, vomiting, and dizziness are less common (Table 1).<sup>3,45,61–63</sup> Watery diarrhea was present in 40% to 70% of patients with SARS and tended to occur about 1 week after illness onset.<sup>24,32</sup> SARS-CoV was detected in the serum and cerebrospinal fluid of 2 patients complicated by status epilepticus.<sup>64,65</sup> Elderly patients with SARS-CoV infection might present with poor appetite, a decrease in general well-being, fracture as a result of fall,<sup>66</sup> and confusion, but some elderly subjects might not be able to mount a febrile response. In contrast, SARS-CoV infection in children aged less than 12 years was generally mild, whereas infection in teenagers resembled that in adults.<sup>67</sup> There was no mortality among young children and teenagers.<sup>58,67</sup> SARS-CoV infection acquired during pregnancy carried a case fatality rate of 25% and was associated with a high incidence of spontaneous miscarriage, preterm delivery, and intrauterine growth retardation without perinatal SARS-CoV infection among the newborn infants.<sup>68</sup>

Asymptomatic SARS-CoV infection was uncommon in 2003; a meta-analysis had shown overall sero-prevalence rates of 0.1% (95% CI, 0.02–0.18) for the general population and 0.23% for health care workers (95% CI, 0.02–0.45) in comparison with healthy blood donors, others from the general community, or patients without SARS-CoV infection recruited from the health care setting (0.16%, 95% CI, 0–0.37).<sup>69</sup>

The clinical course of patients with SARS-CoV infection seemed to manifest in different stages.<sup>32,43,45,70</sup> In the first week of illness of SARS-CoV infection, many patients presented with fever, dry cough, myalgia, and malaise that might improve despite the presence of lung consolidation and rising viral loads on serial samples. During the second week, many patients experienced recurrence of fever, worsening consolidation, and respiratory failure, while about 20% of patients progressed to

**Table 1**  
Clinical features of severe acute respiratory syndrome on presentation

Symptom	% of Patients with Symptoms
Persistent fever >38°C	99–100
Nonproductive cough	57–75
Myalgia	45–61
Chills/rigor	15–73
Headache	20–56
Dyspnea	40–42
Malaise	31–45
Nausea and vomiting	20–35
Diarrhea	20–25
Sore throat	13–25
Dizziness	4.2–43
Sputum production	4.9–29
Rhinorrhea	2.1–23
Arthralgia	10.4

Data from Refs. <sup>3,45,61–63</sup>

ARDS requiring IMV.<sup>32,43,45</sup> Peaking of viral load on day 10 of illness<sup>32</sup> corresponded temporally to peaking of the extent of consolidation radiographically,<sup>71</sup> and a maximal risk of nosocomial transmission, particularly to health care workers.<sup>72</sup>

## DIAGNOSIS AND INVESTIGATIONS

### Laboratory Diagnosis

The detection rates for SARS-CoV infection in 2003 using reverse transcriptase PCR (RT-PCR) on nasopharyngeal specimens, urine, stool, and blood are shown in **Table 2**.<sup>32,73–75</sup> It is important to collect a combination of upper respiratory (nasal, pharyngeal, and nasopharyngeal), lower respiratory (higher yield because of higher viral levels, eg, sputum, tracheal aspirate, and bronchoalveolar lavage), blood, and fecal specimens to maximize the chance of detection. A single negative test in an upper respiratory specimen does not rule out the diagnosis. Because viral kinetics demonstrated an inverted V-shape curve peaking on day 10 of illness with progressive decrease in rates of viral shedding from nasopharynx, stool, and urine (which might persist up to day 21), clinical progression during the second week was thought to be related to immune-mediated lung injury.<sup>32</sup>

Specimens for viral culture require processing in biosafety level 3 facilities, but the results take too long to assist acute clinical management. Serologic diagnosis is largely retrospective and useful for epidemiologic surveillance purposes. A more robust IgG response was observed in severe SARS-CoV infections as reflected by higher IgG levels in patients who required supplemental oxygen, intensive care unit (ICU) admission, those with negative predischARGE fecal RT-PCR results, and those with lymphopenia at presentation.<sup>76</sup> A study in Beijing has shown that, 6 years after SARS-CoV infection, specific IgG Ab to SARS-CoV eventually disappeared and peripheral memory B-cell responses became undetectable in recovered patients with SARS but specific T-cell anamnestic responses could be maintained for at least 6 years.<sup>77</sup>

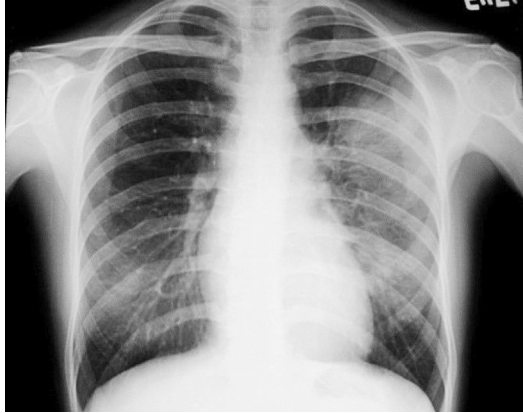
Absolute lymphopenia (lymphocyte count  $<1.0 \times 10^9/L$ ) was observed in 98% of cases of SARS-CoV infection, whereas low CD4 and CD8 lymphocyte counts on hospitalization were associated with adverse clinical outcomes.<sup>78</sup> Liver dysfunction with abnormal alanine transaminases was noted in 29.6% of patients on presentation, but increased to 75.9% of those receiving systemic corticosteroid and ribavirin for treatment of SARS-CoV infection.<sup>79</sup>

### Radiologic Features

The radiographic features of SARS-CoV infection were basically nonspecific. About a quarter of patients might have unremarkable chest radiographs initially,<sup>3,45,61</sup> with

RT-PCR	Detection Rates
Nasopharyngeal aspirate	Conventional RT-PCR: 32% day 3; 68% day 14 <sup>32</sup> Second-generation with real-time quantitative RT-PCR assay: 80% during first 3 d <sup>73</sup>
Stool <sup>32</sup>	97% day 14 of illness
Urine <sup>32</sup>	42% day 15 of illness
Real-time quantitative serum SARS-CoV RNA <sup>74,75</sup>	80% day 1; 75% day 7; 45% day 14
Serology IgG seroconversion to SARS-CoV <sup>32</sup>	15% day 15; 60% day 21; >90% day 28

Data from Refs.<sup>32,73–75</sup>



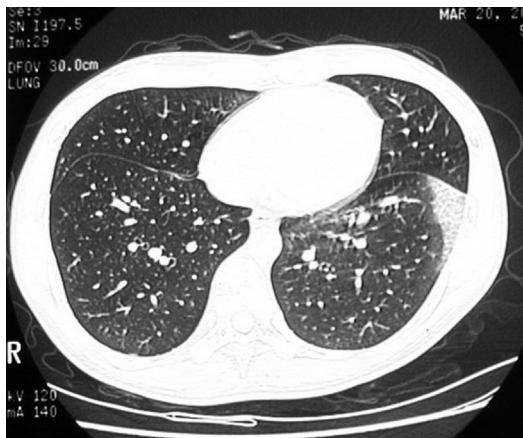
**Fig. 2.** Chest radiograph of a patient showing opacities at the right lower zone and left mid and lower zones.

nonspecific changes, ranging from normal to peribronchial thickening and ill-defined airspace shadowing (**Fig. 2**).

High-resolution computer tomography (HRCT) of the thorax could detect small parenchymal lesions early.<sup>80</sup> Common HRCT findings included interlobular septal and intralobular interstitial thickening, consolidation, and ground-glass opacification, predominantly involving peripheral lung fields and lower lobes, with features closely resembling those found in COPD<sup>45,80</sup> (**Fig. 3**). In an ICU case series of critically ill patients, 12% of patients developed pneumo-mediastinum spontaneously, while 20% of patients developed evidence of ARDS over a period of 3 weeks.<sup>32</sup> Despite the use of lung protective IMV with a low tidal volume, barotrauma occurred in 26% of critically ill cases of SARS-CoV infection, possibly owing to decreased lung compliance.<sup>81</sup>

### PROGNOSTIC MARKERS AND OUTCOME

The prognostic factors associated with a poor outcome (ICU admission or death) in SARS-CoV infection are summarized in **Box 3**.<sup>32,45,61–63,73–75</sup> Infants (preterm or



**Fig. 3.** Chest tomography of another patient with ground-glass opacity at the anterolateral segment of the left lower lobe.

**Box 3****Poor prognostic factors associated with intensive care unit admission and/or deaths in patients with severe acute respiratory syndrome coronavirus infection***Factors*

Advanced age<sup>32,45,59,62,63</sup>

Viral loads: high SARS-CoV viral loads in nasopharyngeal secretions<sup>32</sup>; high plasma SARS-CoV concentrations<sup>74,75</sup>

Comorbidities: chronic hepatitis B,<sup>32</sup> diabetes mellitus, or other co-morbid conditions<sup>61,62</sup>

Laboratory markers: high peak lactate dehydrogenase (LDH),<sup>45</sup> high initial LDH level,<sup>63</sup> high neutrophil count on presentation,<sup>45,63</sup> low counts of CD4 and CD8 at presentation<sup>78</sup>

*Data from Refs.*<sup>32,45,61–63,74,75</sup>

full-term) born to mothers infected with SARS-CoV infection were neither shedding SARS-CoV nor clinically infected in the postnatal period.<sup>82</sup> The clinical course of SARS-CoV infection in elderly patients, particularly those with comorbidities was typically fulminant and often fatal.

## ANTIVIRAL THERAPY AND OTHER POTENTIAL TREATMENTS

### *Ribavirin*

Ribavirin, a nucleoside analog, was widely prescribed for treatment of SARS-CoV infection in 2003.<sup>32,45,61,62</sup> Nevertheless, ribavirin monotherapy had minimal activity against SARS-CoV with concentrations that could be achieved in the clinical setting, and it led to significant hemolysis in many patients.<sup>32,45,83</sup>

### *Antiviral Therapy*

The efficacy of antiviral agents including ribavirin, protease inhibitors, and INF that were used to treat patients with SARS-CoV infection in 2003 is summarized in **Table 3**.<sup>61,83–86</sup> Because of lack of prospective randomized, placebo-controlled clinical trial data, none of these therapies have proven benefit. Good supportive care remains the mainstay of treatment of SARS-CoV infection.

### *Systemic Corticosteroids*

Systemic corticosteroids, in the form of intravenous pulse methylprednisolone (MP) was given to some patients with SARS-CoV infection for several reasons.<sup>32,45,62,63,83</sup> Firstly, there was an assumption that clinical progression of pneumonia and respiratory failure in association with peaking of SARS-CoV viral load might be mediated by the host inflammatory response.<sup>32,71</sup> Also, in many patients there were HRCT<sup>3,45,80</sup> and histologic features of COP, which was a steroid-responsive condition.<sup>30</sup> Systemic corticosteroids significantly reduced IL-8, MCP-1, and IP-10 concentrations from 5 to 8 days after treatment in 20 adults with SARS-CoV infection.<sup>34</sup> In addition, in patients with fatal SARS-CoV infection, there was evidence of hemophagocytosis in the lungs,<sup>28</sup> attributed to cytokine dysregulation.<sup>87</sup> Intervention with systemic corticosteroids was thus given to modulate these immune responses.

Although there was clinical improvement in some patients with resolution of fever and lung consolidation following treatment with intravenously pulsed MP,<sup>3,83</sup> a retrospective cohort analysis in Hong Kong showed that the use of pulsed MP was actually associated with an increased risk of 30-day mortality (adjusted odds ratio [OR] 26.0; 95% CI, 4.4–154.8).<sup>88</sup> In addition, prolonged use of systemic corticosteroid therapy

**Table 3****Agents applied for treatment of humans with severe acute respiratory syndrome coronavirus infection in 2003****Agents**

Ribavirin	Ribavirin given at 1.2 g three times a day orally for 2 wk resulted in a drop in hemoglobin of >2 g/dL from baseline in 59% of patients, with evidence of hemolysis documented in 36%. <sup>83</sup> Based on a higher dosage of ribavirin for treating hemorrhagic fever virus, patients with SARS-CoV infection in Toronto developed more toxicity, including elevated transaminases and bradycardia. <sup>61</sup>
Protease inhibitor	Two retrospective, matched cohort studies have compared the clinical outcome of patients who received protease inhibitors (lopinavir 400 mg/ritonavir 100 mg) in addition to ribavirin, either as initial therapy within 5 d of onset of symptoms or as rescue therapy after pulsed methylprednisolone treatment for worsening respiratory symptoms; these were compared with historical controls who received ribavirin alone as initial antiviral therapy. <sup>84,85</sup> The addition of lopinavir/ritonavir as initial therapy was associated with reduced overall death rate (2.3%) and intubation rate (0%), in comparison with a matched cohort that received standard treatment (15.6% and 11%, respectively) <sup>85</sup> ; there was also evidence of reduction in viral loads. Other beneficial effects included a reduction in methylprednisolone use and less nosocomial infections. <sup>84</sup> However, the subgroup that had received lopinavir/ritonavir as rescue therapy fared no better than the matched cohort, and received a higher mean dose of methylprednisolone. <sup>86</sup> The improved clinical outcome in patients who received lopinavir/ritonavir as part of the initial therapy is supported by the observations that both peak (9.6 µg/mL) and trough (5.5 µg/mL) serum concentrations of lopinavir could inhibit the virus.
Interferon	In an uncontrolled study in Toronto, interferon-alfacon-1 given within 5 d of illness resulted in improved oxygen saturation, more rapid resolution of radiographic lung opacities, and lower rates of intubation (11.1% vs 23.1%) and death (0.0% vs 7.7%); however, the sample size was small (n = 9 vs 13) and confounded by the concomitant use of systemic corticosteroid. <sup>86</sup>

Data from Refs.<sup>61,83–86</sup>

could increase the risk of nosocomial infections, such as disseminated fungal disease,<sup>89</sup> metabolic derangements, psychosis, and osteonecrosis.<sup>90</sup> A randomized controlled trial has shown that plasma SARS-CoV RNA concentrations in the second and third weeks of illness were higher in patients given initial hydrocortisone (n = 10) than those given normal saline as control (n = 7) during the early clinical course of the illness. The data suggest that systemic corticosteroids given early in the course of SARS-CoV infection might prolong viremia.<sup>91</sup> A systematic review concluded that systemic corticosteroid treatment was not associated with definite benefits and was potentially harmful.<sup>92</sup>

### **Convalescent Plasma/Passive Immunotherapy**

Convalescent plasma, donated mostly by health care workers who had fully recovered from SARS-CoV infection, seemed to be clinically useful for treating other patients with progressive SARS-CoV infection.<sup>93,94</sup> In a study comparing patients with SARS-CoV infection who did and did not receive convalescent plasma, 19 patients who received such therapy had higher survival rate (100% vs 66.2%) and higher discharge rate (77.8% vs 23.0%) compared with 21 controls.<sup>94</sup> An exploratory post hoc meta-analysis of studies of SARS-CoV infection and severe influenza showed a

significant reduction in the pooled odds of mortality following convalescent plasma versus placebo or no treatment (OR = 0.25; 95% CI, 0.14–0.45).<sup>95</sup> Early administration of convalescent plasma seemed to be more effective, because, among 80 patients with SARS-CoV infection who had been given convalescent plasma at PWH, the discharge rate at day 22 was 58.3% for patients (n = 48) treated within 14 days of illness onset versus 15.6% for those (n = 32) treated beyond 14 days.<sup>93</sup> In the absence of well-proven and effective antiviral therapy, convalescent plasma and human monoclonal antibody are worth further study for treatment of SARS-CoV if it returns.

## PREVENTION

### *Vaccines*

---

The S protein of SARS-CoV plays an important role in mediating viral infection via receptor binding and membrane fusion between the virion and the host cell, and is a major epitope. An adenoviral-based vaccine could induce strong SARS-CoV-specific immune responses in rhesus macaques, and hold promise for development of a protective vaccine against SARS-CoV.<sup>96</sup> Other investigators reported that the S gene DNA vaccine could induce the production of specific IgG antibody against SARS-CoV efficiently in mice, with a seroconversion ratio of 75% after 3 doses of immunization,<sup>97</sup> whereas viral replication was reduced by more than 6 orders of magnitude in the lungs of mice vaccinated with S plasmid DNA expression vectors, and protection was mediated by a humoral immune mechanism.<sup>98</sup> Recombinant S protein exhibited antigenicity and receptor-binding ability, whereas synthetic peptides eliciting specific antibodies against SARS-CoV S protein might provide another approach for further developing SARS vaccine.

### *General Preventive Measures*

---

Prevention of transmission is crucial for managing this highly infectious disease. The primary mode of transmission of SARS-CoV infection is through direct contact and exposure to infectious respiratory droplets, or fomites, and it is therefore necessary to maintain good personal and environmental hygiene, and to implement stringent contact and droplet precautions among health care workers. To prevent community transmission, contact tracing, quarantine/isolation of close contacts, and public education are important measures.<sup>44</sup> Between December 16, 2003, and January 30, 2004, 4 new cases of SARS-CoV infection emerged in Guangdong, and a link was established between humans and small wild animals. The Guangdong government and Department of Public Health took public health measures and implemented strict controls over the wildlife market, including banning the rearing, transport, slaughter, sales, and food processing of small wild mammals and civet cats.<sup>99</sup>

### *Hospital Infection Control Measures*

---

Nosocomial transmission was a hallmark of SARS-CoV infection in 2003, with 1706 out of 8096 (21%) of patients with SARS globally being health care workers.<sup>5</sup> A plausible reason is that viral loads reached their highest levels 10 days from disease onset, when the patient was most symptomatic and dyspneic, and close observation/treatment of these patients became necessary for the health care workers.<sup>32</sup> Different medical wards should be designated for patient triage (for undifferentiated fever), confirmed SARS cases, and other patients in whom SARS has been ruled out. In the event of a late detection of a nosocomial outbreak, hospital closure is required to contain onward disease transmission. However, outbreaks that are detected early



and limited to few patients, may be managed by isolating the infected patients in place or, alternatively, relocating the affected patients to a designated location. Early case detection followed by isolation should ideally be performed in negative pressure isolation rooms if available. Implementing droplet precautions and contact precautions seemed adequate to reduce the risk of infection after general exposure to patients with mild SARS-CoV infection. Airborne precautions (hand hygiene, gown, gloves, N95 masks, and eye protection) should be implemented if aerosol-generating procedures are to be undertaken.<sup>100</sup>

## SUMMARY

The SARS epidemic demonstrated that novel highly pathogenic viruses crossing the animal-human barrier remain a major threat to global health security. SARS posed a major challenge for global public health services because of its sudden appearance, rapid spread, and disappearance. The knowledge and lessons learnt from SARS-CoV epidemiology, mode of transmission, clinical course, complications, clinical management, predictors of poor outcome, and infection control have been invaluable.

Although no major outbreaks have occurred since the last reported SARS cases involving laboratory personnel in Singapore and Taiwan, and 4 residents in Guangdong, an epidemic is possible at any time. Whether SARS will reappear and cause another pandemic remains unknown. The appearance of MERS-CoV in 2012 as another highly pathogenic zoonotic CoV which continues to circulate in the Middle East is a reminder to physicians and public health authorities that the threat of CoV outbreaks is ever present.

## ACKNOWLEDGMENTS

A. Zumla is in receipt of an NIH Research (NIHR) senior investigator award and acknowledges support from the PANDORA-ID-NET EDCTP Reg/Grant RIA2016E-1609, funded by the European and Developing Countries Clinical Trials Partnership (EDCTP2) programme, Horizon 2020, the European Union's Framework Programme for Research and Innovation.

## REFERENCES

1. Zhao Z, Zhang F, Xu M, et al. Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. *J Med Microbiol* 2003;52:715–20.
2. WHO. List of blue print priority diseases. Available at: <https://www.who.int/blueprint/priority-diseases/en/>. Accessed January 7, 2019.
3. Tsang KW, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003;348:1977–85.
4. Peiris JS, Lai ST, Poon LL, et al, SARS study group. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003;361(9366):1319–25.
5. WHO. Summary of probable SARS cases with onset of illness from 1 November to 31 July 2003. 2003. Available at: [http://www.who.int/csr/sars/country/table2004\\_04\\_21/en/](http://www.who.int/csr/sars/country/table2004_04_21/en/). Accessed January 10, 2016.
6. [Chapter 5] WHO. SARS: lessons from a new disease. The World Health Report; 2003. p. 71–8. Available at: [http://www.who.int/whr/2003/en/whr03\\_en.pdf?ua=1](http://www.who.int/whr/2003/en/whr03_en.pdf?ua=1). Accessed January 10, 2016.
7. Zumla A, Chan JF, Azhar EI, et al. Coronaviruses – drug discovery and therapeutic options. *Nat Rev Drug Discov* 2016;15(5):327–47.

8. Drosten C, Gunther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003;348:1967–76.
9. Ksiazek TG, Erdman D, Goldsmith CS, et al, SARS Working Group. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003;348:1953–66.
10. Marra MA, Jones SJ, Astell CR, et al. The genome sequence of the SARS-associated coronavirus. *Science* 2003;300:1399–404.
11. Ruan YJ, Wei CL, Ee LA, et al. Comparative full-length genome sequence analysis of 14 SARS coronavirus isolates and common mutations associated with putative origins of infection. *Lancet* 2003;361:1779–85.
12. Du L, Qiu JC, Wang M, et al. Analysis on the characteristics of blood serum Ab-IgG detective result of severe acute respiratory syndrome patients in Guangzhou, China. *Zhonghua Liu Xing Bing Xue Za Zhi* 2004;25(11):925–8.
13. Guan Y, Zheng BJ, He YQ, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science* 2003;302:276–8.
14. Yu D, Li H, Xu R, et al, Centers for Disease Control and Prevention (CDC). Prevalence of IgG antibody to SARS-associated coronavirus in animal traders—Guangdong province, China, 2003. *MMWR Morb Mortal Wkly Rep* 2003;52:986–7.
15. Song HD, Tu CC, Zhang GW, et al. Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. *Proc Natl Acad Sci U S A* 2005;102:2430–5.
16. Wang M, Yan M, Xu H, et al. SARS-CoV infection in a restaurant from palm civet. *Emerg Infect Dis* 2005;11:1860–5.
17. Lau SK, Woo PC, Li KS, et al. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. *Proc Natl Acad Sci U S A* 2005;102(39):14040–5.
18. Li W, Shi Z, Yu M, et al. Bats are natural reservoirs of SARS-like coronaviruses. *Science* 2005;310:676–9.
19. Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. *Am J Pathol* 2007;170:1136–47.
20. Chan PK, To KF, Lo AW, et al. Persistent infection of SARS coronavirus in colonic cells in vitro. *J Med Virol* 2004;74:1–7.
21. Simmons G, Gosalia DN, Rennekamp AJ, et al. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. *Proc Natl Acad Sci U S A* 2005;102:11876–81.
22. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003;426:450–4.
23. Hamming I, Timens W, Bulthuis ML, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;203:631–7.
24. Leung WK, To KF, Chan PK, et al. Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection. *Gastroenterology* 2003;125:1011–7.
25. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005;11:875–9.
26. Law PT, Wong CH, Au TC, et al. The 3a protein of severe acute respiratory syndrome-associated coronavirus induces apoptosis in Vero E6 cells. *J Gen Virol* 2005;86(Pt 7):1921–30.

27. Tan YJ, Fielding BC, Goh PY, et al. Overexpression of 7a, a protein specifically encoded by the severe acute respiratory syndrome coronavirus, induces apoptosis via a caspase-dependent pathway. *J Virol* 2004;78:14043–7.
28. Nicholls JM, Poon LL, Lee KC, et al. Lung pathology of fatal severe acute respiratory syndrome. *Lancet* 2003;361:1773–8.
29. Franks TJ, Chong PY, Chui P, et al. Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore. *Hum Pathol* 2003;34:743–8.
30. Tse GM, To KF, Chan PK, et al. Pulmonary pathological features in coronavirus associated severe acute respiratory syndrome (SARS). *J Clin Pathol* 2004;57:260–5.
31. Haagmans BL, Kuiken T, Martina BE, et al. Pegulated interferon- $\alpha$  protects type I pneumocytes against SARS coronavirus infection in macaques. *Nat Med* 2004;10:290–3.
32. Peiris JS, Chu CM, Cheng VC, et al, HKU/UCH SARS Study Group. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003;361:1767–72.
33. Cheng VC, Hung IF, Tang BS, et al. Viral replication in the nasopharynx is associated with diarrhea in patients with severe acute respiratory syndrome. *Clin Infect Dis* 2004;38:467–75.
34. Wong CK, Lam CWK, Wu AK, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol* 2004;136:95–103.
35. Zhao J, Zhao J, Perlman S. T cell responses are required for protection from clinical disease and for virus clearance in severe acute respiratory syndrome coronavirus-infected mice. *J Virol* 2010;84(18):9318–25.
36. Channappanavar R, Fehr AR, Vijay R, et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. *Cell Host Microbe* 2016;19(2):181–93.
37. Totura AL, Whitmore A, Agnihothram S, et al. Toll-like receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. *MBio* 2015;6 [pii:e00638-15].
38. Wang Y, Liu L. The membrane protein of severe acute respiratory syndrome coronavirus functions as a novel cytosolic pathogen-associated molecular pattern to promote beta interferon induction via a Toll-like-receptor-related TRAF3-independent mechanism. *MBio* 2016;7(1) [pii:e01872-15].
39. Tang F, Liu W, Zhang F, et al. IL-12 RB1 genetic variants contribute to human susceptibility to severe acute respiratory syndrome infection among Chinese. *PLoS One* 2008;3(5):e2183.
40. Ip WK, Chan KH, Law HK, et al. Mannose-binding lectin in severe acute respiratory syndrome coronavirus infection. *J Infect Dis* 2005;191(10):1697–704.
41. Liu L, Wei Q, Lin Q, et al. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight* 2019;4(4) [pii:123158].
42. Zhong NS, Zheng BJ, Li YM, et al. Epidemiology and cause of severe acute respiratory syndrome in Guangdong, People's Republic of China, in February 2003. *Lancet* 2003;362:1353–8.
43. Hui DS, Sung JJ. Severe acute respiratory syndrome. *Chest* 2003;124(1):12–5.
44. Peiris JS, Yuen KY, Osterhaus AD, et al. The severe acute respiratory syndrome. *N Engl J Med* 2003;349:2431–41.

45. Lee N, Hui DS, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003;348:1986–94.
46. Wong RS, Hui DS. Index patient and SARS outbreak in Hong Kong. *Emerg Infect Dis* 2004;10:339–41.
47. Loon SC, Teoh SC, Oon LL, et al. The severe acute respiratory syndrome coronavirus in tears. *Br J Ophthalmol* 2004;88(7):861–3.
48. Yu IT, Wong TW, Chiu YL, et al. Temporal-spatial analysis of severe acute respiratory syndrome among hospital inpatients. *Clin Infect Dis* 2005;40:1237–43.
49. Xiao S, Li Y, Wong TW, et al. Role of fomites in SARS transmission during the largest hospital outbreak in Hong Kong. *PLoS One* 2017;12(7):e0181558.
50. Booth TF, Kournikakis B, Bastien N, et al. Detection of airborne severe acute respiratory syndrome (SARS) coronavirus and environmental contamination in SARS outbreak units. *J Infect Dis* 2005;191:1472–7.
51. WHO. Update 95-SARS: chronology of a serial killer. Available at: [http://www.who.int/csr/don/2003\\_07\\_04/en](http://www.who.int/csr/don/2003_07_04/en). Accessed January 10, 2016.
52. Yu IT, Xie ZH, Tsoi KK, et al. Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? *Clin Infect Dis* 2007;44:1017–25.
53. Tran K, Cimon K, Severn M, et al. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One* 2012;7:e35797.
54. Chu CM, Cheng VC, Hung IF, et al. Viral load distribution in SARS outbreak. *Emerg Infect Dis* 2005;11:1882–6.
55. Yu IT, Li Y, Wong TW, et al. Evidence of airborne transmission of the severe acute respiratory syndrome virus. *N Engl J Med* 2004;350:1731–9.
56. Yu IT, Qiu H, Tse LA, et al. Severe acute respiratory syndrome beyond Amoy Gardens: completing the incomplete legacy. *Clin Infect Dis* 2014;58:683–6.
57. Lloyd-Smith JO, Schreiber SJ, Kopp PE, et al. Superspreading and the effect of individual variation on disease emergence. *Nature* 2005;438(7066):355–9.
58. Chiu WK, Cheung PCH, Ng KL, et al. Severe acute respiratory syndrome in children: experience in a regional hospital in Hong Kong. *Pediatr Crit Care Med* 2003;4:279–83.
59. Donnelly CA, Ghani AV, Leung GM, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. *Lancet* 2003;361:1761–6.
60. Leung GM, Hedley AJ, Ho LM, et al. The epidemiology of severe acute respiratory syndrome in the 2003 Hong Kong epidemic: an analysis of all 1755 patients. *Ann Intern Med* 2004;141:662–73.
61. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* 2003;289:2801–9.
62. Chan JW, Ng CK, Chan YH, et al. Short term outcome and risk factors for adverse clinical outcomes in adults with severe acute respiratory syndrome (SARS). *Thorax* 2003;58:686–9.
63. Tsui PT, Kwok ML, Yuen H, et al. Severe acute respiratory syndrome: clinical outcome and prognostic correlates. *Emerg Infect Dis* 2003;9:1064–9.
64. Hung EC, Chim SS, Chan PK, et al. Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. *Clin Chem* 2003;49:2108–9.
65. Lau KK, Yu WC, Chu CM, et al. Possible central nervous system infection by SARS coronavirus. *Emerg Infect Dis* 2004;10:342–4.

66. Wong KC, Leung KS, Hui M. Severe acute respiratory syndrome (SARS) in a geriatric patient with a hip fracture. A case report. *J Bone Joint Surg Am* 2003;85A:1339–42.
67. Hon KL, Leung CW, Cheng WT, et al. Clinical presentations and outcome of severe acute respiratory syndrome in children. *Lancet* 2003;361:1701–3.
68. Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *Am J Obstet Gynecol* 2004;191:292–7.
69. Leung GM, Lim WW, Ho LM, et al. Seroprevalence of IgG antibodies to SARS-coronavirus in asymptomatic or subclinical population groups. *Epidemiol Infect* 2006;134:211–21.
70. Hui DS, Wong PC, Wang C. SARS: clinical features and diagnosis. *Respirology* 2003;8(Suppl):S20–4.
71. Hui DS, Wong KT, Antonio GE, et al. Severe acute respiratory syndrome: correlation between clinical outcome and radiologic features. *Radiology* 2004;233:579–85.
72. Pitzer VE, Leung GM, Lipstich M. Estimating variability in the transmission of severe acute respiratory syndrome to household contacts in Hong Kong, China. *Am J Epidemiol* 2007;166:355–63.
73. Poon LL, Chan KH, Wong OK, et al. Early diagnosis of SARS coronavirus infection by real time RT-PCR. *J Clin Virol* 2003;28:233–8.
74. Ng EK, Hui DS, Chan KC, et al. Quantitative analysis and prognostic implication of SARS coronavirus in the plasma and serum of patients with severe acute respiratory syndrome. *Clin Chem* 2003;49:1976–80.
75. Ng EK, Ng PC, Hon KL, et al. Serial analysis of the plasma concentration of SARS coronavirus RNA in pediatric patients with severe acute respiratory syndrome. *Clin Chem* 2003;49:2085–8.
76. Lee N, Chan PK, Ip M, et al. Anti-SARS-CoV IgG response in relation to disease severity of severe acute respiratory syndrome. *J Clin Virol* 2006;35:179–84.
77. Tang F, Quan Y, Xin ZT, et al. Lack of peripheral memory B cell responses in recovered patients with severe acute respiratory syndrome: a six-year follow-up study. *J Immunol* 2011;186:7264–8.
78. Wong RS, Wu A, To KF, et al. Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. *Br Med J* 2003;326:1358–62.
79. Wong WM, Ho JC, Hung IF, et al. Temporal patterns of hepatic dysfunction and disease severity in patients with SARS. *JAMA* 2003;290:2663–5.
80. Wong KT, Antonio GE, Hui DS, et al. Thin section CT of severe acute respiratory syndrome: evaluation of 73 patients exposed to or with the disease. *Radiology* 2003;228:395–400.
81. Gomersall CD, Joynt GM, Lam P, et al. Short-term outcome of critically ill patients with severe acute respiratory syndrome. *Intensive Care Med* 2004;30:381–7.
82. Shek CC, Ng PC, Fung GP, et al. Infants born to mothers with severe acute respiratory syndrome. *Pediatrics* 2003;112:e254–6.
83. Sung JJ, Wu A, Joynt GM, et al. Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. *Thorax* 2004;59:414–20.
84. Chu CM, Cheng VC, Hung IF, et al, HKU/UCH SARS Study Group. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004;59:252–6.

85. Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicenter retrospective matched cohort study. *Hong Kong Med J* 2003;9:399–406.
86. Loutfy MR, Blatt LM, Siminovitch KA, et al. Interferon Alfacon-1 plus corticosteroids in severe acute respiratory syndrome. A preliminary study. *JAMA* 2003;290:3222–8.
87. Fisman DN. Hemophagocytic syndrome and infection. *Emerg Infect Dis* 2000;6:601–8.
88. Tsang OT, Chau TN, Choi KW, et al. Coronavirus-positive nasopharyngeal aspirate as predictor for severe acute respiratory syndrome mortality. *Emerg Infect Dis* 2003;9:1381–7.
89. Wang H, Ding Y, Li X, et al. Fatal aspergillosis in a patient with SARS who was treated with corticosteroids. *N Engl J Med* 2003;349:507–8.
90. Griffith JF, Antonio GE, Kumta SM, et al. Osteonecrosis of hip and knee in patients with severe acute respiratory syndrome treated with steroids. *Radiology* 2005;235:168–75.
91. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. *J Clin Virol* 2004;31:304–9.
92. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med* 2006;3:e343.
93. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* 2005;24:44–6.
94. Soo Y, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clin Microbiol Infect* 2004;10:676–8.
95. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al, Convalescent Plasma Study Group. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis* 2015;211:80–90.
96. Gao W, Tamin A, Soloff A, et al. Effects of a SARS-associated coronavirus vaccine in monkeys. *Lancet* 2003;362:1895–6.
97. Zhao P, Ke JS, Qin ZL, et al. DNA vaccine of SARS-CoV S gene induces antibody response in mice. *Acta Biochim Biophys Sin (Shanghai)* 2004;36:37–41.
98. Yang ZY, Kong WP, Huang Y, et al. A DNA vaccine induces SARS coronavirus neutralization and protective immunity in mice. *Nature* 2004;428:561–4.
99. Zhong NS, Zeng GQ. Pandemic planning in China: applying lessons from severe acute respiratory syndrome. *Respirology* 2008;13(Suppl 1):S33–5.
100. Seto WH, Conly JM, Pessoa-Silva CL, et al. Infection prevention and control measures for acute respiratory infections in healthcare settings: an update. *East Mediterr Health J* 2013;19(Suppl 1):S39–47.