Severe acute respiratory syndrome: What have we learned two years later?

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On March 12, 2003, the World Health Organization (WHO) issued a global alert describing cases of atypical pneumonia occurring in Hong Kong, China and Vietnam (1). In retrospect, it was determined that the outbreak originated in the Guangdong province of China, with the first patient, having what came to be known as severe acute respiratory syndrome (SARS), reported in November 2002 (2). A physician from Guangdong, who cared for SARS patients, travelled to Hong Kong while symptomatic, and is deemed to be the direct source for transmissions to 10 other individuals who subsequently took the etiological agent to Canada, Ireland, Germany, Singapore, Vietnam and the United States (3). From the first case diagnosed in November 2002 to the end of the epidemic in July 2003, there were 8096 probable cases of SARS reported worldwide (4). Of these, 1706 (21%) were health care workers (HCW). In the Toronto, Ontario outbreak, the majority of SARS cases were related to hospital exposure (1). Canada was the country most impacted by SARS outside of Asia, with the great majority of cases occurring in the Greater Toronto area. This outbreak had a tremendous impact, both medically and economically, with SARS spreading to 58% of Toronto's acute care hospitals (5). At the same time, it was the stimulus to unprecedented international cooperation in describing the clinical and epidemiological features of the syndrome, identifying the causative agent, developing diagnostic tools, exploring therapeutic strategies and, ultimately, controlling its spread. In the months since the outbreak was declared over, investigators have continued to publish their findings on this topic. What have we learned about SARS since we first wrote about it in 2003 (6)?

In terms of its epidemiology, the mean and median incubation periods have been estimated to be six days (1,7) and four days (8), respectively. In household transmission studies (9), cases occurred a maximum of 10 to 14 days after exposure. Overall, 95% of patients developed illness within 14.2 days of exposure (7). The mean and median duration of symptoms before hospitalization were three to six days (7,8).

Within a month of the global alert, descriptions of the clinical features of suspect and probable SARS were published electronically in the *New England Journal of Medicine* (10-12). By definition, all patients had fever, with 57% to 100% having cough, up to 80% had dyspnea, and 20% to 25% had diarrhea at presentation (10-12). Lymphopenia was a frequent laboratory finding (10,12), and approximately 80% of patients had an abnormal chest radiograph, with an absence of pleural effusions, and bilateral infiltrates commonly observed (10-12). These initial impressions were largely confirmed by later and larger studies from a variety of geographical areas (7,12-14). Systemic symptoms such as headache, myalgia and malaise were also relatively common and could precede the fever, which, in turn, may have resolved before the onset of respiratory symptoms (1,11,12,15). Patients may have had a biphasic course with initial improvement and then worsening after eight days (15). Chest examination revealed abnormalities in fewer than 50% of patients at presentation (1,2). Although much less common in children, the clinical presentation appears similar (16). Laboratory abnormalities that have been reported include elevated lactic dehydrogenase or transaminase levels (11,12,14,15). Patients with normal chest radiographs at presentation will usually have an abnormal computed tomography scan (17). Radiographical findings are more frequently peripheral and involve the lower lung zones, without cavitation, effusions or lymphadenopathy (18).

From the clinical descriptions reported, there is little to distinguish SARS from other respiratory illnesses, especially viral respiratory infections. This underlines the key importance of eliciting an epidemiological history of exposure to SARS cases or SARS endemic areas. On the other hand, one group of investigators found that the WHO criteria for SARS had a sensitivity of only 26% (19). The importance of being able to accurately identify a patient with SARS is highlighted by hospital outbreaks related to even one unrecognized patient (20,21). Investigators in Hong Kong, using clinical information from their outbreak, have been developing and validating a clinical prediction rule for identifying patients with SARS in an emergency department setting (22). While the authors acknowledge that their prediction rule may not apply during nonepidemic periods, it had a 90% sensitivity and 62% specificity for a receiver-operating curve area of 85% in an epidemic situation (22).

The search for the etiological agent of SARS required that clinical specimens be tested by a number of different traditional and molecular methods for a broad range of respiratory tract pathogens. Electron microscopy of infected Vero cells showed characteristic coronaviruses (23). Sequencing of the virus revealed it to be a novel coronavirus (23). Serological testing confirmed an etiological association between this coronavirus, subsequently called SARS-CoV (S-CoV), and SARS (23). Because the early cases of SARS in Guangdong reportedly occurred in restaurant workers handling wild mammals as exotic food, investigators in China examined a number of different animals for S-CoV (24). S-CoV-like viruses were isolated from all six Himalayan palm civets tested (24), the animal now identified as the source of the SARS coronavirus. These

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investigators also found that eight of 20 wild animal traders and three of 15 slaughterers, but only one of 20 vegetable traders, were seropositive to S-CoV by neutralization and indirect immunofluorescence assays (24). Of interest, using similar assays, antibodies to S-CoV and/or animal S-CoV-like viruses were identified in 17 of 938 adults (1.8%) who had sera collected in 2001 (25).

Efforts to develop diagnostic tests began soon after the identification of the etiological agent. The main laboratory tests available to diagnose S-CoV infection are RNA detection through reverse transcriptase-polymerase chain reaction (RT-PCR) and serological testing (26). Chan et al (27) found that 322 of 537 patients (60%) with clinical SARS had evidence of S-CoV RNA in clinical specimens by RT-PCR. Only two of 279 non-SARS patients had virus detected (27). The virus was detected in 11% to 42% of respiratory tract specimens within the first four days of illness, with nasopharyngeal aspirates less sensitive than sputum (27%). Stool samples were a more useful diagnostic test after five days. A fourfold antibody rise was found in 92.1% of patients with clinical SARS (27). Of note, viral RNA and serological responses were detected in only 1.4% and 9.1% of suspect SARS patients, respectively (27). In a cohort of HCWs (28), S-CoV antibodies were found only in probable SARS and not in asymptomatic individuals or those with respiratory symptoms who did not meet WHO guidelines. These data suggest that the great majority of 'suspect SARS' cases did not actually have infection with S-CoV. Real-time RT-PCR has increased sensitivity and may improve viral detection at earlier stages of illness (29). Other investigators have found ELISA and immunofluorescence assay techniques to have sensitivities of 98% to 99%, and specificities of 88% to 99% (30). In the clinical setting, laboratory investigations have shown that nasopharyngeal aspirates have a peak viral load at day 10 and a lower load at day 15 than at admission (15). The mean time to seroconversion was 20 days (15). The decrease in viral load and appearance of antibodies in week 2 suggested that the deterioration seen in patients may be related to immunopathological effects rather than viral replication (15).

The overall case fatality rate associated with SARS was 9.6%, with some geographical variation (4). The United States had no fatalities, whereas the case fatality rate was 17% in Canada and Hong Kong, and 33% in Singapore (4). The mortality for ventilated patients was as high as 45% (31). In one Hong Kong cohort, the three-month mortality was 12%, and factors contributing to mortality were respiratory failure, acute renal failure and nosocomial infection (14). In general, however, patients did not have multiorgan failure (31). Independent predictors of mortality were age over 60 years and elevated lactic dehydrogenase at presentation (14). Canadian data (1) from the Toronto area showed that the presence of diabetes or other comorbid conditions were independently associated with poor outcome, defined by death, intensive care unit (ICU) admission or mechanical ventilation.

SARS was also associated with significant morbidity and placed a heavy burden on ICU resources. In Toronto, 38 of 196 patients (19%) became critically ill, at a median of eight days after admission (31). Twenty-nine of these critically ill patients (76%) required mechanical ventilation, and six remained mechanically ventilated at 28 days (31).

During the epidemic, patients empirically received combinations of antibacterial and antiviral therapies (1,2,8,10,14). As expected, there was no impact from antibacterial agents in the absence of superinfection (10). Once the etiological agent was identified, interest focused on ribavirin as a specific antiviral. In a number of centres, patients were routinely treated with ribavirin in the early phase of the outbreak until it was found to have no benefit and appreciable hematological toxicity (1,14). Corticosteroids, with or without interferon, were administered in some patient series (2,10,15,31). None of these regimens were part of a randomized, controlled trial; therefore, it is not possible to ascribe a beneficial effect to any of the pharmacological interventions attempted in the management of SARS.

Hospitals were the setting for many S-CoV transmissions; these transmissions had considerable impact on the ability to care for all patients, not just those with SARS. This impact occurred from an interplay of insufficient resources to meet the health care needs of a large number of sick and suspect SARS patients and the loss of HCWs to illness and quarantine. Different jurisdictions, however, had different experiences with SARS in the health care environment.

During the first wave of the SARS outbreak in Toronto, 77% of patients were exposed to SARS in the hospital setting (1). The transmission of SARS in six ICUs led to the closure of 38% of the tertiary care university medical-surgical ICU beds and the quarantine of 164 HCWs, 10% of whom developed SARS (31). During the second wave of the Toronto epidemic, even more people were exposed in the hospital than in the community, although all of these exposures occurred in wards and none in the ICUs (5). As expected, most of the exposures and subsequent transmissions in the health care setting occurred in relation to individuals not recognized as having SARS (5,8,20,21). In Canada, at least 128 SARS cases were associated with the outbreak introduced by the visitor to Hong Kong (21). Of these, 70% were associated with transmission in the health care setting (21). Attack rates for HCWs in this outbreak were 10.3% for ICU nurses, 22.2% for emergency room nurses and 60% for coronary care unit (CCU) nurses (21). There were varying degrees of exposure to SARS patients in each of these settings, which may offer an explanation for the varying transmission rates. While emergency room and CCU nurses were largely unprotected in terms of barrier precautions, CCU nurses spent greater lengths of time with infected patients. Droplet and contact precautions had been implemented in the ICU.

Different investigators have attempted to identify practices and procedures that posed a higher risk of S-CoV transmission, with a view to developing preventive strategies. Many of the studies are small, making it difficult to identify statistically significant risk factors. One study (32) reported that being present in a room for longer than 31 min during the administration of noninvasive positive pressure ventilation ($P \leq 0.001$) and not using gloves when touching the patient ($P=0.07$) increased the risk of acquiring S-CoV infection. In a retrospective cohort study of 43 critical care nurses in Toronto (33), intubating ($P=0.04$), suctioning before intubation ($P=0.04$) and manipulating an oxygen mask ($P \leq 0.01$) were all independent risk factors for SARS infection in the HCW.

Risk related to intubation procedures became a considerable concern after nine HCWs developed suspect or probable SARS following exposure to a patient during his intubation, leading to doubt about the adequacy of droplet and even airborne precautions (34). Investigation of this cluster revealed incomplete understanding and inconsistencies in the application of barrier

precautions, possibly contributing to exposure in the setting of a patient at increased likelihood of spreading SARS.

On the other hand, not all hospitals had the same experiences. In Taiwan, there were no transmissions to 73 HCWs despite unprotected exposures during intubation, and only one transmission in 150 HCWs after the introduction of full barrier precautions (35). While hospital-associated transmissions were extensive in hospital A in Vietnam, there were none in hospital B, despite exposure to noninvasive positive pressure ventilation, patients receiving aerosolized medications and the use of N95 masks by only 31% of HCWs during the first week of the outbreak (36). In the United States, there was a lack of transmission to 110 HCWs with exposure to six patients with laboratory-confirmed SARS within droplet range (37). Caring for patients without masks (44%), eye protection (70%) or gloves (39%) was common, although exposure to aerosolized medications (four HCWs) and resuscitation or bronchoscopy (one HCW) were very infrequent in that study (37). The experience in one hospital in Hong Kong was similar to the Toronto experience (38). In a case-control study of 72 HCWs with SARS and 144 HCWs without SARS, inconsistent use of goggles, gowns, gloves and caps was associated with a higher risk for SARS (38). There was no increased risk identified in HCWs who performed what were perceived to be high-risk procedures (38). In all likelihood, the transmission of S-CoV in the hospital setting is influenced by the host, the HCW, the use of barrier precautions, environmental factors and the early recognition of cases; a better understanding of the interplay between these factors is required.

Most of the available data point to SARS as droplet and contact spread (21,33,36,38). However, there have been transmissions in both the hospital and community setting that cannot totally be explained by droplet and contact spread. In a study of medical students in Hong Kong (39), while infection risk was highest in those with direct exposure to the index case, four of eight students who were not within 1 m of the patient also contracted SARS. On a 3 h flight from Hong Kong to Beijing in March 2003, passengers within three rows of a symptomatic passenger were at a 3.1 times higher risk of developing SARS than were other patients (40). Although other exposures to the sick index cases cannot be completely excluded, these two situations raise the possibility of airborne spread under certain, apparently uncommon, circumstances. This is also suggested by the Amoy Gardens outbreak, where individuals in other buildings of the complex of apartments also developed SARS (41).

Despite the uncertainties surrounding optimal preventive strategies, there are findings that can provide some guidance. Early identification and isolation of SARS patients is crucial (21,42-44). Surveillance systems to detect nosocomial clusters of respiratory infections are important (45). Application of droplet and contact precautions throughout the hospital and the addition of airborne precautions for SARS patients was successful in controlling the outbreak in one Canadian hospital (21). The finding that less than 2 h of infection control training and not understanding infection control procedures increased the risk of developing SARS points to the necessity of good infection control training for all HCWs (38). Studies in Canada and Hong Kong have demonstrated the protective role of masks, either surgical or N95 (33,46). While N95 masks were not found to be superior to surgical masks, there are those who debate the ability of these studies to detect differences due to study methodology. Gowns (33,46) and hand washing (46) appear to offer additional benefit. Although the relative merits of the various measures may be debated, in all SARS-affected countries, nosocomial transmissions were halted by the enforcement of routine standard, contact and droplet precautions in all areas and the addition of airborne precautions in high-risk areas (45). These strategies cannot be successful in the absence of strong hospital infection control programs.

Ultimately, the combination of hospital infection control and public health interventions halted the outbreak (5,47). In Toronto, this came at a considerable cost. Toronto Public Health investigated 2132 potential cases of SARS, identified 23,103 contacts as requiring quarantine and logged 316,615 calls on its SARS hotline (5). It is acknowledged that over-recognition of contacts may have overestimated the number of persons requiring quarantine (5). Since the end of the outbreak was announced in July 2003, there have been only 17 additional confirmed cases, 13 of which were associated with laboratories (48). These cases remind us that the re-emergence of SARS remains a possibility. We are also reminded of the need for extreme vigilance in laboratories handling S-CoV (49).

There have been a number of editorials reflecting on the lessons learned from the worldwide SARS outbreak. Emanuel (50) outlined four enduring lessons: the need to test the ability of the health system at all levels to respond; the effect on local settings of global situations; the demonstrated dedication of HCWs to care for the sick at their own personal risk; and finally, the need for better occupational protection of frontline healthcare providers. We relearned that emerging infections can capture us by surprise, travel quickly from faraway places and severely tax the health care system (51). The following became clear: animal pathogens can pose major risks to human health; the capabilities of molecular virology are tremendous; epidemiological histories were sufficient to trace the chains of transmission; national and international agencies can achieve much when they work together; basic infection control measures work well when properly applied; and finally, the fact that one person can have an enormous impact, either good or bad (52). Additional planning is needed for surge capacity (laboratory, hospital and public health), surveillance, communication, risk assessment and adherence to infection control measures (53). One result of the SARS outbreak has been the creation of the Canadian Public Health Agency. While this is a welcome initiative, it must not erode resources available to hospital infection control programs, which are already under-resourced. After all, SARS in Toronto was primarily a hospital-acquired illness (5).

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