Severe acute respiratory syndrome from the trenches, at a Singapore university hospital

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The epidemiology and virology of severe acute respiratory syndrome (SARS) have been written about many times and several guidelines on the infection control and public health measures believed necessary to control the spread of the virus have been published. However, there have been few reports of the problems that infectious disease clinicians encounter when dealing with the protean manifestations of this pathogen. This is a qualitative account of some of the issues faced by an infectious disease physician when identifying and treating patients with SARS as well as protecting other healthcare workers and patients, including: identification of the chain of contagion, early recognition of the disease in the absence of a reliable and rapid diagnostic test, appropriate use of personal protective equipment, and the use of isolation to prevent super-spreading events. Many issues need to be addressed if clinicians are to be able to manage the virus should it reappear.

The severe acute respiratory syndrome (SARS) coronavirus is a novel pathogen that emerged in southern China at the end of 2002 and because of a single event in a hotel in Hong Kong one night in February 2003, spread to three continents.[1] WHO issued an unprecedented global alert; by the end of the epidemic, more than 8000 people had been infected with SARS, of whom 774 died, and the economies of several east and southeast Asian countries were damaged. There have been many publications and scholarly reviews on the origin,[2] pathophysiology,[3] virology,[3,4] clinical features,[3] and epidemiology[5] of the virus. However, there are few detailed accounts of the practical issues faced by clinicians in dealing with a novel, lethal, emerging, nosocomial pathogen. This paper describes the experience of a busy infectious disease clinician at a large teaching hospital in Singapore during the SARS outbreak.

An illustrative case

On March 23, 2003, a 43 year old woman who reported having fever, chills, productive cough, and diarrhoea for 5 days came to the National University Hospital (NUH), Singapore; her past medical history included hypertension only.[6] The previous day, the Ministry of Health in Singapore had declared Tan Tock Seng Hospital (TTSH), where the first cluster of SARS infections happened, as the national SARS hospital. All patients who met the WHO criteria for SARS[7] were to be transferred to TTSH for isolation and treatment. In the week before she presented to NUH, our patient visited a friend with hepatitis at TTSH and then travelled to east Malaysia. She had no direct contact with patients with SARS at TTSH and the only SARS affected country she had been to was Singapore. On examination she was febrile to 39°C, tachypnoeic, tachycardiac, and had bilateral infiltrates on chest radiography (figure 1A). Initial pathology analyses were: a white blood cell count of $19 \cdot 3 \times 10^9$/L (polymorphs 90%, lymphocyte 4%), haemoglobin 12·5 g/L, platelet count of 149×10^9/L, urea 7·9 mmol/L, creatinine 257 μmol/L, and lactate dehydrogenase 2513 IU/L.

This patient was admitted to an isolation ward with a diagnosis of community-acquired pneumonia. She was not transferred to TTSH as a suspect SARS case because there had not been any direct contact with patients with SARS and because of her leucocytosis, which was not thought to be a feature of SARS. Even now she would be excluded from Singapore's "post-epidemic SARS surveillance", which mandates the absence of leucocytosis.[8] She was treated with levofloxacin and ceftriaxone, but because she continued to deteriorate, her treatment was changed to ceftazidime and later imipenem. She was transferred to the medical intensive care unit where she was intubated and mechanically ventilated. A bronchoalveolar lavage was done on March 26, 2003 and cultures were negative for bacteria, fungi, respiratory viruses, and mycobacteria. Despite inotropic support, haemofiltration, and intense ventilatory support with high frequency oscillatory ventilation, she died 8 days after her admission (figure 1B).

Later it became known that two patients who were being nursed in the same ward as, two rooms from, the friend our patient visited at TTSH had undiagnosed SARS.[9] At postmortem examination our patient was confirmed to have SARS by a dot-blot immunoassay[10] using a viral lysate in an analysis of a serum sample that was taken from her 3 days after admission. 3 days after the bronchoscopy was done, the intensivist, who wore a N95 mask, gloves, and a gown during the procedure, developed fever, chills, and myalgia and was admitted directly to TTSH. The intensivist progressed to acute respiratory distress syndrome (ARDS), and had mechanical ventilation, but survived. The son of

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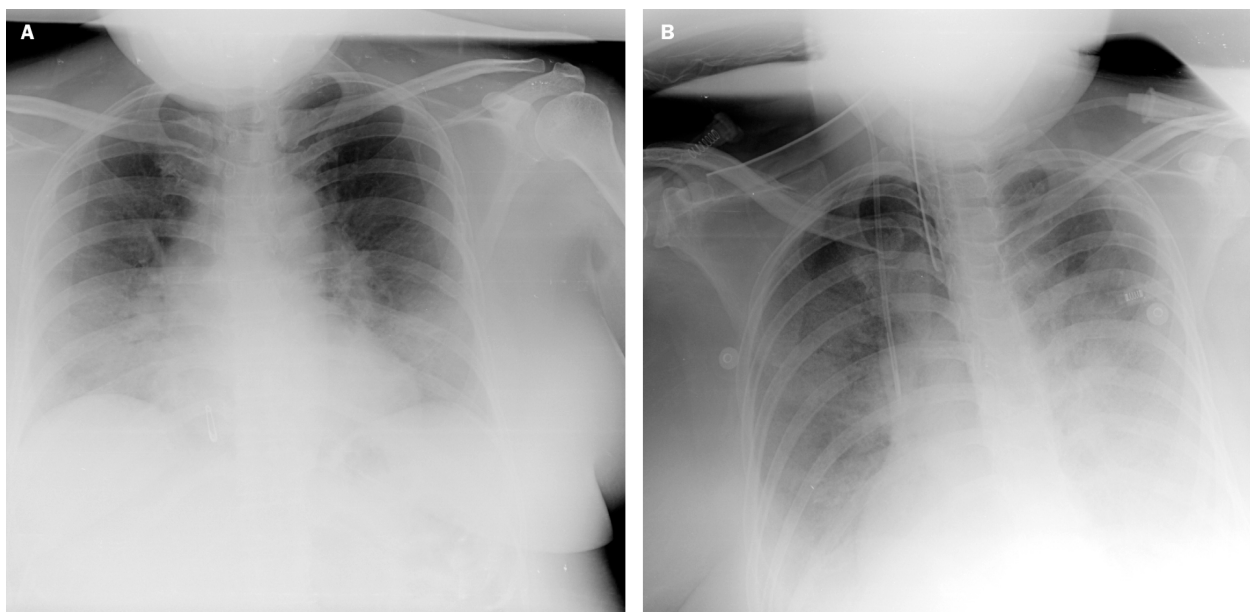
Figure 1. Chest radiograph on initial presentation (A) and after 8 days (B).

our patient was also admitted to TTSH with a diagnosis of SARS. The polytechnic where he was studying was closed for 3 days while contact tracing was done for all students and those with closest contact with him were placed on a restrictive home quarantine order; none had SARS. Careful temperature surveillance and a serological study showed that nobody at the NUH intensive care unit or isolation ward was infected with SARS.[10]

Chain of contagion

The global dissemination of the SARS virus, including that of our patient, can be traced to a hotel in Hong Kong on February 21, 2003.[1] A physician from Guangdong province in China who eventually died from SARS stayed on the ninth floor of the hotel; when other people staying on the ninth floor returned to Vietnam, the USA, Canada, Hong Kong, Ireland, and Singapore they started epidemics in these countries.[11–14] It is striking that despite extensive global air travel from Hong Kong and southern China, both clinical[1] and molecular[15] epidemiological evidence suggest that the entire worldwide epidemic of SARS outside of southern China can be traced back to that single event. Four women from Singapore stayed on the ninth floor that night, three of them returned to Singapore and developed pneumonia in the next week. For reasons that are unclear, only one of these women was associated with transmission of the SARS virus.

Hsu and coauthors[16] have reported the clinical features of the index case and her contacts at TTSH. One of eight doctors and nine of 30 nurses who were caring for this person developed SARS; one of 12 patients in the same ward as this person and nine of 30 friends and family that visited her became infected. When combined with the other "imported" cases of SARS in Singapore, these rates of exposure and infection are comparable to those in Beijing, China.[17] In Beijing, quarantine of 2195 family member or healthcare worker contacts yielded 138 cases—an overall attack rate of 6·3%. In a Beijing hospital study,[18] infection rates were highest in nursing assistants (6·7%) compared with nurses (4·8%) and doctors (2·9%), possibly the result of differences in contact with patients with SARS.

These infection rates are lower than have been reported for airborne viruses,[19] suggesting that contact transmission— through direct contact with infected patients, or their large particle respiratory droplets, or environmental surfaces—is more likely to lead to SARS than airborne transmission in most situations. This suggestion perhaps should lead to re-examination of an infection-control strategy that involves respiratory protection and environmental control of ventilation in hospital facilities. There are situations in which airborne transmission is thought to have resulted from the use of aerosol generating procedures.[20] During 8 days without isolation, a single patient who received nebulised bronchodilator therapy four times a day at the Prince of Wales Hospital in Hong Kong became the source patient for 138 other patients,[21] although, the role of nebulised bronchodilator therapy in that outbreak has been challenged.[22]

Transmission on aeroplanes

When our patient was incubating SARS, she had been on a short holiday by aeroplane. There is no evidence of transmission during her two flights, but this raises the issue of travel advisories. Whereas many countries as well as WHO issued widespread travel advisories, a dispassionate analysis[23] of patients infected with SARS who travelled on aeroplanes showed that, with one exception, SARS was rarely transmitted on aeroplanes. A single flight was associated with the transmission of SARS to 22 passengers (confirmed in a laboratory in 16 cases), some of who were seated at a distance from the source patient and did not meet WHO criteria for close contact. Another flight carrying four symptomatic individuals was not associated with

transmission of SARS and only one of 246 passengers had any symptoms.

The Singapore experience as reported by Wilder-Smith and co-authors[24] is also instructive. Seven aeroplanes carrying nine passengers with SARS, four of who had symptoms, arrived in Singapore. Only one of 156 passengers and crew were infected. This was in spite of one of the symptomatic individuals being a so-called "super-spreader" and another being so critically ill that she had to be intubated and mechanically ventilated shortly after arriving in Singapore. Beijing authorities[17] screened 1·25 million aeroplane passengers for fever, detecting 1945 febrile individuals, ten of whom developed SARS.

Travel advisories had a devastating effect on the economies of the affected countries, but their role in controlling the epidemic is not clear. It is possible that the original purpose of the travel advisories was to prevent the virus from crossing borders but most countries did not implement such intense screening at land borders and by the time the advisories were issued, SARS had already spread to three continents. The impact of a belated travel advisory on the city of Toronto was considerable and has been debated at length.[25] Thankfully, with the recent cases of SARS in southern China and Beijing, travel has not been restricted. Perhaps for a virus that was largely nosocomially transmitted in Canada,[25] Singapore,[9] and Vietnam,[14] travel advisories should have advised only against travel to hospitals in affected countries.

Recognising SARS

One of the problems with the management of SARS was the non-specific nature of the illness. SARS was not recognised in our patient because of a dependence on the case definitions of WHO.[7] These excellent case definitions were designed for epidemiological investigation but had limited utility for clinicians managing cases presenting to busy hospital emergency departments. The WHO criteria[7] required a temperature of greater than 38°C, cough or respiratory symptoms, and direct contact—defined as having cared for, lived with, or had close contact with the respiratory secretions or bodily fluids of a patient with suspect or probable SARS—none of which applied to our patient. The problem with our patient and with many others in Singapore is that the epidemiology was not initially apparent.

Rainer and co-authors[26] reported that the WHO SARS criteria is 25% sensitive for predicting which of the patients presenting to a busy emergency department during the SARS epidemic had SARS. In our hospital, we found[27] that use of the WHO criteria as a clinical screening tool gave a sensitivity of 28%, specificity of 96%, positive predictive value of 11%, and negative predictive value of 99%. Data now emerging on the initial presentations of SARS[13,14,28] suggest that fever and myalgia are more prominent initial symptoms and that respiratory symptoms manifest only later in the illness. Unfortunately, these symptoms are so non-specific that few hospitals anywhere in the world could afford to isolate all patients with fever and malaise. Consequently, SARS-affected countries such as Singapore

had to modify the WHO definitions to suit local conditions; there was a loss in sensitivity as greater specificity was achieved.

A dedicated SARS hospital

On March 22, it was decided that TTSH would be the only hospital in Singapore to treat patients with SARS.[9] Management of all potential cases of SARS at one hospital was introduced to allow the rest of the healthcare system to function normally. The impact on TTSH and other hospitals was considerable; patients were rapidly discharged from TTSH to clear beds for the admission of patients with suspected SARS, and other hospitals had to carry the load from diverted patients. Unfortunately, many of the patients transferred to other hospitals were incubating the SARS virus through casual contact with patients with SARS in the same ward or in common areas such as radiology suites. These patients went on to start epidemics in four of the other five major public hospitals in Singapore.[29] For future outbreaks, we have learnt that all patients in the wards of infected patients are potentially incubating the virus and should be isolated rather than moved to other hospitals. This was practised in September 2003 when an inpatient at the Singapore General Hospital (SGH) was found to have (a laboratory-associated case of) SARS.[30]

Isolation rooms and screening criteria

Our patient was "atypical" because she did not have an obvious contact history at the time of presentation. She also had an elevated white blood cell count, thought to indicate "typical" rather than "atypical" pneumonia, which was the initial description of SARS. Other such cases and subsequent nosocomial transmission led all the other hospitals in Singapore to adopt very broad screening policies. Without a validated, rapid, diagnostic test, we had to isolate and monitor patients who did not meet the WHO criteria for SARS, and thus would not be eligible for assessment at TTSH, but still were of concern for the admitting physicians.

At NUH, we started with one isolation ward but by the peak of the epidemic, we had five isolation wards; large inpatient areas were converted and at NUH these occupied the entire private wing of the hospital. Extractor fans were placed in the rooms to generate a negative pressure relative to the corridor and nurses station, and the fans were exhausted to the exterior—a forested area. 478 patients who did not meet the WHO criteria for SARS and thus could not be transferred to TTSH were isolated; 14 of these patients had SARS.[31]

Isolation was an enormously costly process and it is doubtful that such a strategy is sustainable. An increased risk of adverse events has been associated with isolation,[32] and this was experienced during SARS. Although practices varied across the countries that had an outbreak of SARS,[17,33] it is still unclear whether the designation of a SARS hospital is an effective method of controlling the spread of the virus.

Personal protective equipment

Personal protective equipment (PPE) was key to the public face of SARS infection control. The mask became ubiquitous in hospitals and in many public places in Singapore and

other SARS affected countries. In Singapore,[6,10,34] as in Taiwan,[35] some healthcare workers were infected with SARS despite wearing full PPE—gloves, gown, and N95 mask. The intensivist involved in the case described at the start of this article wore full PPE but became infected during a bronchoscopy. It was speculated that the N95 mask fitted the intensivist poorly, and this led to a crusade to test the fit of the mask on all workers, regardless of the paucity of evidence to support fit testing in extensive studies of the prevention of nosocomial tuberculosis.[36,37] In two retrospective studies of SARS in Hong Kong[38] and Canada,[39] researchers have investigated the use of masks in the protection of healthcare workers. Although both studies found that surgical masks as well as N95 masks were protective, they were limited by small numbers and a possible recall bias.

Early in the epidemic hospital administrators at NUH declared that masks would be available for anyone who wanted to use them, which was very reassuring to healthcare workers. In addition to the primary benefit of reducing infections, the psychological effect of the masks was beneficial.[40] By the end of March, with the head of the hospital's intensive care unit infected with SARS and atypical presentations of SARS, the decision was made to mandate the use of full PPE by all staff in the intensive care unit. The use of powered air purifying respirators for all aerosol generating procedures, including bronchoscopy and intubation, was introduced; these were also used in Canadian intensive care units[39] and are thought to have been protective. The use of nebulisers was also discouraged and metered dose inhalers (with spacers as appropriate) were more widely used. By the second week of April an increased number of atypical cases of SARS were being detected in older patients, who had comorbidities or chronic steroid therapy without fever,[41] and PPE was mandated for all patient contact.

Even though 21 patients with SARS passed through our hospital for an average of 3·9 days (range 0–9 days) before transfer to TTSH, excluding the intensivist described above and five healthcare workers infected during a "super-spreading event", none of the 3233 staff in our hospital were infected. Whereas the universal use of PPE protected staff, an undiagnosed SARS patient, with no recorded fever, was the source of infection for two other patients in the emergency department and for the visitor to the adjacent bed.[42] Our visitor restriction policy began with patients being limited to one visitor and was revised to no visitors when it became clear that we could not provide PPE for large numbers of visitors. The costs of PPE were huge; 6 weeks into the epidemic, the total cost for PPE was at least US$700 000.[31]

As in other settings, the widespread use of PPE seemed effective in controlling the spread of SARS in our hospital but at an immense cost. Again, the challenge will be to find a sustainable approach in the event of a larger recurrence of SARS.

Clinical features

The clinical features of SARS have been described in a range of studies.[13,14,16] Cases identified at our hospital[17,34] were similar to those reported elsewhere except that because we were not a designated SARS hospital, we tended to get patients with atypical presentations. Fever was almost universal; those on steroid therapy did not have a fever and fever tended not to present initially, especially in elderly patients. Myalgia, upper respiratory symptoms, and diarrhoea were also notable clinical features. Most laboratory tests were unhelpful, although many patients had lymphopenia, which can also be detected in a range of viral infections.[43]

Treatment of patients with SARS

The vast majority of patients with SARS in Singapore were managed at the designated SARS hospital. One-sixth of patients developed respiratory distress and were intubated and mechanically ventilated. Lew and colleagues[44] have described the intensive care unit experience in Singapore and it is remarkably similar to that experienced in Toronto. Readers are referred to the review of Peiris and colleagues[3] for a detailed discussion of the therapeutics of SARS. Although ribavirin was initially used in a number of cases, this was stopped when in vitro data showed a lack of efficacy.[45] Others have used ritonavir/lopinavir.[46] Steroids were also used in many patients, especially when it became clear that the viral load of patients declines as patients become worse, suggesting an immunopathogenesis.[47] This suggestion was confirmed by autopsy studies of patients who died from SARS and had large numbers of inflammatory cells in sections of lung tissue.[48] However, as with any other patient with ARDS, steroid therapy was associated with a number of adverse effects.[49] To date, there is no consensus on the best treatment for SARS.

Diagnosis

PCR in respiratory specimens has been used to detect the SARS coronavirus.[50] It is necessary to obtain good specimens for diagnosis of respiratory pathogens but because most patients with SARS have non-productive coughs, it has been a challenge to obtain deep secretions. Clinicians are unwilling to be put at risk of infection by trying to obtain deep respiratory secretions with procedures such as saline nebulisation or bronchoscopy that are associated with transmission to healthcare workers wearing PPE.[6,39] However, it is difficult for laboratory staff to work with scanty specimens. A number of serological assays[10,50,51] are available but are not sensitive until late in the course of the illness, by which time either numerous individuals will have been infected or countless others needlessly isolated. In some patients in Singapore, serological assays did not turn positive until week 6 or 7 of the illness.[51] Thus, the currently available tests have considerable specificity but limited utility in the rapid diagnosis of patients presenting with the non-specific symptoms of early SARS.

Super-spreading events

The unusual features of the SARS epidemic in Singapore included super-spreading events; these were demonstrated by "shoe leather" epidemiology of contact tracing[29] and quarantine of contacts long before the molecular evidence
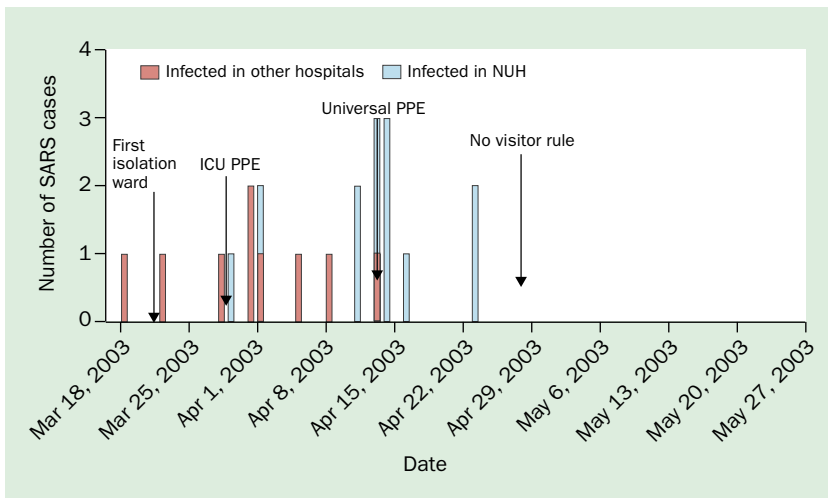
Figure 2. Cases of SARS with the introduction of various preventative measures at the NUH in Singapore. ICU=intensive-care unit; PPE=personal protective equipment.

was available.[15] It has been shown that the most patients with SARS in Singapore did not infect another person,[29] even from the early days of the outbreak before the institution of drastic quarantine laws or strict isolation procedures. Strikingly similar data are available from Vietnam[52] and China.[53] However, a small number of super-spreading events were responsible for the infection of 20–70 people.

Prevention: mass quarantine?

A super-spreading event that happened at NUH is illustrative.[54] A 63-year-old vegetable seller with a history of hypertension and ischaemic heart disease was admitted with shortness of breath. He had no fever, was found to be in atrial fibrillation, and was admitted to a general medical ward with a diagnosis of heart failure. He did not meet SARS criteria for transfer to TTSH or for isolation in our hospital.[31] Despite treatment for heart failure, he deteriorated and had to be intubated and mechanically ventilated; he became the source of infection for an entire shift of nurses and the doctor who had administered high flow oxygen therapy to him while wearing a well-fitting N95 respirator. He was transferred to TTSH when his brother was identified as the source of an even larger cluster of infections at SGH.[55] He died of SARS and the infection of several of his work colleagues led to the closure of Singapore's largest wholesale vegetable market and devastation of the local fresh cuisine industry. Home quarantine orders were issued for more than 2000 people working in the market, none of whom were later found to be infected with SARS.

In Singapore, as with most other things, enforcement is approached very seriously and cameras can be placed in the home to ensure compliance with quarantine. An individual was publicly prosecuted and jailed for breaking quarantine. The social stigma attached to quarantine was considerable; before the installation of cameras, I was officially quarantined and it was not a pleasant experience. It is not known whether quarantine was necessary,[25,33,56] or whether strict isolation and early case finding would have been a better use of resources. In Singapore and elsewhere, isolation

has been shown to be highly effective in reducing the number of secondary cases associated with individuals with SARS. Lipsitch and colleagues[57] showed that as the Singapore epidemic progressed, the time to isolation decreased and the corresponding number of secondary cases decreased, with the notable exception of the SGH cluster.[54]

In any future epidemic we should be able to isolate and detect cases early and may not have to resort to draconian quarantine rules. Alternatively, a careful system of outpatient follow-up and clinical or serosurveillance, as we did with our first case, might be more practical. 80 813 individuals arriving in Taiwan from SARS affected countries were quarantined for 10 days and only one person (0.001% of the total) developed laboratory confirmed SARS.[32]

Prevention: watch for the dual diagnosis

The cluster of infections at SGH that were started by our patient's brother, also reported by Chow and colleagues,[58] were similar to that in our hospital—an alternative diagnosis could explain the patients' clinical presentation. A patient with a documented *Escheria coli* renal abscess and nosocomial pneumonia that responded to carbapenem therapy was also incubating the SARS coronavirus. This patient became the source of infection for 16 healthcare workers, 12 other patients, and eight visitors including our patient. Dual diagnoses are problematic for the management of patients with suspected SARS. What should be the patient management protocol? Do we isolate all patients who were in the same ward as patients with SARS, even if they did not have direct contact with the infected patients? Do we isolate these patients for the duration of their hospital stay in spite of normal chest radiographs and alternative explanations for their fevers? It is clear that we urgently need a rapid diagnostic test. The current diagnostic tests have severe limitations in clinical practice.[50,59]

In Singapore hospitals, some measures used to control the epidemic initially were continued for a year. Staff continued recording their temperatures twice daily even though the infected staff in our hospital were detected by contact tracing of infected patients, not temperature screening. PPE use is still mandated in emergency departments and isolation areas at the time of writing, although we have not had a single case of SARS in our hospital since the end of April 2003. The September 2003 laboratory acquired SARS case[30] was a setback to our SARS containment plans.

It is hard to evaluate the effect of the draconian measures that were put in place (figure 2). The epidemic was already in decline when the no visitor policy was instigated in our hospital; the policy was partly in recognition of our inability to protect visitors from contracting SARS in the hospital. It

is unlikely that a randomised trial could be done to show the measures necessary to prevent the spread of SARS, should there be an outbreak in the future.

Asymptomatic carriers

We did a seroepidemiological study of 372 healthcare workers at NUH,[10] to understand the risk factors for infection and to determine if there were any asymptomatic carriers of the infection. While all six clinical cases of SARS were found to be seropositive, we found two additional healthcare workers with mild symptoms, including fever that resolved within 3 days, no changes on serial chest radiographs, and evidence of SARS on two separate serological assays that were done in two separate, blinded, offsite laboratories. This study confirms the findings of other investigators who found few if any asymptomatic seroconverters in Hong Kong.[60,61] This finding is interesting given the observation that handlers of civet cats in the wild animal markets of Guandong had serological evidence of SARS but no clinical disease.[62] Although this finding has been cited as evidence for the civet cat as the source of the virus but I look forward to emerging data to help to identify the origin of the virus.[2]

What did we learn from the trenches of the SARS wars?

SARS patients have a pneumonia; typically, it does not present with any respiratory symptoms but with the non-specific symptoms of fever and malaise[13,14,16] that are seen in a huge proportion of any general practice. The virus can be detected by sophisticated laboratory tests[50] but only after a period of time,[59] during which many people have either been infected or unnecessarily isolated. A broad triage policy can detect most, but not all, patients with SARS during an epidemic[31] and any patient that is not identified can start a major epidemic.[53,54] There are some treatment possibilities for SARS and some indications of which patients are likely to spread the disease. PPE is effective most of the time, but some of the time additional protection is needed.[6,39] Importantly, this virus is here to stay and much remains unknown about it. A reliable, rapid, diagnostic test and some rigorous data on control, prevention, and treatment are needed.

Conflicts of interest
I declare that I have no conflict of interest.

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