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Review

# Clinical management and infection control of SARS: Lessons learned

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ABSTRACT

The outbreak of severe acute respiratory syndrome (SARS) in 2003 was the first emergence of an important human pathogen in the 21st century. Responding to the epidemic provided clinicians with extensive experience in diagnosing and treating a novel respiratory viral disease. In this article, we review the experience of the SARS epidemic, focusing on measures taken to identify and isolate patients, prevent the transmission of infection to healthcare workers and develop effective therapies. Lessons learned from the SARS epidemic will be especially important in responding to the current emergence of another highly pathogenic human coronavirus, the agent of Middle East respiratory syndrome (MERS), and to the recently emerging H7N9 influenza A virus in China. This paper forms part of a symposium in *Antiviral Research* on "From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses."



**Contents**



## 1. Introduction

It has been 10 years since the outbreak of severe acute respiratory syndrome (SARS) caused by a novel coronavirus which was subsequently named SARS coronavirus (SARS-CoV) (Peiris et al., 2003b). SARS-CoV is phylogenetically diverged from other known coronaviruses associated with human infections including human coronavirus (HCoV)-OC43, HCoV-229E, HCoV-NL63 and Middle East respiratory syndrome coronavirus (MERS-CoV), but closely related to the civet and the bat SARS-CoVs, a group of lineage B betacoronaviruses found in civets, raccoon dogs, ferret badgers and Chinese horseshoe bats (*Rhinolophus sinicus*) in Guangdong Province of South China (Chan et al., 2013c) The Chinese horseshoe bat appears to be the natural reservoir of the ancestral SARS-CoV, because the Ka/Ks ratios (rate of nonsynonymous mutation/rate of synonymous mutation) of the S, orf3a, and nsp3 genes were low, while those of the civet strains in both the 2003 and the minor 2004 outbreaks were high, suggesting a rapidly evolving process of gene adaptation in the animals (Lau et al., 2005b; Li et al., 2005a).

SARS emerged as an outbreak of atypical acute, community-acquired pneumonia in late 2002. The initial cases were animal handlers in Guangzhou Province having regular contact with wild game food animals, suggesting that civets could serve as an

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intermediate amplification host, and later the patients' close household and hospital contacts. The human SARS-CoV subsequently evolved and was capable of person-to-person transmission. The epidemic was rapidly and globally disseminated when a medical professor from a teaching hospital in Guangzhou, who was considered as a "super-spreader" of SARS, came to Hong Kong on 21 February 2003. During his stay in hotel M, he transmitted the infection to other residents, and the secondary cases spread the disease to hospitals in Hong Kong, and to other countries including Vietnam, Singapore, and Canada. Eventually, a total of 8096 patients were infected in over 30 countries among 5 continents and 774 (9.5%) of them died (Cheng et al., 2007a).

As there were no known effective antiviral agents for SARS, supportive care and the use of broad-spectrum antibiotics to cover secondary bacterial infection were the key treatment regimen. The use of existing antiviral therapies including conventional ones like ribavirin, interferon alpha (Infacon), and convalescent plasma, or those with inhibitory effects on SARS-CoV such as lopinavir/ritonavir, with or without corticosteroid use has been reported in non-randomized clinical trials (Cheng et al., 2004b). Since the clinical efficacy of these antiviral agents were found to be uncertain in retrospective analysis (Leong et al., 2004), effective public health and infection control measures including contact tracing and quarantine of close contacts played an important role in preventing further transmission of SARS in the communities and hospitals (Pang et al., 2003; Svoboda et al., 2004).

International collaboration, uniting laboratories with different technologies and capacities, allowed research laboratories to rapidly fulfill all postulates for establishing SARS-CoV as the cause of SARS. The epidemic came to an end when there was no further transmission of SARS in Taiwan on 5 July 2003 (Cheng et al., 2007a). However, there was a brief reemergence (Che et al., 2006), from accidental laboratory exposures in Singapore, Taiwan, and Beijing, and from recurrent animal-to-human transmissions in Guangzhou in late 2003 and early 2004 (Liang et al., 2004; Lim et al., 2004; Normile, 2004a, b), which posed a potential threat to public health.

## 2. Clinical features

The incubation period of SARS is generally 2–14 days with occasional cases of up to 21 days in a family cohort in Hong Kong (Chan et al., 2004c). Most patients were admitted to hospitals 3–5 days after onset of symptoms (Donnelly et al., 2003). The typical clinical presentation includes fever, chills, rigors, cough, headache, myalgia, fatigue and malaise, whereas sore throat, rhinorrhea, dizziness, and chest pain are less frequently seen (Table 1). However, symptoms may be milder in children, and an atypical presentation without fever may occur in elderly patients (Chow et al., 2004; Fisher et al., 2003; Kwan et al., 2004) but rarely in healthy young adults (Woo et al., 2004). Diarrhea at presentation occurred in 12.8% and 23.2% of patients in Asia and North America respectively, but in up to 73% of patients after a mean of 7.5 days after onset of symptoms in a community cohort (Peiris et al., 2003a), which was positively correlated with a higher mean viral load in nasopharyngeal specimens (Cheng et al., 2004a).

Higher initial viral load is independently associated with worse prognosis in SARS (Chu et al., 2004c). Rapid respiratory deterioration was observed one week after the onset of illness, with 20% of patients progressing to acute respiratory distress syndrome (ARDS) which required mechanical ventilation (Peiris et al., 2003a). The radiographic features of SARS were similar to viral pneumonia, but ground-glass opacities and focal consolidations as demonstrated in chest radiographs predominantly involved the peripheral and subpleural regions of the lower zones (Grinblat et al., 2003; Hsieh et al., 2004; Lai et al., 2005a). Spontaneous pneumomediastium was found in about 12% of cases (Chu et al., 2004b), whereas 26% of patients developed barotrauma during mechanical ventilation (Gomersall et al., 2004).

**Table 1**
Clinical features of probable and laboratory-confirmed cases of SARS, Cases in Asia include 1693 reported from Beijing, 575 from Hong Kong, 190 from Guangzhou, 159 from Taiwan, 118 from Singapore and 62 from Vietnam, of which 606 (21.7%) were healthcare workers. Cases in North America include 168 reported from Canada, of which 87 (51.8%) were healthcare workers. NM, not mentioned. References for SARS in Asia are (Chen et al., 2006; Fan et al., 2006; Hsu et al., 2003; Jang et al., 2004; Lee et al., 2003; Liang et al., 2004; Peiris et al., 2003a; Peiris et al., 2003b; Rainer et al., 2003; So et al., 2003; Tsang et al., 2003a; Tsang et al., 2003b; Vu et al., 2004; Yeh et al., 2005; Zhao et al., 2003). References for SARS in North America are (Avendano et al., 2003; Booth et al., 2003; Poutanen et al., 2003).

| Clinical symptom | Number/total (% with sign or symptom) | |
|---|---|---|
| | SARS in Asia ($n$ = 2797) | SARS in North America ($n$ = 168) |
| Fever | 2708/2797 (96.8%) | 130/168 (77.4%) |
| Chills | 554/934 (59.3%) | NM |
| Rigors | 411/804 (51.1%) | NM |
| Cough | 1373/2797 (49.1%) | 116/168 (69.0%) |
| Sore throat | 85/445 (19.1%) | 21/154 (13.6%) |
| Rhinorrhea | 65/492 (13.2%) | 3/144 (2.1%) |
| Headache | 335/822 (40.8%) | 61/168 (36.3%) |
| Dizziness | 201/753 (26.7%) | 6/144 (4.2%) |
| Dyspnea | 460/2477 (18.6%) | 68/154 (44.2%) |
| Chest pain or tightness | 404/2208 (18.3%) | 18/154 (11.7%) |
| Fatigue or malaise | 437/653 (66.9%) | 60/168 (35.7%) |
| Nausea or vomiting | 79/564 (14.0%) | 32/168 (19.0%) |
| Diarrhea | 349/2725 (12.8%) | 39/168 (23.2%) |
| Myalgia | 459/944 (48.6%) | 84/168 (50.0%) |
| Arthralgia | NM | 15/144 (10.4%) |

In addition to upper and lower respiratory tract disease, extrapulmonary manifestations were also reported for SARS. These included liver and renal impairment (Chau et al., 2004; Chu et al., 2005c), bradycardia and hypotension due to diastolic cardiac dysfunction (Li et al., 2003), pulmonary arterial thrombosis (Ng et al., 2005), rhabdomyolysis (Wang et al., 2003b), neuromuscular disorder (Tsai et al., 2004), and an acute neurological syndrome with status epilepticus (Lau et al., 2004d). Lymphopenia, leucopenia, thrombocytopenia were commonly observed (Lee et al., 2003).

## 3. Diagnosis of SARS

The diagnostic criteria for SARS were based on a list of clinical features suggested by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) during the initial phase of the epidemic. According to the WHO criteria, a suspected case was defined as a person presenting after 1 November 2002 who had a history of fever >38 °C, with cough or difficulty breathing, and had close contact with a person who was a suspected or probable case of SARS, or had a history of traveling to or residing in an area with transmission of SARS within 10 days before the onset of symptoms. In addition, a person with an unexplained acute respiratory illness resulting in death, with epidemiological exposure similar to that described above, but on whom no autopsy was performed, also fulfilled the clinical criteria of suspected SARS.

A probable case of SARS was defined as a suspected case with chest X-ray evidence of infiltrates consistent with pneumonia or acute respiratory distress syndrome, with a positive test result for SARS-CoV by one or more laboratory diagnostic assays, and/or with autopsy findings consistent with the pathology of ARDS, without an identifiable cause (WHO, 2003b). The overall accuracy of the WHO guidelines for identifying suspected SARS was found to be 83% with an negative predictive value of 86% (Rainer et al., 2003).

A laboratory case definition for the diagnosis of a re-emergence of SARS was set up by the WHO after the epidemic. A person with clinically suggestive symptoms and signs and with one or more positive laboratory findings including

1. Reverse transcriptase- polymerase chain reaction (RT-PCR) positive for SARS-CoV, using a validated method from at least two different clinical specimens or the same clinical specimen collected on two or more occasions during the course of illness, or two different assays against different gene targets, or repeated RT-PCR using a new RNA extract from the original clinical sample on each occasion of testing;
2. seroconversion by enzyme-linked immunosorbent assay (ELISA) or indirect fluorescent antibody (IFA) assay; or
3. isolation in cell culture of SARS-CoV from any specimen and with RT-PCR confirmation using a validated method (WHO, 2003a).

The CDC case definition of SARS was also based on a combination of clinical, epidemiological and laboratory criteria, with exclusion criteria for cases in which an alternative diagnosis could fully explain the illness, or the convalescent phase serum sample obtained >28 days after symptom onset was negative for antibody to SARS-CoV, or the case was reported on the basis of contact with an index patient who was subsequently excluded as a case, providing other possible epidemiological exposure criteria were not available (CDC, 2003).

Rapid laboratory diagnosis mostly relied on nucleic acid amplification assays, using the SARS-CoV open reading frame 1b or nucleoprotein gene as targets in the detection of respiratory specimens, stool, urine, blood, and lung tissue (Chan et al., 2004b; Lau et al., 2005a; Poon et al., 2003; Poon et al., 2004; Poon et al., 2005b). Diagnosis rarely relied on enzyme immunoassay (EIA) for viral nucleocapsid protein antigen detection on patients' sera (Che et al., 2004a; Che et al., 2004b; Lau et al., 2004c). The nucleoprotein (NP) gene and protein were chosen as targets for RT-PCR and EIA because NP is the most abundantly expressed mRNA and protein in the infected cells, and should therefore give a higher sensitivity. Real-time quantitative RT-PCR of nasopharyngeal aspirates was found to have a sensitivity of 80%, even if the specimen was collected within the first 5 days of symptom onset (Poon et al., 2004).

The shedding of virus correlated with the clinical course. Among 14 SARS patients with serial collection of nasopharyngeal aspirates on days 5, 10 and 15 after symptom onset, viral loads peaked on around day 10, with an inverted V pattern (Peiris et al., 2003a). In additional to respiratory and stool samples (Cheng et al., 2004a), quantitative measurement of viral loads were also performed on other specimens including serum, urine, and saliva (Hung et al., 2009; Wang et al., 2004b). Detection of virus by RT-PCR could persist for up to 51 days in lung tissue (Farcas et al., 2005).

## 4. Treatment

Because no therapy was proven effective in randomized control trials, supportive treatment played an important role in the treatment of SARS. Since the etiological agent of SARS was unknown during the initial phase of the epidemic, patients were given empirical antibiotics for the treatment of community-acquired pneumonia, with coverage of both typical and atypical bacterial pathogens (So et al., 2003). Broad-spectrum antibiotics were indicated in patients who developed nosocomial bacteremia, catheter-related sepsis, and nosocomial pneumonia due to *Escherichia coli, Klebsiella pneumoniae,* and *Stenotrophomonas maltophilia* (Peiris et al., 2003a). Effective antiviral agents are needed to control viral replication, and hence inflammation and tissue damage, as the high viral load was positively correlated with the development of organ failure and death in a subsequent study (Hung et al., 2009). Before the identification of SARS-CoV as the etiological agent of SARS, the neuraminidase inhibitor oseltamivir was also prescribed to some patients in Toronto and Singapore which obviously was unlikely to affect the prognosis (Booth et al., 2003; Hsu et al., 2003; Poutanen et al., 2003).

Another broad spectrum antiviral agent, ribavirin, a purine nucleoside analogue that inhibits guanosine triphosphate synthesis and viral RNA polymerase activity, was commonly given to patients in Asia and North America. Of 2546 patients with descriptions of medical treatment for SARS reported in the literature, 1316 (51.7%) of them received ribavirin, either as the primary treatment regimen or in combination with a corticosteroid or other antiviral agent such as lopinavir/ritonavir (Table 2). The regimens of ribavirin included:

**Table 2**
Medical treatment of SARS in adult and pediatric patients. Patients in Asia include 1119 from mainland China, 1059 from Hong Kong, 111 from Singapore, and 78 from Taiwan. Patients in North America include 179 patients from Toronto.

| Regimens (references) | Asia (N=2367) | North America (*N* = 179) |
|---|---|---|
| *Initial therapy with antiviral and / or immunomodulation*[a] | | |
| Ribavirin (Avendano et al., 2003; Bitnun et al., 2003; Chiu et al., 2003; Hsu et al., 2003; Leong et al., 2004; Poutanen et al., 2003; Zhao et al., 2003) | 155[b] | 21[c] |
| Ribavirin and corticosteroid with or without pulse steroid at clinical deterioration (Avendano et al., 2003; Booth et al., 2003; Chiu et al., 2003; Choi et al., 2003; Ho et al., 2003b; Hon et al., 2003; Lau et al., 2004a; Peiris et al., 2003a; Peiris et al., 2003b; So et al., 2003; Sung et al., 2004; Tsang et al., 2003a; Tsang et al., 2003b; Wang et al., 2004a) | 960[d] | 136 |
| Lopinavir/ritonavir, ribavirin, and corticosteroid (Chan et al., 2003; Chu et al., 2004a)[e] | 44 | 0 |
| Corticosteroid alone (Chen et al., 2006; Loutfy et al., 2003; Wang et al., 2004a) | 404 | 13 |
| Interferon and corticosteroid (Loutfy et al., 2003; Zhao et al., 2003) | 105 | 9 |
| Recombinant interferon alpha (Zhao et al., 2003) | 30 | 0 |
| *Rescue therapy with antiviral and / or immunomodulation* | | |
| Lopinavir/ritonavir (Chan et al., 2003) | 31 | 0 |
| Convalescent plasma (Cheng et al., 2005) | 83 | 0 |
| Immunoglobulin (Lew et al., 2003; Lin et al., 2003) | 93 | 0 |
| Pentaglobulin (Ho et al., 2004) | 12 | 0 |
| Integration of Chinese and western medicine (Lin et al., 2003; Liu et al., 2012) | 450 | 0 |

[a] In addition to the empirical antibacterial agents and oseltamivir.
[b] Including 4 pediatric cases.
[c] Including 10 pediatric cases.
[d] Including 23 pediatric cases.
[e] 41 of 44 reported cases were also reported by (Chu et al., 2004a).

- intravenous formulation of 8 mg/kg every 8 h for 14 days;
- intravenous formulation of 8 mg/kg every 8 h for 5 days, followed by oral formulation of 1200 mg every 8 h, for a total of 10–14 days;
- intravenous loading dose of 2 g, followed by intravenous formulation of 1 g every 6 h for 4 days, then 500 mg every 8 h for 3 days; or
- oral formulation of 2.4 g for one dose, followed by 1.2 g every 8 h for 12 days (Booth et al., 2003; Peiris et al., 2003a; Sung et al., 2004).

However, the role of ribavirin remained uncertain, as there was no obvious clinical benefit in a retrospective, uncontrolled cohort analysis involving 229 patients in Singapore (Leong et al., 2004).

Although *in vitro* studies also demonstrated that ribavirin had no significant activity against SARS-CoV in Vero cells (Cinatl et al., 2003), ribavirin had good activity when it was tested in human Caco-2 and pig kidney cell lines (Morgenstern et al., 2005). Moreover, ribavirin was shown to be synergistic with interferon in *in vitro* combination assays (Chen et al., 2004). The low level of *in vitro* activity against SARS-CoV might be attributed to cellular toxicity, as the 50% cytotoxic dose of ribavirin on various cell lines has been reported to be approximately 200–1000 μg/mL (Tan et al., 2004). Adverse effects of ribavirin were not uncommon. In a cohort of 110 patients in Toronto, dose-related hemolytic anemia was observed in 61% of patients, whereas hypocalcaemia and hypomagnesaemia was reported in 58% and 46% respectively (Knowles et al., 2003). In another cohort of 44 patients in Taiwan, 73% of patients had a drop in hemoglobin level 3 days after therapy with ribavirin which was found to be an independent prognostic factor of hypoxemia or mortality (Chiou et al., 2005).

Some patients were treated with a boosted HIV protease inhibitor, with a combination of lopinavir and ritonavir as either initial therapy or rescue therapy along with ribavirin in the evolving epidemic (Chan et al., 2003; Chu et al., 2004a). *In vitro* antiviral susceptibility testing showed that the cytopathic effect of SARS-CoV was inhibited by lopinavir at 4 μg/ml and ribavirin at 50 μg/ml after 48 h of incubation. Inhibition of the cytopathic effect was achieved down to a lopinavir concentration 1 μg/ml combined with ribavirin 6.25 μg/ml, only when the viral inoculum was reduced to 50 $TCID_{50}$ or below, suggesting potential synergistic activity (Chu et al., 2004a). The addition of lopinavir/ritonavir as initial treatment was associated with a reduction in the overall death rate (2.3%) and intubation rate (0%), when compared with a matched cohort who received standard treatment with ribavirin (15.6% and 11.0% respectively, $P < 0.05$). However, the use of lopinavir/ritonavir as rescue therapy showed no difference in the overall death rate or in rates of oxygen desaturation and intubation, compared with the matched cohort in subgroup analysis (Chan et al., 2003). In view of the weak antiviral activity of protease inhibitors, further studies should be done to ascertain whether the clinical benefit could be attributed to their anti-apoptotic rather than their antiviral activity (Matarrese et al., 2003).

In the early phase of the SARS epidemic, before the identification of the causative agent, histopathological changes in open lung biopsy specimens suggested the possibility of immunopathological damage (Nicholls et al., 2003). Immunomodulators including corticosteroid, convalescent plasma, and pentaglobulin were therefore empirically used as initial and rescue treatment. As initial therapy, a corticosteroid without antiviral therapy was initiated in 417 (16.4%) of 2546 patients (Chen et al., 2006; Loutfy et al., 2003; Wang et al., 2004a), while recombinant interferon-alpha was given to 30 (1.2%) (Zhao et al., 2003) and a combination of corticosteroid and interferon was given in 114 (4.5%) (Loutfy et al., 2003; Zhao et al., 2003).

In a preliminary uncontrolled study of 24 patients in Toronto, 13 patients were treated with corticosteroid alone and 9 patients were treated with corticosteroid and interferon alfacon-1. Among the corticosteroid group, 5 (38.5%) required intensive care, 3 required mechanical ventilation, and one died, while there was no mortality among the corticosteroid plus interferon alfacon-1 group and only 3 and 1 patient required intensive care and mechanical ventilation respectively. In addition, the combination of corticosteroid and interferon alfacon-1 appeared to result in improvements in oxygenation requirement and faster resolution of chest radiograph abnormalities (Loutfy et al., 2003). However, *in vitro* susceptibility testing of interferons against SARS-CoV showed inconsistent results for interferon-ß1a and interferon-α2b (Cinatl et al., 2003; Hensley et al., 2004; Stroher et al., 2004), although inhibition of cytopathic effects of SARS-CoV in culture was observed for interferon-ß, interferon-αn1, interferon-αn3, and leukocytic interferon-α (Tan et al., 2004). Treatment with both interferon-ß and interferon-γ synergistically inhibited SARS-CoV plaque formation by 30-fold and replication by 3000-fold at 24 h, and by more than $10^5$-fold at 48 and 72 h post-infection in Vero E6 cells (Sainz et al., 2004). Prophylactic treatment of SARS-CoV-infected macaques with pegylated interferon-alpha reduced viral replication and excretion, and viral antigen expression by type 1 pneumocytes (Haagmans et al., 2004).

Before the longitudinal serial viral load profile of SARS-CoV during the course of infection was known, corticosteroid therapy was often used together with ribavirin. Without the availability of extracorporeal membrane oxygenation (ECMO), pulse steroid was also given as rescue therapy if patients had clinical deterioration with increasing shortness of breath, oxygen desaturation, and radiological worsening despite ventilator support (Peiris et al., 2003a). Various regimens of corticosteroid therapy were used (Sung et al., 2004; Tsang et al., 2003a), but a standard treatment protocol for adult SARS patients, comprising a tailing dose of intravenous methylprednisolone from 1 mg/kg every 8 h to oral prednisolone 0.25 mg/kg throughout a course of 21 days was proposed (So et al., 2003). A retrospective analysis of 72 SARS patients showed that among 17 patients who initially received a pulse dose of methylprednisolone of $\geqslant$500 mg/day had a lower oxygen requirement and better radiographic outcome, when compared with another 55 patients who initially received non-pulse doses of methylprednisolone of <500 mg/day, even though the cumulative steroid dosage, intensive care unit admission, mechanical ventilation, mortality rates, hematologic and biochemical parameters were similar in both groups after 21 days (Ho et al., 2003b). In a retrospective analysis in Guangzhou, corticosteroid treatment was shown to lower the overall mortality and shorten hospitalization stay in the critically ill SARS patients (Chen et al., 2006).

However, short- and long-term complications such as disseminated fungal infection and avascular necrosis of bone associated with prolonged high-dose corticosteroid use in the treatment of SARS were frequently reported in both adults and children (Chan et al., 2004a; Hong and Du, 2004; Wang et al., 2003a). In a longitudinal follow up of 71 patients (mainly healthcare workers) who had been treated with corticosteroid, 39% developed avascular necrosis of the hips within 3–4 months after starting treatment, and 58% of 71 patients had avascular necrosis after 3 years of follow up (Lv et al., 2009). The number of osteonecrotic lesions was directly related to the dosage of corticosteroid, and a peak dose of more than 200 mg or a cumulative methylprednisolone- equivalent dose of more than 4000 mg were significant risk factors for multifocal osteonecrosis, with both epiphyseal and diaphyseal lesions (Zhang et al., 2008). Up to this stage, no randomized control trial data on the use of steroid was available, and therefore such

treatment should not be recommended, especially when ECMO is available.

Because a neutralizing antibody response was consistently reported in patients recovering from SARS (Chan et al., 2005), convalescent plasma collected from these patients may be useful for the treatment of severely ill patients. Among 80 SARS patients who had received convalescent plasma in Hong Kong, a higher day-22 discharge rate was observed in patients treated before day 14 of illness (58.3% vs 15.6%; $P < 0.001$) and in patients with positive RT-PCR and SARS-CoV antibodies at the time of plasma infusion (66.7% vs 20%; $P = 0.001$) (Cheng et al., 2005). Three healthcare workers received convalescent plasma therapy in Taiwan. The viral load of blood samples dropped from $4.9–6.5 \times 10^5$ copies/mL to undetectable levels one day after transfusion (Yeh et al., 2005).

Pentaglobin, an IgM-enriched immunoglobulin preparation, was given to 12 severely ill SARS patients who continued to deteriorate despite corticosteroid and ribavirin therapy. There was significant improvement in radiographic scores and oxygen requirement after commencement of pentaglobin treatment, and 10 patients made an uneventful recovery (Ho et al., 2004). There were no reported adverse events attributable to pentaglobin administration, compared with the use of high-dose intravenous gamma globulin (0.4 g/kg/day for 3 consecutive days), which may be associated with deep venous thrombosis and pulmonary embolism (Lew et al., 2003). Thymic peptides and recombinant human thymus protein were also given to a few patients, with uncertain clinical benefit (Zhao et al., 2003).

Traditional Chinese medications were used in the treatment of SARS in mainland China. Except for glycyrrhizin, an active component of liquorice roots, which was shown to have *in vitro* activity against SARS-CoV (Chen et al., 2004; Cinatl et al., 2003), other regimens of Chinese medicine were not independently assessed *in vitro*. Nevertheless, 450 (17.7%) of 2546 patients were given Chinese medicine as adjunctive therapy during the epidemic in mainland China (Table 2). In general, Chinese medicines were used to modulate or restore the immune system and to eliminate the toxin as a result of SARS, but without randomized control trial data, it was difficult to assess their efficacies, especially when heterogeneous mixtures of different components of Chinese medicine were used (Lin et al., 2003; Liu et al., 2012).

## 5. Risk factors for transmission

Like most other respiratory virus infections, SARS is predominantly transmitted by respiratory droplets, direct contact with infectious secretions or contact with contaminated fomites. In view of the super-spreading phenomenon from an index patient in Hong Kong leading to the global dissemination of SARS, airborne transmission of SARS-CoV was considered possible under special circumstances (Chu et al., 2005a; Roy and Milton, 2004). Numerous studies were done to identify potential risk factors for transmission in community and hospital settings (Tables 3A–C). In a case-control study conducted in Beijing to investigate the risk factors for community transmission among persons without known contact with SARS patients, it was found that consistent wearing of a mask outdoors was associated with a 70% risk reduction, compared to not wearing a mask, while consistently washing hands after returning home showed a smaller risk reduction (Wu et al., 2004a). These findings suggest that basic infection control measures with good hand hygiene practice can reduce the risk of community transmission.

For nosocomial transmission or outbreaks of SARS, most risk factor studies performed during or after the epidemic emphasized the importance of the appropriate use of surgical mask or an N95 respirator. Consistently wearing a surgical mask or respirator while caring for patients was protective for the nurses who worked in two critical care units in Toronto (Loeb et al., 2004). Mask wearing was shown to be protective in multivariate analysis in a case-control study conducted in a teaching hospital in Hong Kong (Seto et al., 2003). The risk of developing SARS was 12.6 times higher for those who did not wear a mask during patient care (Nishiyama et al., 2008). Because of the physical stability of SARS-CoV, it can survive for 4 days in diarrheal stool samples with an alkaline pH, and it can remain infectious in respiratory specimens for over 7 days at room temperature (Lai et al., 2005b). Contact with respiratory secretions was a significant risk factor for SARS transmission (Teleman et al., 2004). Exposure to body fluids of healthcare workers' eyes and mucous membranes was also associated with an increased risk of transmission (Raboud et al., 2010). Inconsistent use of goggles, gowns, gloves, and caps was associated with a higher risk of infection (Lau et al., 2004b).

Performing high-risk patient care procedures such as intubation, manual ventilation, chest physiotherapy, suctioning, use of bi-level positive airway pressure, high-flow mechanical ventilation, and nebulizer therapy had been associated with nosocomial transmission of SARS among 17 healthcare workers in Toronto (Ofner-Agostini et al., 2006). In particular, endotracheal intubation was a high-risk procedure which deserved further investigation. A case-control study conducted in Guangzhou showed that the incidence of SARS among healthcare workers was significantly associated with performing endotracheal intubations for SARS patients with an odds ratio of 2.76 (Chen et al., 2009).

In a retrospective cohort study to identify risk factors for SARS transmission among 122 critical care unit staff at risk, 8 of 10 infected healthcare workers had either assisted or performed intubation, resulting in a relative risk of 13.29 with 95% confidence interval of 2.99 to 59.04. It was also interesting to note that the relative risk may be higher for nurses than physicians. This might be explained by the longer duration of exposure that nurses likely had in the peri-intubation period, whereas physician exposure was often limited to the procedure itself (Fowler et al., 2004). In fact, proximity and duration of contact with SARS patients may be associated with a higher risk of viral transmission. Transmission of SARS also occurred in 3 of 5 persons present during the endotracheal intubation, including one who wore gloves, gown, and an N95 respirator (Scales et al., 2003).

Aerosol-generating procedures may also contribute to the transmission of SARS. Infection occurred in a healthcare worker who assisted patients ventilated by a bag-valve-mask for 10 to 15 min before the intubation procedure during cardiopulmonary resuscitation, despite having worn an N95 respirator (Christian et al., 2004). The mechanism of transmission remains to be elucidated. However, transmission of SARS-CoV by indirect contact with contaminated environment might be one of the possibilities, as SARS-CoV can survive in the environment for 72–120 h (Chan et al., 2011; Duan et al., 2003), while infectivity is retained for up to 6 days on a dried surface (Rabenau et al., 2005).

Hospital design with augmented air changes may be protective against nosocomial transmission of SARS. In Hanoi, Vietnam, there was no transmission in a hospital with designated isolation wards of large spacious rooms with high ceilings and ceiling fans that were kept running while the large windows were kept open for natural ventilation (Le et al., 2004). The infection rate of SARS among healthcare workers also correlated with the ratios of the area of the ventilation windows to the area of the room. The greatest transmission was in the ward with the smallest area of 61.9 $m^2$ and no window, resulting in 52 (73%) of healthcare workers becoming infected after caring for one SARS patient. In contrast, in the ward with the highest ratio of ventilation windows to the area of the room up to 1:40 ($m^2/m^2$), only 5 (1.7%) healthcare workers wre infected after exposure to 96 SARS patients during the study period (Jiang et al., 2003).

**Table 3A**
Analysis of risk factors and infection control interventions in relation to transmission of SARS in Hong Kong and China.

| City or country | Study design and setting | Major findings | References |
|---|---|---|---|
| Hong Kong | Case-control (13 vs 241) study to identify risk factors for nosocomial transmission among HCWs a hospital | Usage of mask (either surgical or N95 respirator) was shown to be protective in multivariate analysis ($p = 0.011$) | (Seto et al., 2003) |
| Hong Kong | Case-control (72 vs 144) study to identify risk factors for nosocomial transmission among HCWs in 5 hospitals | Inconsistent use of goggles, gowns, gloves, and caps was associated with a higher risk for SARS infection (unadjusted OR 2.42 to 20.54, $p < 0.05$) | (Lau et al., 2004b) |
| Hong Kong | Retrospective cohort study to identify risk factors for nosocomial transmission among 66 Medical students at risk | Visiting index case's cubicle had 7-fold increased risk than those who did not (10/27 [41%] versus 1/20 [5%], RR 7.4; 95% CI 1.0 to 53.3), when mask or glove were not available in the initial phase of outbreak | (Wong et al., 2004) |
| Hong Kong | Retrospective descriptive study of 40 infected HCWs in a community hospital | All infected workers had used surgical masks or N95 respirators. Some had used gloves (58%), gowns (55%), and eye shields (28%), and 73% regularly washed their hands. Three cleaners had no direct patient contact, suggestive of possible environmental contamination | (Ho et al., 2003a) |
| Hong Kong | Retrospective studies to evaluate the effectiveness of a triage policy and risk-stratified infection control measures in a tertiary paediatric & neonatal centres | Stringent infection control precautions, appropriate triage and prompt isolation of potential SARS patients may have contributed to a lack of nosocomial spread and HCW acquisition of SARS | (Leung et al., 2004; Ng et al., 2005) |
| Beijing | Case-control study (147 vs 296) to identify risk factors for nosocomial transmission among HCWs | Use of double exposure suits ($OR = 0.053$), education ($OR = 0.072$), gloves ($OR = 0.102$), hands sterilized by iodine ($OR = 0.231$), room air ventilation ($OR = 0.32$), were significantly protective; conversely, tracheal intubation ($OR = 30.793$) was a significant risk factor in multivariate analysis | (Pei et al., 2006) |
| Beijing | Case-control study (94 vs 281) to identify risk factors for community transmission of SARS | Always wearing a mask when going out was associated with a 70% reduction in risk compared with never wearing a mask. Always washed hands after returning home showed smaller reduction in risk | (Wu et al., 2004a) |
| Guangzhou | Case-control study (91 vs 657) to identify risk factors for nosocomial transmission among HCWs | Incidence of SARS among HCWs was significantly associated with performing tracheal intubations for SARS patients, OR 2.76, 95%CI, 1.16 to 6.53, $p < 0.05$ | (Chen et al., 2009) |
| Guangzhou | Retrospectively studied the ventilation of wards and nosocomial transmission of SARS | Among 4 types of isolation wards, when the ratios of the area of the ventilation windows to the volume of the room were 0, 0, 1:95, and 1:40, and the total time of hospitalization were 43, 168, 110, and 1272 h, the infection rates of the HCWs in the areas mentioned above were 73.2%, 32.1%, 27.5% and 1.7%, respectively | (Jiang et al., 2003) |

HCWs, healthcare workers; *OR*, odd ratio; RR, relative risk; 95% CI, 95% confidence interval.

**Table 3B**
Analysis of risk factors and infection control interventions in relation to transmission of SARS in Vietnam, Singapore, and Taiwan.

| City or country | Study design and setting | Major findings | References |
|---|---|---|---|
| Vietnam | Case-control study (43 vs 103) to identify risk factors for nosocomial transmission among HCWs in a hospital | Risk of developing SARS is 12.6 times higher in those who did not wear a mask. | (Nishiyama et al., 2008) |
| Vietnam | Retrospective descriptive study to identify the attack rate of SARS among 193 HCWs at risk in a hospital | The highest SARS attack rates occurred among nurses who worked in the outpatient and inpatient general wards (57.1%, 47.4%, respectively). Nurses assigned to the operating room/intensive care unit, experienced the lowest attack rates (7.1%) among all clinical staff | (Reynolds et al., 2006) |
| Vietnam | Case-control study (28 vs 98) to identify risk factors for nosocomial transmission among HCWs in Hanoi French Hospital | Masks (OR 0.3; 95% CI, 0.1 to 0.7) and gowns (OR 0.2; 95% CI, 0.0 to 0.8) appeared to prevent SARS transmission | (Nishiura et al., 2005) |
| Vietnam | Retrospective descriptive study to demonstrate lack of SARS transmission among 62 HCWs at risk in hospital B | Hospital B had designated SARS isolation wards and large spacious rooms with high ceilings and ceiling fans and large windows kept open for cross-ventilation | (Le et al., 2004) |
| Singapore | Case-control study (36 vs 50) to identify risk factors for nosocomial transmission among HCWs in Tan Tock Seng Hospital | Contact with respiratory secretions (adjusted OR 21.8, 95% CI, 1.7 to 274.8, $P = 0.017$) was significant risk factor, whereas hand washing (adjusted OR 0.07, 95% CI, 0.008 to 0.66, $P = 0.02$) and wearing of N95 respirators (adjusted OR 0.1, 95% CI, 0.02 to 0.86, $P = 0.04$) remained strongly protective by multivariate analysis | (Teleman et al., 2004) |
| Kaohsiung | Integrated infection control strategy involving triaging patients using barriers, zones of risk, and extensive installation of alcohol dispensers for glove-on hand rubbing in a study hospital in Kaohsiung, Taiwan | Two HCWs contracted SARS in the study hospital (0.03 cases/bed) compared with 93 HCWs in the 86 Taiwan hospitals that did not use the integrated infection control strategy (0.13 cases/bed) during the same three-week period | (Yen et al., 2006) |
| Taipei | Retrospectively studied the serial infection control measures to determine factors most effective in preventing nosocomial infections of HCWs in Taiwan | Checkpoint alcohol dispensers for glove-on hand rubbing between zones of risk, and fever screening at the fever screen station outside the emergency department were the significant methods effectively minimizing nosocomial SARS infection of HCWs ($P < 0.05$) | (Yen et al., 2011) |

HCWs, healthcare workers; *OR*, odd ratio; 95% CI, 95% confidence interval.

## 6. Nosocomial outbreaks

Numerous nosocomial outbreaks were reported in Toronto, Hong Kong, Guangzhou, Kaohsiung, Singapore, and Vietnam during the SARS epidemic (Tables 4A–C). As a result of the admission of infected index patients, there were a total of 716 secondary and tertiary cases, among whom 410 (52.3%) were healthcare workers. In an outbreak in an intensive care unit, 7 (10.1%) of 69 exposed

**Table 3C**
Analysis of risk factors and infection control interventions in relation to transmission of SARS in Canada.

| City | Study design and setting | Major findings | References |
|---|---|---|---|
| Toronto | Retrospective cohort study to identify risk factors for nosocomial transmission among 43 nurses who worked in two critical care units with SARS patients | Eight (25%) of 32 nurses who entered a SARS patient's room were infected. The probability of SARS infection was 6% per shift worked. Consistently wearing a mask (either surgical or N95) while caring for a SARS patient was protective for the nurses | (Loeb et al., 2004) |
| Toronto | Case series to describe the possible route of infection among 17 infected HCWs from 6 hospitals | Performance of high-risk patient care procedures, inconsistent use of personal protective equipment, fatigue, and lack of adequate infection control training were likely responsible for SARS infection | (Ofner-Agostini et al., 2006) |
| Toronto | Retrospective cohort study to identify intubation as a specific risk factor for SARS transmission among 624 HCWs caring 45 SARS patients | Presence in the room during fiberoptic intubation (*OR* = 2.79, *p* = 0.04), and HCW's eyes & mucous membranes exposure to body fluids was associated with increased risk of transmission in multivariate analysis (*OR* = 7.34, *p* = 0 .001) | (Raboud et al., 2010) |
| Toronto | Retrospective cohort study to identify intubation as a specific risk factor for SARS transmission among 122 critical care staff at risk | Ten (8.2%) (5 critical care nurses, 2 respiratory therapists, and 3 physicians) had probable SARS. Performing endotracheal intubation (RR, 13.29; 95% CI, 2.99 to 59.04; p = 0.003), had an increased risk | (Fowler et al., 2004) |
| Toronto | Retrospective cohort study to identify intubation as a specific risk factor for SARS transmission among 64 HCWs in ICU at risk | SARS occurred in 3 of 5 persons present during the endotracheal intubation, including one who wore gloves, gown, and N95 respirator | (Scales et al., 2003) |
| Toronto | Case series to describe the possible transmission of SARS among 9 HCWs at risk during CPR | All healthcare workers adopted contact and droplet precautions. One (11.1%) confirmed to be infected. Ventilated with a bag-valve-mask that may have contributed to aerosolization of SARS-CoV | (Christian et al., 2004) |
| Toronto | Report of nosocomial outbreak control of 128 probable and suspect cases of SARS, including 47 (36.7%) HCWs | Outbreak was under control when contact and droplet precautions were implemented throughout the hospital on March 25, 2003 | (Varia et al., 2003) |
| Ontario | Case series to identify NIPP & nebulized medication as a specific risk factor for SARS transmission among 10 infected HCWs | 9 HCW had unprotected exposure to the index patient. | (Dwosh et al., 2003) |

CPR, cardiopulmonary resuscitation; HCWs, healthcare workers; ICU, intensive care unit; NIPP, non-invasive positive pressure ventilation; *OR*, odd ratio; RR, relative risk; 95% CI, 95% confidence interval.

healthcare workers were infected (Scales et al., 2003). A super-spreading phenomenon was described in the earliest nosocomial outbreak in Guangzhou, in which an index patient directly or indirectly transmitted the infection to over 80 healthcare workers within 2 days of hospitalization (Wu et al., 2004b). A delay in recognition of symptomatic patients and inappropriate infection control measures were the most important reasons for nosocomial outbreaks. Among outbreaks with detailed descriptions, the median time between the admission of the index patient and patient isolation in a designated SARS ward was 4.5 days, with a range of 1–13 days (Dwosh et al., 2003; Gopalakrishna et al., 2004; Liu et al., 2006; Nishiura et al., 2005; Scales et al., 2003; Teleman et al., 2004; Wu et al., 2004b), especially longer patients without an epidemiological link with a SARS contact (Wong et al., 2005).

Once nosocomial outbreaks were recognized, enhanced infection control measures were implemented in the hospitals. Because the mode of transmission was not fully understood in the initial phase of the SARS epidemic, infection control measures varied from center to center, depending on the availability of resources and administrative support. In a private hospital with less than 60 beds in Hanoi, Vietnam, SARS patients were cohorted with the use of barrier precautions. N95 respirators, goggles, and face shields were not available until 6 days after the outbreak (Reynolds et al., 2006). In contrast, in a tertiary hospital with 1400 beds in Singapore, N95 respirators, gloves, gowns, and goggles were immediately provided to healthcare workers working in emergency room, intensive care unit, and isolation ward, whereas powered air purified respirators were available for high-risk procedures such as intubation (Gopalakrishna et al., 2004). In a community hospital in Toronto, in addition to droplet and contact precautions and caring for SARS patients in airborne infection isolation ward, healthcare workers wore double gloves, double gowns, goggles, cap and shoe covers workers in the isolation ward, intensive care unit and emergency room (Dwosh et al., 2003). In Kaohsiung, Taiwan, construction of standard negative-pressure isolation rooms was expedited, and the emergency room was moved outside the hospital complex for patient triage (Liu et al., 2006). In a hospital in Hong Kong, when the demand for personal protective equipment was high in the outbreak setting, their provision to healthcare workers was stratified according to the risk of exposure to SARS patients (Ho et al., 2003a).

In an effort to control nosocomial outbreaks, responses included the temporary closure of wards (Gopalakrishna et al., 2004), outpatient clinics (Liu et al., 2006), inpatient admission (Reynolds et al., 2006), and both inpatient and outpatient services (Nishiura et al., 2005; Varia et al., 2003). Home quarantine of healthcare workers with SARS contact was also mandated in some centers (Dwosh et al., 2003; Gopalakrishna et al., 2004). The median time between admission of index patients and closure of hospital services was 18.5 days (range, 3–21 days), whereas the median time between admission of index patients and termination of nosocomial outbreaks of SARS was 30 days (range, 17–40 days) (Tables 4A–C). However, it is still uncertain if the persistent detection of SARS-CoV by RT-PCR in specimens from infected patients represented live virus shedding and actually contributed to ongoing nosocomial outbreaks (Chu et al., 2005b).

The largest nosocomial outbreak of SARS occurred in a teaching hospital in Hong Kong (Lee et al., 2003). A total of 112 secondary and 26 tertiary cases were epidemiologically linked to the 26-year-old male index patient who presented to ward 8A on 4 March 2003. It was assumed that the use of nebulizer therapy for the index case might have contributed to the large number of secondary cases, with an overall attack rate of SARS of 41% among hospital inpatients (Yu et al., 2005). However, there was no detailed description of outbreak control (Lee et al., 2003).

Retrospective on-site inspections, measurements of the ventilation design, air distribution system and bio-aerosol dispersion were carried out in July 2003. The predicted bio-aerosol concentration distribution in the ward seemed to agree fairly well with the spatial infection pattern of SARS cases (Li et al., 2005b). Even though the patient cubicles were in positive pressure with respect to the corridor, the virus-containing bio-aerosols generated

**Table 4A**
Description of nosocomial outbreak of SARS and its infection control measures in Hong Kong and China.

| City or country | Hospital or clinical setting | Index patient | Description of outbreak | Infection Control measures | Reference |
|---|---|---|---|---|---|
| Hong Kong | 529-bed community hospital | 2 febrile patients admitted to ward A on Mar 23 | 40 HCWs infected; mean age of 36 years; female 31 (77.5%) | At the end of Mar: segregation hospital into ultra-high-risk areas (isolation rooms and ICU) and high-risk areas (medical and pediatric wards) with provision of N95 respirators, gloves, gowns, and eye shields; low-risk area (the rest of hospital) with provision of surgical masks; Apr 14: two isolation wards established for SARS patients; Apr 22: no new infection of HCWs | (Ho et al., 2003a) |
| Hong Kong | University affiliated hospital | M/26 febrile patient admitted on Mar 4 | 112 secondary and 26 tertiary cases (including 69 HCWs) linked to the index patient | Not mentioned | (Lee et al., 2003) |
| Guangzhou | University affiliated hospital | M/44 admitted on Jan 30; isolated after D2 of admission | 35 secondary and 49 tertiary cases, 81 of 84 cases were HCWs | Not mentioned | (Wu et al., 2004b) |

D, day; ICU, intensive care unit.

**Table 4B**
Description of nosocomial outbreak of SARS and its infection control measures in Vietnam, Singapore, and Taiwan.

| City or country | Hospital or clinical setting | Index patient | Description of outbreak | Infection control measures | Reference |
|---|---|---|---|---|---|
| Vietnam | Private hospital of <60 bed | Index patient admitted on Feb 26 to Mar 5 | 22 HCW infected from the index patient | Mar 6: enhanced infection control practices, cohorting of patients, and increased use of barrier protections; Mar 12: N95 respirators, goggles, and face shields were available to staff; Mar 18: temporarily closure of hospital | (Reynolds et al., 2006) |
| Vietnam | 56-bed secondary care hospital | Index patient admitted on Feb 26; isolated after D3 of admission | 38 persons infected (at least 28 HCWs) | Mar 8: Closure of all outpatient & inpatient services, and HCWs advised not to return home; Mar 11: dedicated floor to care SARS patients with strict isolation; Apr 7: no more transmission | (Nishiura et al., 2005) |
| Singapore | Public tertiary hospital | F/23 returned from visit to Hong Kong, admitted on Mar 1; isolated after D5 of admission | 23 secondary cases (including 13 HCWs) from index patient; 49 tertiary cases (including 31 HCWs) | End of first week of Mar: provision of N95 respirators to HCWs when nursing index patient and her contacts; end of second week of Mar: practice of droplet precautions in ICU, ER, and communicable disease wards; wearing N95 respirators (Mar 22), gloves and gowns (Apr 6), and goggles (Apr 25) for all patient contact; Mar 22: no more transmission | (Teleman et al., 2004) |
| Singapore | 1400-bed tertiary hospital | Index patient admitted on Mar 1; isolated after D6 of admission | 24 secondary cases (including 9 HCWs, 5 patients, and 10 visitors), and 25 tertiary cases (including 12 HCWs, 4 patients, 8 visitors, and 1 household contact) | Mar 16: Screening & triage at ER, PPE (N95 respirators, gloves, gowns, and goggles if dealing with suspicious cases; powered air purified respirators for high-risk procedures such as intubation) for staff in ER, ICU, and isolation ward; Mar 22: closure of hospital, and home quarantine of SARS contacts; Apr 8: full PPE for HCW in all areas in hospital; Apr 12: last case of nosocomial transmission | (Gopalakrishna et al., 2004) |
| Singapore | 1600-bed tertiary hospital | Index patient admitted on Mar 24; isolated after D9 of admission | 13 HCWs as secondary cases and 47 tertiary cases (including 11 HCWs, 11 patients, 2 outpatients, 12 visitors, and 11 household contacts) | Apr 5: Transferal of exposed patients and HCWs to the designated SARS hospital; Apr 8: full PPE for HCW in all areas in hospital; Apr 15: last case of nosocomial transmission | (Gopalakrishna et al., 2004) |
| Singapore | A tertiary hospital | Index patient admitted on Apr 8; transferred to designated hospital for isolation on D2 | 6 secondary cases (including 3 HCWs, 2 inpatients, 1 visitor), and 3 tertiary cases (inpatients) | Apr 11: closure of exposed wards for 10 days; transferal of infected cases to the designated SARS hospital; Apr 25: last case of nosocomial transmission | (Gopalakrishna et al., 2004) |
| Kaohsiung | 2300-bed medical center | Index patient admitted on Apr 26; isolated after D4 of admission | 55 secondary cases (52 probable and 3 suspected SARS) including 16 HCWs | Apr 30: wearing of N95 respirators in caring index patient; May 1: screening patients for possible SARS; May 11: expediting construction of standard negative pressure isolation rooms; May 16: cohorting patients with probable and suspected SARS, closure of outpatient clinics, moving ER to temporal quarters outside for patient triage; May 26: last case of nosocomial transmission | (Liu et al., 2006) |

D, day; ER, emergency room; ICU, intensive care unit; PPE, personal protective equipment.

from the index patient's cubicle were still transmitted to the other cubicles. Using a computational fluid dynamic simulation test in a retrospective analysis, it was found that the air exchange related to the small temperature differences between cubicles might have contributed to SARS transmission (Chen et al., 2011).

**Table 4C**
Description of nosocomial outbreak of SARS and its infection control measures in Canada.

| City | Hospital or clinical setting | Index patient | Description of outbreak | Infection control measures | Reference |
|---|---|---|---|---|---|
| Toronto | 249-bed secondary care community hospital with ER, ICU, and CCU | Visitor to Hong Kong who returned to Toronto on Feb 23 and infected her son who admission on Mar 7 | Secondary cases: 128 (72 probable, 56 suspected); mean age of 44.8 years; female 77 (60.2%); HCWs 47 (36.7%); 17 patients died with an overall case-fatality rate of 13.3% | Mar 13: Implementation of airborne, contact and droplet precautions for known cases of SARS; Mar 22: contact and droplet precautions for all patients in ICU; Mar 23: closed ER and ICU; Mar 24: closed hospital admission & outpatient clinics; use of gloves, gowns, N95 respirators, eye protection and handwashing for all patient care with outbreak control | (Varia et al., 2003) |
| Toronto | 419-bed community hospital | M/77 admitted on Mar 16; isolated after D13 of admission | 14 secondary cases (including 10 HCWs and 4 patients) | Mar 28: Implementation of droplet and contact precautions and caring of SARS patients in dedicated SARS ward with negative pressure by dedicated medical team; wearing double gloves, double gowns, cap and shoe covers in ER, ICU, and SARS ward; use of goggle in patient care areas; voluntary quarantine of 10 days from last exposure to the hospital | (Dwosh et al., 2003) |
| Toronto | ICU of a hospital | M/74 transferred to ICU on Mar 23; with the use of humidified high-flow oxygen (5 h), NIPPV (18.25 h), and MV (7.5 h) before isolation | 7 (6 probable & 1 suspected cases) of 69 HCWs infected | Not mentioned | (Scales et al., 2003) |

CCU, coronary care unit; D, day; ER, emergency room; ICU, intensive care unit; MV, mechanical ventilation; NIPPV, noninvasive positive pressure ventilation.

## 7. Infection control

In view of the lack of effective antiviral therapy and vaccines, infection control measures remain the most important modality to prevent human-to-human transmission of SARS. Early isolation of suspected patients is important to prevent nosocomial transmission (Chowell et al., 2003). In Hong Kong, patients triaged at the emergency department and transferred from other hospitals were evaluated using a set of clinical and epidemiological criteria, such as fever over 38 °C, cough, or shortness of breath, and with history of close contact to SARS case. Patients fulfilling those criteria were admitted to designated wards, where the number of beds in each cubicle was reduced to allow a bed-to-bed distance of at least 2 meters, so as to minimize the risk of transmission (Ho et al., 2003c). A dedicated team of physicians and nurses, led by experienced respiratory and infectious disease experts, was established to provide special care to all patients admitted to the designated wards. Active surveillance of patients with community or nosocomial acquired pneumonia was also conducted in general wards to identify and isolate any unrecognized cases. Standard, contact, and droplet precautions were enforced in all clinical areas in the hospital.

Risk-stratified infection control measures were proposed in acute pediatric wards in Hong Kong. By stratifying the clinical areas into ultrahigh-, high- and moderate-risk areas, according to different risk levels of nosocomial SARS transmission and the implementation of different levels of infection control precautions, there was no nosocomial transmission of SARS in the pediatric service (Leung et al., 2004).

In Taiwan, an integrated infection control approach was implemented at a SARS designated hospital where airborne infection isolation rooms were not available. Fever screening stations, triage of fever patients, separating SARS patients from other patients, separation of entrances and passageways between patients and healthcare workers, and increase of hand-washing facilities all demonstrated a protective effect for healthcare workers (Yen et al., 2011, 2006).

Besides the infection control preparedness in the emergency department, triage areas, general wards, and designated SARS wards, special arrangements were also made for operating rooms. For instance, reorganization of staff deployment was made to minimize the potential exposure of healthcare workers. Physical modification of the ventilation system was done to minimize the outflow of contaminated air from the operating room into the rest of the operating room complex. With these key arrangements, 41 operative procedures, including 15 high-risk procedures (surgical tracheostomy), were performed on SARS patients by 124 healthcare workers in the operating room complex in Singapore, without any transmission of SARS (Chee et al., 2004).

Because the viral load was relatively low during the initial phase of symptoms (Peiris et al., 2003a), timely contact tracing of exposed persons and quarantine were effective in the control of SARS transmission in the community. In Beijing, extensive contact tracing of over 30,000 persons for quarantine measures was carried out in 2003. Among 2195 quarantined close contacts, the overall attack rate of SARS was 6.3%, ranging from 15.4% among spouses to 0.36% among work and school contacts. Without such measures, SARS might have persisted in the community and hospitals (Pang et al., 2003).

## 8. Lessons learned and the way forward

With the emergence of the MERS-CoV in the Middle East and avian influenza A H7N9 infections in China, which are both associated with unusually high mortality rates (Chan et al., 2013a; Chan et al., 2013b; Chan et al., 2012; Chan et al., 2013d; Chen et al., 2013), it is time to consolidate what we have learnt from SARS and adopt proactive infection control measures. Novel pathogens may emerge from wild animals as a result of their close interactions with humans in markets and restaurants. Besides the surveillance of these animal sources (Lau et al., 2010; Poon et al., 2005a; Wong et al., 2007), it is even more important to enhance our clinical awareness for the early recognition of infection caused by novel microbial agents. Appropriate infection control measures, with provision of personal protective equipment and isolation of patients, should be implemented early.

With the advancement of laboratory technologies, diagnostic tests can be performed within a short period of time. In fact, we

have successfully implemented these actions during the outbreak of pandemic influenza A H1N1 in 2009, thus preventing the occurrence of a nosocomial outbreak in our hospital (Cheng et al., 2010b; Cheng et al., 2012b). Rapid laboratory diagnostic testing has been integrated into proactive infection control measures against various bacteria and viruses with the potential for nosocomial outbreaks (Cheng et al., 2011b; Cheng et al., 2011c; Cheng et al., 2012d). The introduction of sophisticated molecular and sequencing techniques has also facilitated our investigation of outbreaks and pseudo-outbreaks caused by unusual pathogens (Cheng et al., 2009a; Cheng et al., 2012c; To et al., 2013).

Because SARS affected a large number of healthcare workers with fatalities (Cooper et al., 2009), their protection is an important aspect of infection control training, in addition to patient safety. Hand hygiene with the use of an alcohol-based hand rub has become a key infection control measure. We have further promoted hand hygiene by introducing a concept of directly-observed hand hygiene and electronic monitoring of compliance (Cheng et al., 2011a; Cheng et al., 2007b), resulting in better control of endemic and sporadic pathogens in the hospital (Cheng et al., 2010a; Cheng et al., 2009c). The concept of extensive contact tracing during the SARS outbreak has been harnessed for the control of multiple drug-resistant organisms which are not yet endemic in our healthcare setting (Cheng et al., 2009b; Cheng et al., 2012a). Ten years after the SARS outbreak, our healthcare system is better prepared for the new challenges posed by known and unknown emerging pathogens.

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