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8th Jan 2004

Miss Flora TAI
Clerk to Select Committee
Legislative Council
8 Jackson Rd.,
Central, HK

Fax: 2248 2011
Your ref: CB2/SC2

Dear Miss Tai,

Thank you for your document dated 30th Dec 2003 requesting me to respond to the questions raised by the Select Committee. I have enclosed here my response and my short CV for your reference.

Yours sincerely,

David Hui

Dr David Shu Cheong HUI
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RESPONSE TO THE QUESTIONS RAISED
BY THE SELECT COMMITTEE OF THE LEGISLATIVE COUNCIL

David Hui
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Q1a) What was the condition of the Amoy Gardens index patient when he was admitted to the hospital? What was the diagnosis?

I started looking after YY [redacted] (Amoy Gardens index patient) only during his second admission after he had been transferred to the intensive care unit on 23 Mar 2003. Thus my answers are based on the information recorded by my colleagues (Drs Angela Wang, SF Lui, Linda Yu and Andrew CF Hui) during the first admission from 15-19 Mar 2003, and case discussion with Dr Andrew Hui (Senior Medical Officer) at our clinical case meeting on 19 Mar 2003. [redacted], YY who worked and lived in a rented flat in Shenzhen, China, had been coming to our hospital for haemodialysis (HD) twice weekly since 1987. On 15 March 2003, he presented to PWH ward 8C (renal unit) for routine HD. Upon his arrival on 15 Mar 2003, he did not complain of any specific symptoms. He charted his own temperature as 37°C. During HD, he was noted to be unwell. On re-checking his body temperature by the nursing staff, it was 38C. He then admitted to have had some cough overnight, with some myalgia and arthralgia. Chest radiograph was organized by our nephrologist on 15 Mar 2003 and revealed right lower zone infiltrate. White cell count (WCC) taken during HD was 1.9 (NB. transient leucopenia is a common feature during HD). In view of his fever, chest x-ray changes, and his regular travel to Shenzhen, a provisional diagnosis of atypical pneumonia was made. He was then assessed by the infection control team and admitted (cohorted) to Ward 8A as a suspected case of atypical pneumonia. His WCC, which was re-checked later in the evening, was 7.0 with lymphocyte count of 0.5. He was commenced on Cefotaxime, levofloxacin and Oseltamivir.

His fever gradually subsided over the next 24 hours and he was afebrile by 4 pm of 17 March 2003. He remained afebrile till discharge. There was significant resolution of the right lower zone infiltrate on his serial chest radiographs. On 18th March 2003, the result of the nasopharyngeal aspirate (NPA), which had been taken on admission, was available and positive for influenza A. On 19th March 2003, as he remained afebrile with almost complete resolution of the Chest xray changes in addition to a positive identification of influenza A from the NPA, he was then discharged from Ward 8A. Thus the diagnosis was influenza A, possibly complicated by secondary bacterial pneumonia. His illness at the time could be fully explained by the alternative diagnosis of Influenza A, possibly complicated by secondary pneumonia, as reflected by his favorable clinical and radiological response to treatment with Oseltamivir and antibiotics (1).

NB In retrospect (after managing many cases of SARS), YY [redacted] had both influenza A and SARS with a most unusual phase 1 presentation. Most patients with SARS have persistent pneumonia during phase 1 followed by progression to bilateral lung disease with respiratory failure during phase 2 (around Day 8 from fever onset). The almost

complete radiological resolution of his right lower lobe infiltrate during phase 1 (15-19 Mar) was most "atypical" although he did have progression to phase 2 with bilateral pneumonia and respiratory failure on 22 Mar 2003 (2).

Q1b) Did the healthcare workers (HCW's) who attended to him take any infection control measures? If so, what were these infection control measures?

Yes, HCW's who attended to him did take any infection control measures.
During HD, our renal nurses routinely wear surgical masks and gloves during cannulation of the arterial-venous fistula.
Since 12 Mar 2003, we started to cohort patients with atypical pneumonia in ward 8A and began to wear N-95 masks on the same day. We had also stepped up the infection control measures and personal protective gears according to instructions and guidelines from Infection Control Team and HA guidelines. Thus HCW's, who had attended to [redacted] after his admission to ward 8A, were wearing N95 masks, gloves, and gowns.

Q1c) Were you aware of any HCW's being infected between the admission of the Amoy Gardens index patient and his discharge? If there were such infection cases, were you aware of the causes for the infection?

According to the investigation by my colleague, Dr CB Leung (Nephrologist), two renal nurses (one female and one male) were infected as a result of contact with [redacted] during HD on 22 Mar 2003.
The female nurse, aged 32 years, looked after [redacted] during HD on 22 Mar 2003. She developed symptoms with fever, cough, myalgia, and chills on 26 Mar 2003.
The male nurse, aged 42 years, looked after [redacted] during HD on 22 Mar 2003. He also developed symptoms on 26 Mar 2003.
NB. In retrospect and after acquiring more knowledge about this new disease, [redacted] was highly infectious around 22 Mar 2003 (day 8 from fever onset).

Q2a) When were patients first discharged from ward 8A of PWH after it had been closed to admission, discharge and visiting on 10 Mar 2003? What were the factors considered in making such a decision and by whom was the decision made? Had the risk of discharging patients from the ward and hence posing danger to the wider community been considered? Had the source of the infection been identified prior to making the decision? Were discharged patients placed under observation or surveillance? When was the step-down ward set up?

My roles early in the outbreak of atypical pneumonia were to manage the HCW's admitted to the Observation room at the Accident & Emergency on and after 11 Mar 2003, and provide advice on any patients that had deteriorated or required transfer to the intensive care. I was not directly involved in the discharge of patients from 8A, which was managed by other ward physicians. As far as I could remember from my attendance at clinical meetings, patients were first discharged from Ward 8A on 12 March 2003. Early in the outbreak at PWH, there was no information about the aetiology, infectivity and mode of transmission of this newly emerged infection. The clustering of cases among

our ward 8A staff did suggest that there might be a source of infection within the medical ward. It was thought that patients, who were fit for discharge and did not have any evidence of infection, might potentially contract the disease if they were kept in the ward. Thus the main reason for discharging patients from 8A was for their protection. We also considered the possibility that the patients might still develop symptoms of the illness after they had been discharged. Thus the patients were told to return to our Accident & Emergency if they developed symptoms at home. In addition, they were advised to stay home and maintain good personal hygiene. We were also aware that we had no legal right for retaining patients in hospital.

The source of the infection (PWH index patient) was identified on 13 Mar and confirmed by the Department of Health (DH) on 14 Mar 2003. DH was informed of every patient discharged from our hospital for contact tracing if necessary.

The decision of discharging patients from 8A was made by the hospital management and the Faculty of Medicine in the Cluster Committee of Atypical Pneumonia. Each individual case of discharge was reviewed by senior physicians in charge of the wards. The administration's decision to allow the discharge of the non-SARS patients was based on the understanding with DH that DH would be doing surveillance on all discharged patients. The arrangement was agreed with DH in one of the earliest meetings around 12 Mar 2003.

The so-called "step-down" ward system was set up on 29 March 2003 after we had acquired more knowledge about the incubation period, period of infectivity and clinical course of the illness.

Q2b) When the Amoy Gardens index patient was discharged from a ward housing confirmed SARS and highly suspected SARS patients, why was the patient not placed in the step-down ward? Were you aware that there was an incubation period for the unknown disease? If so, when did you know?

In answering these questions, it is most important to remember the actual sequence of events. Twenty three HCWs with atypical pneumonia were admitted to PWH late on 11 Mar 2003. As a result of the major outbreak, WHO issued a global warning of atypical pneumonia on 12 Mar 2003. The aetiology, incubation period, and clinical course of this newly emerged infectious disease were totally unknown at the time. There were speculations such as influenza, avian influenza, Chlamydia as possible causes of the disease. The term "SARS" was first coined by WHO on 15 Mar 2003 and SARS coronavirus was identified as the causative agent on 22 Mar 2003. Diagnostic tests for SARS such as RTPCR and IgG serology only became available at PWH from 1 Apr 2003 and 23 Apr 2003 respectively.

YY [redacted] was discharged on 19 Mar 2003 because his illness could be fully explained by an alternative diagnosis of influenza A, possibly complicated by secondary bacterial pneumonia, with significant clinical and radiological improvement (1). The decision for his discharge was made well before the aetiology or clinical course of SARS was known and certainly well before any diagnostic tests were available.

Following the admission of our HCW's with atypical pneumonia late at night on 11 Mar 2003 at PWH, a disease control center was set up on 12 Mar 2003 on the second floor of

PWH to co-ordinate reporting and exchange of information with DH. A questionnaire survey was conducted by the DH staff over the next few days to evaluate symptoms and the incubation period of the newly emerged disease. It obviously would take time to conduct the survey and thus there were no data for days. I was first aware of preliminary data on the incubation period of the disease provided by the WHO Office in Hanoi around 14 Mar 2003, and it was estimated as 4.4 days (3). Our CUHK community physician and epidemiologist, Prof TW WONG, was invited on 14 Mar 2003 to help work out the incubation period together with our research staff. Prof ZHONG Nan Shan gave a 20 min talk on the clinical features and his clinical experience managing the disease at the Hong Kong Thoracic Society Annual Scientific Meeting on 15 Mar 2003 at the HK Convention Center. All the respiratory physicians were there and it was the first time I heard about the clinical experience of my colleague from Kwong Wah Hospital (Dr KS Yee) in managing the early cases of atypical pneumonia. More preliminary information about symptoms and incubation period of SARS was available on 21 March 2003 from CDC (4) and it was estimated as 3-5 days (range 2-7 days).
The step down ward became available on 29 Mar 2003 after we had sufficient information in late Mar 2003 to work out accurately the incubation period, which was 6 days (median) and ranged from 2-16 days in our PWH cohort. We had disseminated the information including clinical features worldwide through our publication in the New Engl J Med (Lee N, Hui DS, Wu A, et al.) with an electronic publication on 7 Apr 2003 (5). The first journal publication on the incubation period of SARS, based on 10 epidemiologically linked cases, was available on internet on 31 Mar 2003 in a paper by Tsang KW et al. and it was estimated as 2-11 days.

3a) Was Department of Health (DH) informed of the fact that patients were being discharged from 8A and of their details; if so, what information was provided for DH?

Since 12 March 2003, a Disease Control Center (DCC) had been set up on the second floor of PWH to keep track with admission and discharge of patients with febrile illness. In the Disease Control Center, staff from PWH, Chinese University of Hong Kong, and DH were working very closely to monitor the data. I understand that DH was informed of the details of every patient discharged from our hospital for contact tracing if necessary. In addition, updated information was forwarded to the head office of Hospital Authority daily.

3b) What information relating to the Amoy Gardens index patient, if any, was provided for DH on his discharge? Did you know whether DH had taken any follow-up action to monitor the Amoy Gardens index patient after his discharge?

I understand that information regarding the diagnosis and discharge of YY [redacted] from ward 8A was passed on to DH by Dr Louis Chan, medical officer, based at the PWH Disease Control Center. My role throughout the SARS epidemic from Mar to June 2003 was to manage the SARS inpatients and follow up the confirmed cases at the designated SARS outpatient clinics. It was however not my duty to check whether DH had taken any

follow-up action to monitor YY after his discharge on 19 Mar 2003. Therefore I did not know whether DH had taken any follow-up action.

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Ref 1

Case Definitions for Surveillance of Severe Acute Respi Syndrome (SARS)

Objective
To describe the epidemiology of SARS and to monitor the magnitude and the spread of tl order to provide advice on prevention and control.

Case definitions (revised 1 May 2003)

Introduction
The surveillance case definitions based on available clinical and epidemiological data are supplemented by a number of laboratory tests and will continue to be reviewed as tests in research settings become more widely available as diagnostic tests. Preliminary clinica Severe Acute Respiratory Syndrome summarizes what is currently known about the clini SARS. Countries may need to adapt case definitions depending on their own disease situ Retrospective surveillance is not expected.

Clinicians are advised that patients should not have their case definition catego downgraded while awaiting results of laboratory testing or on the bases of neg
See Use of laboratory methods for SARS diagnosis.

Suspect case

1. A person presenting after 1 November 2002[1] with history of:
- high fever (>38 °C)
AND
- cough or breathing difficulty
AND one or more of the following exposures during the 10 days prior to onset of sympto
- **close contact**[2] with a person who is a suspect or probable case of SARS;
- history of travel, to an area with recent local transmission of SARS
- residing in an area with recent local transmission of SARS

2. A person with an unexplained acute respiratory illness resulting in death after 1 Nove but on whom no autopsy has been performed
AND one or more of the following exposures during to 10 days prior to onset of symptom
- **close contact,**[2] with a person who is a suspect or probable case of SARS;
- history of travel to an area with recent local transmission of SARS
- residing in an area with recent local transmission of SARS

Probable case

1. A suspect case with radiographic evidence of infiltrates consistent with pneumonia or distress syndrome (RDS) on chest X-ray (CXR).
2. A suspect case of SARS that is positive for SARS coronavirus by one or more assays. laboratory methods for SARS diagnosis.
3. A suspect case with autopsy findings consistent with the pathology of RDS without a cause.

Exclusion criteria
A case should be excluded if an alternative diagnosis can fully explain their illness.

Reclassification of cases
As SARS is currently a diagnosis of exclusion, the status of a reported case may change patient should always be managed as clinically appropriate, regardless of their case statu
- A case initially classified as suspect or probable, for whom an alternative diagnosis ca the illness, should be discarded after carefully considering the possibility of co-infection.
- A suspect case who, after investigation, fulfils the probable case definition should be r "probable".
- A suspect case with a normal CXR should be treated, as deemed appropriate, and mo days. Those cases in whom recovery is inadequate should be re-evaluated by CXR.
- Those suspect cases in whom recovery is adequate but whose illness cannot be fully e alternative diagnosis should remain as "suspect".
- A suspect case who dies, on whom no autopsy is conducted, should remain classified However, if this case is identified as being part of a chain transmission of SARS, the case reclassified as "probable".
- If an autopsy is conducted and no pathological evidence of RDS is found, the case shc "discarded".

[1] The surveillance period begins on 1 November 2002 to capture cases of atypical pneu now recognized as SARS. International transmission of SARS was first reported in March with onset in February 2003.

[2] **Close contact:** having cared for, lived with, or had direct contact with respiratory se fluids of a suspect or probable case of SARS.

Reporting procedures
- **All probable SARS cases should be managed in the same way for the purposes control and outbreak containment** See Management of Severe Acute Respiratory Syr

-**At this time, WHO is maintaining surveillance for clinically apparent cases only and suspect cases of SARS.** (Testing of clinically well contacts of probable or suspect S community based serological surveys are being conducted as part of epidemiological stu ultimately change our understanding of SARS transmission. However, persons who test S positive in these studies will not be notified as SARS cases to WHO at this time).

- Where laboratory tests are not available or not done, probable SARS cases as currently should continue to be reported in the agreed format.

- Suspect cases with positive laboratory results will be reclassified as probable cases for purposes **only if the testing laboratories use appropriate quality control procedu**

- No distinction will be made between probable cases with or without a positive laborator suspect cases with a positive result for the purposes of global surveillance. WHO will neg surveillance of SARS with selected partners to collect detailed epidemiological, laboratory data.

- Cases that meet the surveillance case definition for SARS should not be discarded on th negative laboratory tests at this time.

Rationale for retaining the current surveillance case definitions for SARS
The reason for retaining the clinical and epidemiological basis for the case definitions is t there is no validated, widely and consistently available test for infection with the SARS c Antibody tests may not become positive for three or more weeks after the onset of symp not yet know if all patients will mount an antibody response. Molecular assays must be p appropriate reagents and controls under strictly controlled conditions, and may not be p early stages of illness using currently available reagents. We are not yet able to define th specimen to be tested at any given stage of the illness. This information is accruing as m being performed on patients with known exposures and/or accompanied by good clinical epidemiological information. We hope that in the near future an accessible and validated assay(s) will become available which can be employed with confidence at a defined, earl illness.

pneumonia had not been the "friend of the aged." Nuland observed, "By and large dying is a messy business."

The stark contrast between the findings of the study by Heyland et al and the SUPPORT studies is troublesome. Is that difference due to cultural, attitudinal, and organizational differences for the delivery of critical care in Canada and America? The easy explanation that American patients want more treatment even at the risk of discomfort may or may not be true. After years of public and often acrimonious debate, á la Quinlan and Cruzan, physicians may feel unsettled with the following question. Are our medical practices regarding the dying more humane than they were 30 or 40 years ago?

Legally and ethically, a lot of ground has been covered. The death-with-dignity movement, living wills, durable power of attorney, and even assisted suicide (in Oregon) are society's attempts to deal with difficult bioethical issues. Yet why do most family members feel betrayed and burdened when their next of kin die in the ICU? The vigorous ethical debates do nothing for the anguish of surrogates caught in the maze of "full code" and "DNR" designations in the hospital. Practically, who decides the question of whether to institute mechanical ventilation or artificial feeding becomes more important than the essential goodness of the decisions.

Although the current study did not report too many out-of-control treatments, many families are fearful. Callahan[3] has referred to the illusion that we could master our medical choices: "Yet there is hardly below the surface, a remarkable and rising anxiety about dying—not necessarily death as such but the combination of an extended critical illness gradually transformed into an extended dying." His personal considerations border on accepting decline and death in an almost fatalistic manner, which is unusual in Western thought.

In an ever-shrinking world, we should not underestimate the effect of life-support technology and medical know-how in societies in which ethical and legal constraints are weak or nonexistent. One often hears of the "illegality" of discontinuing mechanical ventilation in dying patients! Yet, with few support systems, these interventions may be stopped abruptly after the financial ruin of the families. Unfortunately, the immorality of such practices is rarely questioned. Decision making in these highly paternalistic medical systems requires some scrutiny. I feel that we have an obligation to our colleagues in less affluent societies. A universal ethical code for the use of life-support technology in this young century is a laudable goal.

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Ref 2

Severe Acute Respiratory Syndrome

Severe acute respiratory syndrome (SARS) is an emerging infectious disease with a formidable morbidity and mortality. In March 2003, there was a serious outbreak of SARS in Hong Kong.[1] Within a month, the disease also spread to Singapore,[2] Vietnam, Taiwan, Germany, Canada,[3] and the United States. As of May 10, 2003, 7,296 cases have been reported in 30 countries, with a death toll of 526.[4]

EPIDEMIOLOGY

The early cases of SARS probably occurred in southern China. In November 2002, there were many cases of severe pneumonia of unknown etiology in Guangdong Province in southern China, with a high rate of transmission to healthcare workers.[5] A 64-year-old physician from southern China, who visited Hong Kong on February 21, 2003, and died 10 days later of severe pneumonia, is believed to have been the source of infection, causing subsequent outbreaks of SARS in Hong Kong,[1,6] Vietnam, Singapore,[2] and Canada.[3] The index patients of these cities had been exposed to the Guangdong physician while they were visiting China or had been staying on the same floor of the same hotel. While investigating the outbreak of SARS in Hanoi, Dr. Carlo Urbani unfortunately contracted the disease and died.

SARS appears to spread by close person-to-

person contact via droplet transmission or fomite.[7] The high level of infectivity of this viral illness is highlighted by the fact that 158 patients were hospitalized with SARS within 2 weeks as a result of exposure to one single patient on a general medical ward in Hong Kong. The use of a jet nebulizer for administering bronchodilators to the index case, who presented clinically with community-acquired pneumonia, could increase the droplet load around the patient and, together with the overcrowding condition on the hospital ward, had contributed to this major hospital outbreak.[1] A novel coronavirus (CoV) is now identified as the main pathogen responsible for SARS,[8–11] although the presence of a metapneumovirus also was inferred in studies from Canada[11] and Hong Kong.[1] Several laboratories have recently completed the sequencing of the genome of the CoV that has led to the global epidemic of SARS, and they have noted that the SARS-CoV is not closely related to any of the previously characterized CoVs.[12–14]

Clinical and Laboratory Features

The mean incubation period of SARS is estimated to be 6.4 days (95% confidence interval, 5.2 to 7.7), and the mean time from onset of clinical symptoms to hospital admission varied between 3 and 5 days.[15] The major clinical features on presentation include persistent fever, chills/rigor, myalgia, dry cough, headache, and dizziness. Less common symptoms include sputum production, sore throat, coryza, nausea and vomiting, and diarrhea.[1–3] Watery diarrhea has been reported in a subgroup of patients 1 week down the clinical course. This was reported in a cohort infected in a community outbreak that has been linked to a faulty sewage system, presumably due to involvement of the GI tract via the fecal-oral route.[16]

Lymphopenia (*ie*, the destruction of both CD4 and CD8 lymphocytes), features of low-grade disseminated intravascular coagulation (*ie*, thrombocytopenia, prolonged activated partial thromboplastin time, and elevated d-dimer levels), and elevated lactate dehydrogenase levels (reflecting lung injury) and creatinine kinase levels (reflecting myositis) are common laboratory features of SARS.[1–3,8,11]

The clinical course of SARS appears to follow a triphasic pattern. Phase 1 (viral replication) is associated with increasing viral load and is clinically characterized by fever, myalgia, and other systemic symptoms that generally improve after a few days. Phase 2 (immunopathologic damage) is characterized by the recurrence of fever, oxygen desaturation, and radiologic progression of pneumonia with falls in viral load. The majority of patients will respond to treatment with a combination of ribavirin and IV steroids, but 20% of patients may progress into the phase 3, which is characterized by ARDS necessitating ventilatory support.[16] Compared with adults and teenagers, SARS seems to run a less aggressive clinical course in younger children, with no children in one case series[17] requiring supplementary oxygen.

Pulmonary Features

The radiographic appearances of SARS share features in common with other causes of pneumonia. At fever onset, almost 80% of patients with SARS have abnormal chest radiographs, all of which show airspace consolidation. All patients will eventually develop airway opacities during the course of the disease. In our study, the opacities occupy a peripheral or mixed peripheral and axial location in 88% of patients.[18] The predominant involvement of the lung periphery and the lower zone, in addition to the absence of cavitation, hilar lymphadenopathy, or pleural effusion, are the more distinctive radiographic features of SARS.[1,18] Radiographic progression from unilateral focal airspace opacity to either multifocal or bilateral involvement during the second week of the disease course, followed by radiographic improvement with treatment, is commonly encountered.[1,18] In one case series,[16] 12% of patients developed spontaneous pneumomediastinum and 20% of patients developed evidence of ARDS over a period of 3 weeks. In general, the incidence of barotrauma in ICU admissions seems higher than expected despite treatment with low-volume and low-pressure mechanical ventilation. Chest radiographs and CT scans have not demonstrated excessive hyperinflation or bullous lung disease, and it is difficult to explain this observation.[19]

High-resolution CT scanning of the thorax is useful in detecting lung opacities in patients with unremarkable chest radiograph findings. Common findings include ground-glass opacification, sometimes with consolidation, and interlobular septal and intralobular interstitial thickening, with predominantly peripheral and lower lobe involvement. The characteristic peripheral alveolar opacities are very similar to those found in patients with bronchiolitis obliterans-organizing pneumonia.[1,19]

The postmortem examination of lung tissues in SARS patients has shown various levels of disease severity. Changes include gross consolidation of the lungs, the presence of interstitial mononuclear inflammatory infiltrates, desquamation of pneumocytes in alveolar spaces, pulmonary edema with hyaline membrane formation, and cellular fibromyxoid-orga-

nizing exudates in airspaces, indicating the organizing phase of alveolar damage. Viral inclusions were not detected.[1,10]

Diagnostic Criteria

The diagnosis of SARS is based on clinical, epidemiologic, and laboratory criteria that have been laid down by the Centers for Disease Control and Prevention.[20] The clinical criteria include the following: (1) asymptomatic or mild respiratory illness; (2) moderate respiratory illness (*ie*, temperature, > 100.4°F or 38°C) and at least one respiratory feature (*ie*, cough, dyspnea, difficulty breathing, or hypoxia); (3) severe respiratory illness (features of the second criterion and radiographic evidence of pneumonia, the presence of respiratory distress syndrome, autopsy findings consistent with pneumonia, or the presence of respiratory distress syndrome without an identifiable cause). The epidemiologic criteria include travel (including transit in an airport) within 10 days of the onset of symptoms to an area with current, recently documented, or suspected community transmission of SARS, or close contact within 10 days of the onset of symptoms with a person known or suspected to have SARS infection. Laboratory criteria include the following: (1) the detection of an antibody to SARS-CoV in specimens obtained during acute illness or 21 days after illness onset; (2) the detection SARS-CoV RNA by reverse-transcriptase polymerase chain reaction (PCR) that was confirmed by a second PCR assay by using a second aliquot of the specimen and a different set of PCR primers; or (3) the isolation of SARS-CoV. A case of *probable SARS* is defined as having met the clinical criteria for severe respiratory illness of unknown etiology with onset since February 1, 2003, and epidemiologic criteria, irrespective of the laboratory result. A case of *suspect SARS* is defined as having met the clinical criteria for moderate respiratory illness of unknown etiology with onset since February 1, 2003, and epidemiologic criteria, irrespective of the laboratory result.[20]

Treatment

The treatment of SARS has been empirical during the recent outbreak. Anecdotal experience using a combination of ribavirin and steroids has been described by two studies in Hong Kong.[1,21] Oral ribavirin (1.2 g tid orally or 400 mg q8h IV) and corticosteroids (*ie*, prednisolone, 1 mg/kg/d) were prescribed as combination therapy.[1] During phase 2, when there was radiologic progression of pneumonia and/or hypoxemia, IV high-dose methylprednisolone, 0.5 g daily for up to 6 doses in most cases, is administered to prevent immunopathologic lung injury, with the rationale that progression of the pulmonary disease may be mediated by the host inflammatory response.[16] The majority of our cohort (90% of 138 patients) appeared to have a favorable response to the combination treatment with resolution of fever and lung opacities within 2 weeks, whereas about 23% and 14%, respectively, of the same cohort required ICU admission and invasive ventilatory support.[1] The use of ribavirin therapy in SARS patients is associated with significant toxicity, including hemolysis (76% of patients) and a decrease in hemoglobin of 2 g/dL (49% of patients), elevated transaminase levels (40% of patients), and bradycardia (14% of patients).[3] Any treatment regimen for SARS needs to be tested with a randomized placebo-controlled design. New antiviral agents and immunomodulating agents are also under investigation.

Noninvasive positive-pressure ventilation has been used for treatment with some success in a small number of SARS patients with respiratory failure.[21] However, therapy with noninvasive positive-pressure ventilation should be carried out only if there is adequate protection for the health-care workers (*eg*, an isolation room with adequate air exchange) because of the potential risk of viral transmission via mask leakage and flow compensation causing the dispersion of a contaminated aerosol.

Prognosis/Outcome

The calculation of case fatality rates in the situation of an emerging epidemic is difficult, but it has been estimated to be 13.2% (95% CI, 9.8 to 16.8%) for patients < 60 years of age and 43.3% (95% CI, 35.2 to 52.4%) for those ≥ 60 years of age.[15] The prognostic factors associated with a poor outcome (*ie*, ICU admission or death) include age,[1,15,16] chronic hepatitis B treated with lamivudine,[16] high peak lactate dehydrogenase,[1] high neutrophil count on presentation,[1] or presence of diabetes mellitus or other comorbid conditions.[3]

In conclusion, with the recent onset of the SARS epidemic worldwide, research on the development diagnostic tests and an effective treatment is urgently needed. We hope that the availability of the genome sequence of the SARS-CoV[12–14] will facilitate efforts to develop new and rapid diagnostic tests, antiviral agents, and vaccines in the long run. SARS patients who have recovered from the acute illness should be monitored carefully for the possibility of continued viral shedding[16] and the potential development of pulmonary fibrosis or late postviral complications. The prevention of spread is most important for this highly infectious disease. Isolation facilities, strict precautions against droplet exposure (*ie*, hand hy-

giene, and the wearing of gowns, gloves, N95 masks, and eye protection) among health-care workers managing SARS patients,[22] the avoidance of the use of nebulizers on a general medical ward,[1] contact tracing, and quarantine isolation for close contacts are all important measures.

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Ref 3

EPI Update of Acute Respiratory Syndrome in Hanoi.

- a preminary analysis

- based on data provided by WHO Office in Hanoi through March 13.

Summary Table

Data from Hanoi French Hospital	Best Mean Estimate
Time from Exposure to Onset of Symptoms	4.4 days
Attack rate among exposed HCWs (Index-to-HCW)	>56%
Proportion of HCWs with symptoms who progressed to pneumonia or ARDS	69%
Time from Onset of Symptoms to mildly abnormal X-ray findings	3-5 days *
Time from Onset of Symptoms to severely abnormal lung findings/intubation/ARDS	8-11 days *

**About 1/3 of all symptomatic cases that we know about did not develop lower resp. symptoms.

1. The limitations of data at hand

The data used in this report were based on situation reports, e.g., the daily number of patients that were symptomatic and of their status. Consequently we know very little about those who recovered, and so all severity estimates are affected.

There were one major (French Hospital) and several minor (business office, a few family members) foci of the Hanoi outbreak. For the purpose of quantifying, this document is focused on the Health Care Workers (doctors, nurses, lab staff) at the French Hospital. **We know that 25 HCWs were exposed to the index case in the first 10 days or so.** The following situation of hospitalization of a large proportion of these HCWs led to the **additional exposure of about 46 HCWs who cared for their sick colleagues,** and presumably some of these were among those who fell ill more

recently. As a consequence, we have only an approximate handle on all denominators, and so all estimates are preliminary.

2. Estimates of Attack Rates in the French Hospital.

There were apparently 25 HCWs caring for the index case up to March 7 or so. At this time there were 14 symptomatic HCWs, all of them without lower respiratory symptoms. **Assuming all transmission was Index-to-HCW in this phase, we estimate a minimum attack rate of 56%** (14/25).

Starting March 8, a growing number of HCWs had developed pneumonia, and so we **assume HCW-HCW transmission began**. On March 12, there were 26 symptomatic HCWs and 46 HCWs cared for them, for a total denominator of 72 exposed HCWs. Assuming that 5-10 HCWs had recovered and were not counted in the March 12 figure of symtomatic HCWs, **we estimate a minimum attack rate of 43%** (=(26+5)/72).

3. Incubation Period.

Again assuming all transmission during the 10 days after the index case was admitted (Feb26 to March 7), we considered all 14 HCWs who had information about first exposure to index cases, and interview dates for first onset of symptoms. Of these 14 HCWs, the time from first exposure to index case (day when they began caring for him) could be estimated for 10; the mean time to 1st symptoms (incubation period) was **4.4 days**.

If we include all 16 HCWs for which the dates of first exposure and onset of symptoms has been reported to us, the incubation period was **5.4 days**. The latter is probably an overestimate, as some of the latest cases were probably HCW-HCW transmission and so the time from exposure to symptoms was overstimated.

4. Proportion of cases who progressed to severe disease.

On March 12, **20 of the 26 symptomatic HCWs were 25 of them had progressed to pneumonia and/or ARDS.** Assuming 5-10 HCWs had

recovered, we estimate that **a minimum of 69%** (=25/(26+10) of symptomatic HCWs progressed to severe illness.

A very preliminary and not very satisfactory estimate of the case fatality rate is 3% among HCWs as of March 13, after the index case died today (calculation: CF=1/(26 HCWs currently symptomatic+10 recovered+1indexcase)). However, as several of the HCWs are critically ill, and since the disease in all 2this estimate will likely increase greatly over the next week(s).

5. Pattern of Progression to severe disease

The impression of the clinical picture is that of a febrile illness with upper respiratory symptoms that progress to pneumonia, ARDS and death in some cases. To quantify this picture, we considered the degree of abnormal signs on the X-rays and correlated these findings with the days of illness (e.g., days since first report of symptoms) as they were reported for 19 patients on March 11 and March 12 (so two observations for most patients).

For those patients who had at least one abnormal X-ray reading, there was a positive correlation between severity of X-ray findings and days since onset. This means that the patients on ventilators and X-ray findings indicated as +++ or ++++ were those who had been symptomatic for the longest time.

A preliminary interpretation would suggest that the mean time to early signs of lower respiratory involvement (+ on X-ray) was 3-5 days after onset of febrile illness. Also, this most/many patients who had mildly abnormal X-ray findings will progress to severe illness (ARDS) and require ventilation pessimistically suggests that 8-11 days after onset of febrile illness.

MMWR

Ref 4

Weekly

March 21, 2003 / 52(11);226-228

Outbreak of Severe Acute Respiratory Syndrome --- Worldwide, 2003

Please note: An erratum has been published for this article. To view the erratum, please click here.

Since late February 2003, CDC has been supporting the World Health Organization (WHO) in the investigation of a multicountry outbreak of atypical pneumonia of unknown etiology. The illness is being referred to as severe acute respiratory syndrome (SARS). This report describes the scope of the outbreak, preliminary case definition, and interim infection control guidance for the United States.

On February 11, the Chinese Ministry of Health notified WHO that 305 cases of acute respiratory syndrome of unknown etiology had occurred in six municipalities in Guangdong province in southern China during November 16, 2002--February 9, 2003. The disease was characterized by transmission to health-care workers and household contacts; five deaths were reported (*1*). On February 26, a man aged 47 years who had traveled in mainland China and Hong Kong became ill with a respiratory illness and was hospitalized shortly after arriving in Hanoi, Vietnam. Health-care providers at the hospital in Hanoi subsequently developed a similar illness. The patient died on March 13 after transfer to an isolation facility in Hong Kong. During late February, an outbreak of a similar respiratory illness was reported in Hong Kong among workers at another hospital; this cluster was linked to a patient who had traveled previously to southern China. On March 12, WHO issued a global alert about the outbreak and instituted worldwide surveillance.

As of March 19, WHO has received reports of 264 patients from 11 countries with suspected and probable* SARS (Table). Areas with reported local transmission include Hong Kong and Guangdong province, China; Hanoi, Vietnam; and Singapore. More limited transmission has been reported in Taipei, Taiwan, and Toronto, Canada. The initial cases reported in Singapore, Taiwan, and Toronto were among persons who all had traveled to China.

On March 15, after issuing a preliminary case definition for suspected cases (Box, CDC initiated enhanced domestic surveillance for SARS. CDC also issued a travel advisory suggesting that persons planning nonessential travel to Hong Kong, Guangdong, or Hanoi consider postponing their travel (http://www.cdc.gov/travel/other/acute_resp_syn_multi.htm). On March 16, CDC began advising passengers arriving on direct flights from these three locations to seek medical attention if they have symptoms of febrile respiratory illness. As of March 18, approximately 12,000 advisory notices had been distributed to airline passengers. In addition, surveillance is being heightened for suspected cases of SARS among arriving passengers. As of March 19, a total of 11 suspected cases of SARS in the United States are under investigation by CDC and state health authorities.

Among patients reported worldwide as of March 19, the disease has been characterized by rapid onset of high fever, myalgia, chills, rigor, and sore throat, followed by shortness of breath, cough, and radiographic evidence of pneumonia. The incubation period has generally been 3--5 days (range: 2--7 days). Laboratory findings have included thrombocytopenia and leukopenia. Many patients have had respiratory distress or severe pneumonia requiring hospitalization, and several have required mechanical ventilation. Of the 264 suspected and probable cases reported by WHO, nine (3%) persons have died. In addition, secondary attack rates of >50% have been observed among health-care workers caring for patients with SARS in both Hong Kong and Hanoi. Additional clinical and epidemiologic details are available from WHO at http://www.who.int/wer/pdf/2003/wer7812.pdf.

In the United States, initial diagnostic testing for persons with suspected SARS should include chest radiograph, pulse oximetry, blood cultures, sputum Gram stain and culture, and testing for viral respiratory pathogens, particularly influenza types A and B and respiratory syncytial virus. Clinicians should save any available clinical specimens (e.g., respiratory samples, blood, serum, tissue, and biopsies) for additional testing until diagnosis is confirmed. Instructions for specimen collection are available from CDC at http://www.cdc.gov/ncidod/sars/pdf/specimencollection-sars.pdf. Specimens should be forwarded to CDC by state

health departments after consultation with the SARS State Support Team at the CDC Emergency Operations Center.

Clinicians evaluating suspected cases should use standard precautions (e.g., hand hygiene) together with airborne (e.g., N-95 respirator) and contact (e.g., gowns and gloves) precautions (http://www.cdc.gov/ncidod/sars/infectioncontrol.htm). Until the mode of transmission has been defined more precisely, eye protection also should be worn for all patient contact. As more clinical and epidemiologic information becomes available, interim recommendations will be updated.

Reported by: *CDC SARS Investigative Team; AT Fleischauer, PhD, EIS Officer, CDC.*

Editorial Note:

During 2000, approximately 83 million nonresident passengers arrived in China, 13 million in Hong Kong, and 2 million in Vietnam, and approximately 460,000 residents of China, Hong Kong, and Vietnam traveled to the United States (*2*). During January 1, 1997--March 18, 2003, an estimated 5% of ill tourists worldwide who sought post-travel care from one of 35 worldwide GeoSentinel travel clinics had pneumonia (International Society of Tropical Medicine, unpublished data, 2003). In the United States, approximately 500,000 persons with pneumonia require hospitalization each year; in approximately half of these cases, no etiologic agent is identified despite intensive investigation (*3,4*). On the basis of these data and the broad and necessarily nonspecific case definition, cases meeting the criteria for SARS are anticipated worldwide and in the United States. However, most of the anticipated cases are expected to be unrelated to the current outbreak.

Electron microscopic identification of paramxyovirus-like particles has been reported from Germany and Hong Kong (*5*). This family of viruses includes measles, mumps, human parainfluenza viruses, and respiratory syncytial virus in addition to the recently identified henipaviruses and metapneumovirus. Additional testing is under way to confirm a definitive etiology. Identification of the causative agent should lead to specific diagnostic tests, simplify surveillance, and focus treatment guidelines and infection control guidance.

Clinicians and public health officials who suspect cases of SARS are requested to report such cases to their state health departments. CDC requests that reports of suspect cases from state health departments, international airlines, cruise ships, or cargo carriers be directed to the SARS Investigative Team at the CDC Emergency Operations Center, telephone 770-488-7100. Additional information about SARS (e.g., infection control guidance and procedures for reporting suspected cases) is available at http://www.cdc.gov/ncidod/sars. Global case counts are available at http://www.who.int.

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* Suspected cases (Box with either a) radiographic evidence of pneumonia or respiratory distress syndrome or b) evidence of unexplained respiratory distress syndrome by autopsy are designated probable cases by the WHO case definition.

Table

TABLE. Number of suspected and probable cases and deaths from severe acute respiratory syndrome, by location — Worldwide, 2003*

Location	No. cases	Deaths No.	Deaths (%)
Hong Kong	150	5	(3)
Vietnam	56	2	(4)
Singapore	31	0	—
Canada	8	2	(25)
Taiwan	3	0	—
Germany	1	0	—
Thailand	1	0	—
Slovenia	1	0	—
United Kingdom	1	0	—
United States	11	0	—
Spain	1	0	—
Total	**264**	**9**	**(3)**

* As of March 19, 2003.
Source: World Health Organization.

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Box

BOX. CDC preliminary case definition for severe acute respiratory syndrome (SARS)*

Suspected case

Respiratory illness of unknown etiology with onset since February 1, 2003, and the following criteria:

- Documented temperature >100.4°F (>38.0°C)
- One or more symptoms of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or radiographic findings of pneumonia or acute respiratory distress syndrome)
- Close contact† within 10 days of onset of symptoms with a person under investigation for or suspected of having SARS or travel within 10 days of onset of symptoms to an area with documented transmission of SARS as defined by the World Health Organization (WHO).

* As of March 19, 2003.
† Defined as having cared for, having lived with, or having had direct contact with respiratory secretions and/or body fluids of a person suspected of having SARS.

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publication.

Ref 5

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Major Outbreak of Severe Acute Respiratory Syndrome in Hong Kong

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ABSTRACT

BACKGROUND

There has been an outbreak of the severe acute respiratory syndrome (SARS) worldwide. We report the clinical, laboratory, and radiologic features of 138 cases of suspected SARS during a hospital outbreak in Hong Kong.

METHODS

From March 11 to 25, 2003, all patients with suspected SARS after exposure to an index patient or ward were admitted to the isolation wards of the Prince of Wales Hospital. Their demographic, clinical, laboratory, and radiologic characteristics were analyzed. Clinical end points included the need for intensive care and death. Univariate and multivariate analyses were performed.

RESULTS

There were 66 male patients and 72 female patients in this cohort, 69 of whom were health care workers. The most common symptoms included fever (in 100 percent of the patients); chills, rigors, or both (73.2 percent); and myalgia (60.9 percent). Cough and headache were also reported in more than 50 percent of the patients. Other common findings were lymphopenia (in 69.6 percent), thrombocytopenia (44.8 percent), and elevated lactate dehydrogenase and creatine kinase levels (71.0 percent and 32.1 percent, respectively). Peripheral air-space consolidation was commonly observed on thoracic computed tomographic scanning. A total of 32 patients (23.2 percent) were admitted to the intensive care unit; 5 patients died, all of whom had coexisting conditions. In a multivariate analysis, the independent predictors of an adverse outcome were advanced age (odds ratio per decade of life, 1.80; 95 percent confidence interval, 1.16 to 2.81; P=0.009), a high peak lactate dehydrogenase level (odds ratio per 100 U per liter, 2.09; 95 percent confidence interval, 1.28 to 3.42; P=0.003), and an absolute neutrophil count that exceeded the upper limit of the normal range on presentation (odds ratio, 1.60; 95 percent confidence interval, 1.03 to 2.50; P=0.04).

CONCLUSIONS

SARS is a serious respiratory illness that led to significant morbidity and mortality in our cohort.

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IN MARCH 2003, THERE WAS AN OUTBREAK of atypical pneumonia in Hong Kong. As of March 27, there were 367 reported cases in Hong Kong and more than 1400 cases worldwide.[1] The disease may progress rapidly and often results in the acute respiratory distress syndrome (ARDS). As of this writing, there have been 10 deaths in Hong Kong related to the illness, which the World Health Organization (WHO) has named the severe acute respiratory syndrome (SARS). Globally, there have been at least 53 deaths related to SARS.[1] Schools have been closed in Hong Kong, and more than 1000 people who had a history of contact with a patient with SARS were quarantined.

We describe the clinical, laboratory, and radiologic features of patients with SARS who were seen at the Prince of Wales Hospital, Hong Kong. These patients were either health care workers in a medical ward of the hospital or persons who had a history of contact with an index patient or exposure to the same medical ward. We also included patients who had contracted the disease through direct contact with these cases.

METHODS

On March 10, 18 health care workers in a medical ward of the Prince of Wales Hospital reported that they were ill. Through telephone contact, more than 50 of the hospital's health care workers were identified as having had a febrile illness over the previous few days. On March 11, 23 of them were admitted to an isolation ward in the hospital. A team of "atypical pneumonia physicians" was formed to take responsibility for screening of suspected cases and subsequent management. The team included physicians from the Department of Medicine and Therapeutics (infectious disease, respiratory medicine, and general medicine), the Department of Emergency Medicine, and the intensive care unit (ICU). Clinical findings and laboratory data were documented prospectively.

Since the etiologic agent was not known at the onset of the outbreak, the diagnosis was based on clinical symptoms and the ruling out of common bacterial and viral pathogens that cause pneumonia. On the basis of the criteria for SARS that have been established by the Centers for Disease Control and Prevention (CDC),[2] our case definition was a fever (temperature, >38°C), a chest radiograph (a plain radiograph, a computed tomographic [CT] image of the thorax, or both) showing evidence of consolidation with or without respiratory symptoms (e.g., cough and shortness of breath), and a history of exposure to an index patient suspected to have SARS or direct contact with a person who became ill after exposure to an index patient.

All patients were initially admitted to medical wards with isolation facilities. Initial investigations included a complete blood count (with a differential count), clotting profile (prothrombin time, activated partial-thromboplastin time, international normalized ratio, and D-dimer) and serum biochemical measurements (including electrolytes, renal-function and liver-function values, creatine kinase, and lactate dehydrogenase). These studies and chest radiography were performed daily until the fever had subsided for three days. Nasopharyngeal-aspirate samples obtained from all study patients were screened for common viruses, including influenzaviruses A and B, respiratory syncytial virus, adenovirus, and parainfluenzavirus types 1, 2, and 3, with the use of commercial immunofluorescence assays. In addition, virus culture was performed with the use of various cell lines (LLC-MK2, MDCK, Hep2, human embryonic lung fibroblast, Buffalo green-monkey kidney, and Vero cells). In addition, multiplex reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays for influenzavirus A, influenzavirus B, and respiratory syncytial virus were performed in 65 randomly selected patients. Electron microscopy was used to study nasopharyngeal aspirates in selected cases. Sputum cultures and blood cultures were performed in all cases to complete the microbiologic workup. PCR assays for mycoplasma and *Chlamydia pneumoniae* were performed in 65 randomly selected patients. A legionella urinary antigen assay was performed in the first 25 patients.

Initial treatment included cefotaxime and clarithromycin (or levofloxacin) to target common pathogens causing community-acquired pneumonia, according to current recommendations.[3,4] Oseltamivir (Tamiflu) was also given initially to treat possible influenza infection. If fever persisted for more than 48 hours and the blood count showed leukopenia, thrombocytopenia, or both, oral ribavirin (1.2 g three times a day) and corticosteroid therapy (prednisolone at a dose of 1 mg per kilogram of body weight per day) was given as a combined regimen. Patients with persistent fever and worsening lung opacities were given intravenous ribavirin (400 mg every eight hours) and corticosteroid therapy (an additional two to three pulses of 0.5 g of methylprednisolone daily). Patients in whom hypoxemia

developed were given oxygen through a nasal cannula. Patients were admitted to the ICU if respiratory failure developed, as evidenced by an arterial oxygen saturation of less than 90 percent while the patient was receiving 50 percent supplemental oxygen, a respiratory rate that exceeded 35 breaths per minute, or both.

An epidemiologic study was conducted shortly after the outbreak. We identified our index patient, whose exposure history has been described elsewhere.[5] He was a 26-year-old ethnic Chinese man who was admitted to the Prince of Wales Hospital on March 4, 2003, with a high temperature, myalgia, and cough. His chest radiograph showed an ill-defined air-space opacity in the periphery of the right upper lobe. He was treated with amoxicillin–clavulanate and clarithromycin. All bacteriologic and virologic tests were unrevealing. The right lung opacity progressed to bilateral consolidation. After seven days of antibiotic therapy, his fever gradually diminished, and the lung opacities started to resolve. During this period, he was treated with albuterol (0.5 mg through a jet nebulizer, delivered by oxygen at a flow rate of 6 liters per minute, four times daily for a total of seven days).

From our contact tracing, we found that the first patients began to have symptoms two days after the index patient's admission. Moreover, all doctors and nurses who participated in the care of the patient, all medical students who had examined him, and the patients around him were the ones who first reported febrile illness, on March 10. We therefore defined all cases that developed in persons who had had direct contact with the index patient or who had been exposed to him in the medical ward as secondary cases. Cases in patients who contracted the disease from these patients (e.g., family members of health care workers or of patients who had stayed in this medical ward) were defined as tertiary cases.

STUDY POPULATION AND DATA ANALYSIS

Our study cohort included all secondary and tertiary cases. Their demographic, clinical, laboratory, and radiologic characteristics were reported and analyzed. The clinical composite end point was the need for care in the ICU, death, or both. Univariate and multivariate analyses of clinical and laboratory data were performed to identify prognostic variables. Statistical analysis was performed with SYSTAT software (version 7.0, SPSS, Chicago). Data are reported as means ±SD unless otherwise specified. Univariate analysis was performed to compare patients who reached the end point and those who did not, with the use of an unpaired Student's t-test or chi-square test, as appropriate. Multivariate logistic-regression analysis was then performed, with backward stepwise analysis, to identify independent predictors of the end point. All comparisons of clinical variables with a P value of less than 0.20 by univariate analysis were entered into the model. A P value of less than 0.05 was considered to indicate statistical significance. All probabilities are two-tailed.

RESULTS

Between March 11 and March 25, 2003, a total of 156 patients were hospitalized with SARS, of whom 138 were identified as having either secondary or tertiary cases as a result of exposure to our index patient. There were 112 patients with secondary cases and 26 with tertiary cases in this cohort, including 69 health care workers (20 doctors, 34 nurses, and 15 allied health workers) and 16 medical students who had worked in the index ward, plus 53 patients who were either in the same medical ward or had visited their relatives there. There were 66 male patients and 72 female patients; their mean age was 39.3±16.8 years. A total of 19 patients had coexisting conditions: cardiovascular disease in 4, the myelodysplastic syndrome in 2, chronic liver disease in 3, diabetes mellitus in 5, chronic renal failure in 2, and chronic pulmonary disease in 3. Most of the health care workers were previously healthy. All patients were ethnic Chinese.

CLINICAL FEATURES

The interval between exposure to the index patient or ward and the onset of fever ranged from 2 to 16 days. The median incubation period was six days. The most common symptoms at presentation were fever (in 100 percent of the patients); chills, rigor, or both (73.2 percent); myalgia (60.9 percent); cough (57.3 percent); headache (55.8 percent); and dizziness (42.8 percent). Less common symptoms included sputum production (in 29.0 percent), sore throat (23.2 percent), coryza (22.5 percent), nausea and vomiting (19.6 percent), and diarrhea (19.6 percent). Physical examination on admission revealed a high body temperature in most patients (median temperature, 38.4°C; range, 35 to 40.3°C). Inspiratory crackles could be heard at the base of the lung. Wheezing was absent except in one patient with a history of asthma. Rash, lymphadenopathy, and purpura were not seen in this cohort.

HEMATOLOGIC FINDINGS

The initial blood count showed leukopenia (total white-cell count, $<3.5\times10^9$ per liter) in 33.9 percent of patients. Whereas the neutrophil count (median, 3500 per cubic millimeter; range, 500 to 11,800) and the monocyte count were normal in most cases, 69.6 percent of the patients had moderate lymphopenia (absolute lymphocyte count, <1000 per cubic millimeter). Thrombocytopenia (platelet count, <150,000 per cubic millimeter) was documented in 44.8 percent of the patients on presentation. The lymphocyte count continued to drop within the first few days after admission (Table 1). A prolonged activated partial-thromboplastin time (>38 seconds) was noted in 42.8 percent of the patients, whereas the prothrombin time remained normal in most cases. In 45.0 percent of the patients, the D-dimer level was also elevated. Reactive lymphocytes were detected in peripheral-blood films in 15.2 percent of cases.

BIOCHEMICAL FINDINGS

Serum chemical values were normal in the majority of cases. There were, however, several abnormalities in a substantial proportion of patients. Serum alanine aminotransferase levels were elevated (>45 IU per milliliter) in 23.4 percent of patients (mean level, 60.4±150.4 IU per milliliter); only two patients had a history of chronic liver disease. Creatine kinase levels were elevated in 32.1 percent of patients (median level, 126 U per liter; range, 29 to 4644). None of the patients with elevated creatine kinase levels had abnormal values for creatine kinase MB or troponin T, indicating that the source of creatine kinase was unlikely to be cardiac muscle. The lactate dehydrogenase level was elevated in 71.0 percent of patients. Hyponatremia (sodium level, <134 mmol per liter) was documented in 20.3 percent of patients, and hypokalemia (potassium level, <3.5 mmol per liter) in 25.2 percent of patients. The results of laboratory tests performed during the first week of hospitalization are listed in Table 1.

MICROBIOLOGIC AND VIROLOGIC FINDINGS

In our cohort of 138 patients, there were five positive sputum cultures; three were positive for *Haemophilus influenzae*, one for *Streptococcus pneumoniae*, and one for *Klebsiella pneumoniae*. None of the blood cultures were positive. Other bacteriologic investigations were unrevealing. Of all the nasopharyngeal aspirates collected, one was positive for influenzavirus A, one was positive for influenzavirus B,

Table 1. Mean (±SD) Laboratory Results in 138 Patients in the Study Cohort during the First Seven Days of Hospitalization.

Variable*	Day 1	Day 3	Day 5	Day 7
Hemoglobin (g/dl)	13.5±1.7	13.1±1.7	13.0±1.6	12.9±1.7
Platelets ($\times10^{-9}$/liter)	150.2±60.1	153.2±61.3	164.9±70.7	206.3±89.9
White cells ($\times10^{-9}$/liter)	5.1±2.1	5.1±2.7	6.0±3.4	8.3±4.9
Neutrophils ($\times10^{-9}$/liter)	3.9±2.0	4.0±2.7	5.0±3.3	7.2±4.7
Lymphocytes ($\times10^{-9}$/liter)	0.9±0.7	0.8±0.7	0.7±0.4	0.6±0.4
Prothrombin time (sec)	11.2±4.7	12.7±8.6	11.2±4.6	11.3±4.0
Activated partial-thromboplastin time (sec)	41.6±8.9	44.8±12.8	41.2±8.1	36.3±6.9
Sodium (mmol/liter)	135.6±3.4	135.9±3.5	137.0±4.4	139.2±4.9
Potassium (mmol/liter)	3.7±0.4	3.8±0.5	3.8±0.4	3.9±0.4
Urea (mmol/liter)	4.7±5.1	4.5±4.5	4.6±3.8	6.3±7.2
Creatinine (μmol/liter)	99.0±111.8	94.3±100.4	82.8±23.8	82.7±27.2
Bilirubin (mmol/liter)	10.0±19.4	10.7±17.8	12.5±19.3	14.3±16.3
Alanine aminotransferase (IU/liter)	60.4±150.4	67.4±113.7	69.4±72.3	89.8±104.5

* To convert values for creatinine to milligrams per deciliter, divide by 88.4, and to convert values for bilirubin to milligrams per deciliter, divide by 17.1.

and two were positive for respiratory syncytial virus. Microscopical examination of nasopharyngeal aspirates from five patients showed paramyxovirus-like viral particles in one and coronavirus-like viral particles in another. The aspirates from the other three patients were negative. Further virologic studies are in progress.

FINDINGS ON CHEST RADIOGRAPHS

At the onset of fever, 108 of the 138 patients (78.3 percent) had abnormal chest radiographs, all of which showed air-space consolidation. Of these 108 patients, 59 (54.6 percent) had unilateral focal involvement (Fig. 1) and 49 (45.4 percent) had either unilateral multifocal or bilateral involvement. Air-space opacities developed in all patients eventually during the course of the disease.

The initial radiographic changes were indistinguishable from those associated with other causes of bronchopneumonia. Interestingly, peripheral-zone involvement was predominant. Pleural effusion, cavitation, and hilar lymphadenopathy were absent in our cohort. Among patients with clinical deterioration, serial chest radiographs showed progression of pulmonary infiltrates approximately 7 to 10 days after admission. Lung opacities enlarged, and multiple areas of involvement were often seen (Fig. 2A and 2B). A successful response to therapy could be demonstrated by serial chest radiographs showing the resolution of lung opacities (Fig. 2C). In cases in which typical lung opacities could not be found on the initial plain chest radiograph, conventional and high-resolution CT images of the thorax proved to be useful. The typical finding on thoracic CT images, as shown in 25 cases, was ill-defined, ground-glass opacification in the periphery of the affected lung parenchyma, usually in a subpleural location (Fig. 3). The characteristic peripheral alveolar opacities were very similar to those found in bronchiolitis obliterans with organizing pneumonia.[6,7] There was no obvious bronchial dilatation.

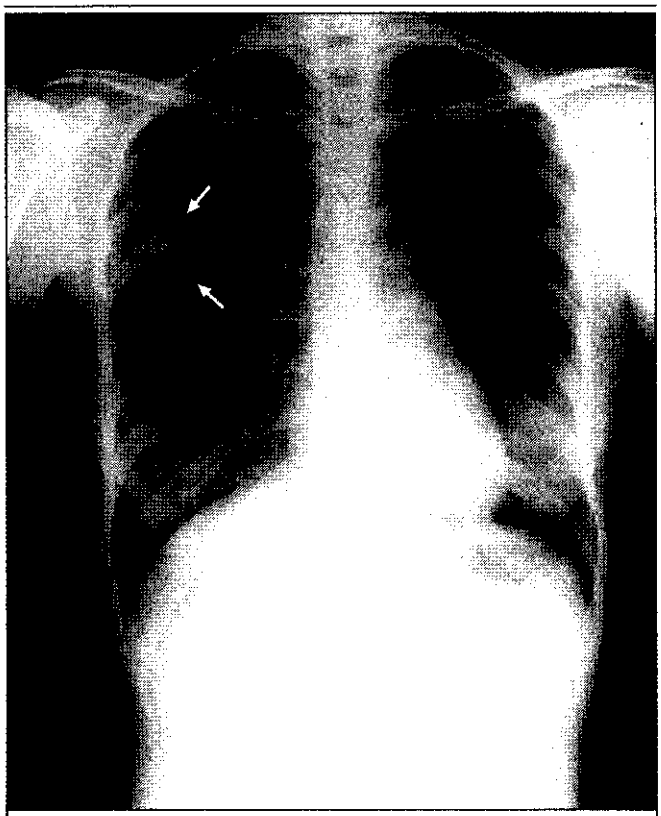


Figure 1. Frontal Chest Radiograph in a 25-Year-Old Woman Showing Ill-Defined Air-Space Shadowing (Arrows).
There is no associated pleural effusion or hilar or mediastinal adenopathy.

CLINICAL OUTCOMES

Of the 138 patients, 32 (23.2 percent) were admitted to the ICU, all because of respiratory failure. Mechanical ventilatory support with positive end-expiratory pressure was required in 19 patients (13.8 percent). Among the 32 patients in the ICU, dramatic increases in lung opacity, shortness of breath, and hypoxemia occurred at a median of 6.5 days (range, 3 to 12) and led to their ICU admission. By day 21 of the outbreak, five patients had died (crude mortality rate, 3.6 percent). All five had originally been admitted because of major medical conditions. Two patients had the myelodysplastic syndrome, one had congestive heart failure, one had alcoholic liver cirrhosis, and one had a reactivation of hepatitis B. None of the health care workers or medical students died. At this writing, a total of 76 patients (55.1 percent) have been discharged, of whom 44 (31.9 percent) were health care workers. Fitness for discharge was based on defervescence for at least 96 hours, with radiographic evidence of improvement in lung consolidation.

FACTORS PREDICTIVE OF ICU ADMISSION AND DEATH

Univariate analysis showed that advanced age, male sex, a high peak creatine kinase value, a high lactate

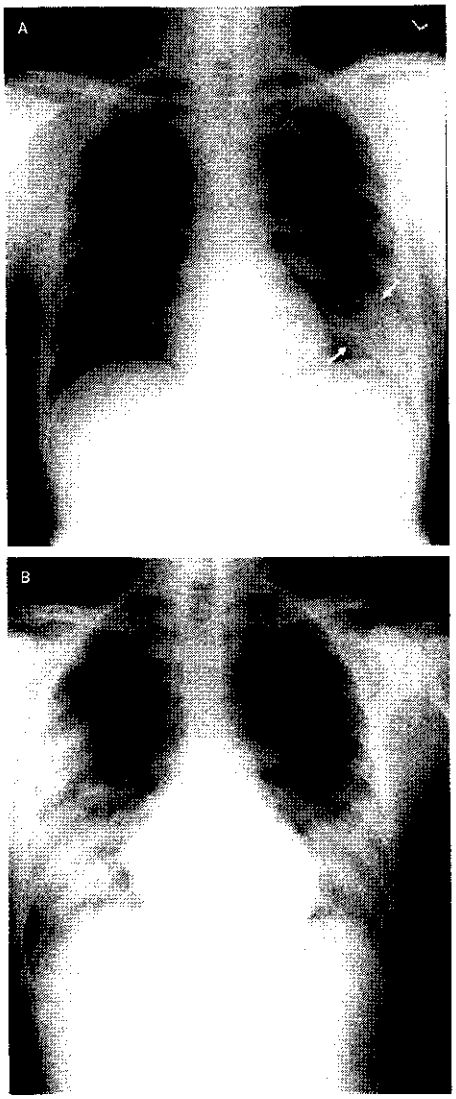
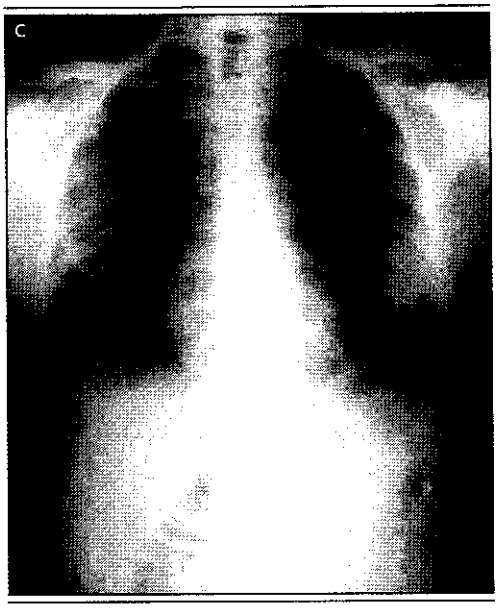


Figure 2. **Frontal Chest Radiographs in a 46-Year-Old Man.**
Panel A shows an obvious area of air-space shadowing (arrows) on the left side. A follow-up chest radiograph showed progression of the disease, with multiple, bilateral areas of involvement (Panel B). A subsequent chest radiograph shows improvement of bilateral lung opacities after therapy (Panel C).



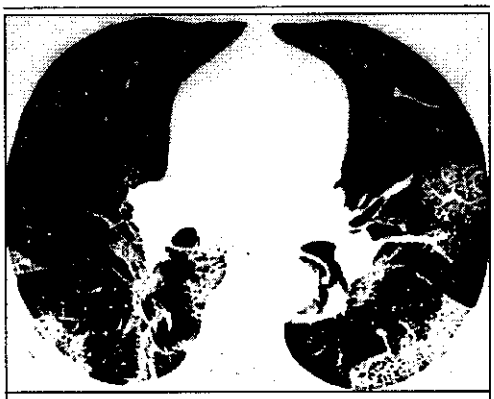


Figure 3. **A High-Resolution CT Scan Showing the Characteristic Ground-Glass Abnormality in a Subpleural Location.**
There is no cavitation. A conventional CT scan did not show pleural effusion or lymphadenopathy.

dehydrogenase level on presentation and a high peak value, a high initial absolute neutrophil count, and a low serum sodium level were significant predictive factors for ICU admission and death (Table 2). The presence of coexisting conditions (in 19 patients) did not appear to be associated with a worse clinical outcome (P=0.14). On multivariate analysis, the only factors that were predictive of an

Table 2. Univariate Analyses of Clinical and Laboratory Variables Associated with the Combined Outcome of ICU Care or Death.*

Variable	No ICU Care	ICU Care or Death	P Value
Age (yr)	36.1±14.6	50.2±18.4	0.007
Male sex (%)	41.9	66.7	0.01
Peak D-dimer (ng/ml)	951.0±1197.9	1686.9±2132.3	0.31
Platelets ($\times 10^{-9}$/liter)	156.8±61.2	131.7±64.9	0.06
Neutrophils ($\times 10^{-9}$/liter)	3.7±1.9	4.6±2.1	0.02
Lymphocytes ($\times 10^{-9}$/liter)	0.9±0.7	0.8±0.5	0.49
Activated partial-thromboplastin time (sec)	41.0±7.5	43.6±11.7	0.23
Sodium (mmol/liter)	136.1±2.7	134.0±4.6	0.02
Urea (mmol/liter)	3.8±1.1	7.3±9.6	0.05
Creatinine (μmol/liter)†	86.1±19.4	135.5±218.0	0.21
Alanine aminotransferase (IU/liter)	46.5±81.4	99.4±262.0	0.27
Creatine kinase (U/liter)			
On presentation	268.5±434.8	609.3±973.2	0.06
Peak	352.7±544.0	697.4±971.1	0.04
Lactate dehydrogenase (U/liter)			
On presentation	287.7±143.3	558.0±258.0	<0.001
Peak	310.0±153.8	629.7±283.5	<0.001

* Plus–minus values are means ±SD. ICU denotes intensive care unit.
† To convert values for creatinine to milligrams per deciliter, divide by 88.4.

adverse outcome were advanced age (odds ratio for every 10 years of age, 1.80; 95 percent confidence interval, 1.16 to 2.81; P=0.009), a high peak lactate dehydrogenase level (odds ratio for every 100 U per liter, 2.09; 95 percent confidence interval, 1.28 to 3.42; P=0.003), and an absolute neutrophil count that exceeded the upper limit of the normal range on presentation (odds ratio, 1.60; 95 percent confidence interval, 1.03 to 2.50; P=0.04).

POSTMORTEM FINDINGS

Postmortem examination in two cases showed gross consolidation of the lungs. Histologic features varied from region to region. The early phase and organizing phase of diffuse alveolar damage were seen in different parts of the lung. The early phase was characterized by pulmonary edema with hyaline membrane formation suggestive of the early phase of ARDS (Fig. 4). Cellular fibromyxoid organizing exudates in air spaces indicated the organizing phase of alveolar damage. There was a scanty lymphocytic inflammatory infiltrate in the interstitium. Vacuolated and multinucleated pneumocytes were also identified. Viral inclusions were not detected. There was no evidence of the involvement of other organs.

DISCUSSION

We report an outbreak in our hospital of a deadly pneumonia, which caused rapid deterioration of pulmonary function requiring ICU admission in 23.2 percent of cases and mechanical ventilation in 13.8 percent. Within a period of less than two months, SARS has become a global health problem, prompting the WHO to issue a global alert for the first time in more than a decade.[1]

SARS developed in 69 health care workers and 16 medical students, all with unremarkable medical histories, after exposure at work in the medical ward for men where our index patient was hospitalized. The high infectivity was also demonstrated by the fact that there were 26 tertiary cases, which included family members of the infected health care workers. We suspected that the infection was transmitted by droplets and possibly by fomites, and we therefore instituted both airborne precautions (e.g., use of the N-95 respirator) and contact precautions (e.g., use of gowns and gloves), as recommended by the CDC.[8] However, the use of a jet nebulizer to administer aerosolized albuterol in the index patient had probably aggravated the spread of the disease by droplet infections.

The clinical presentation and radiologic features of SARS bear some resemblance to the syndrome commonly referred to as "atypical pneumonia"; mycoplasma, chlamydia, and legionella are the usual pathogens implicated in this syndrome. Fever, chills, headache, myalgia, and dry cough are the common features in patients presenting with the syndrome. However, the clinical and radiographic characteristics of atypical pneumonia are not useful in differentiating these pathogens from usual bacterial pathogens such as *S. pneumoniae* and *H. influenzae*. The exclusion of common extracellular pathogens and a response to empirical therapy with macrolides or quinolones are the usual strategy of management. In our cohort, most of the common bacterial pathogens were ruled out, in addition to viral diseases such as influenza and respiratory syncytial virus infection. Moreover, lack of a response

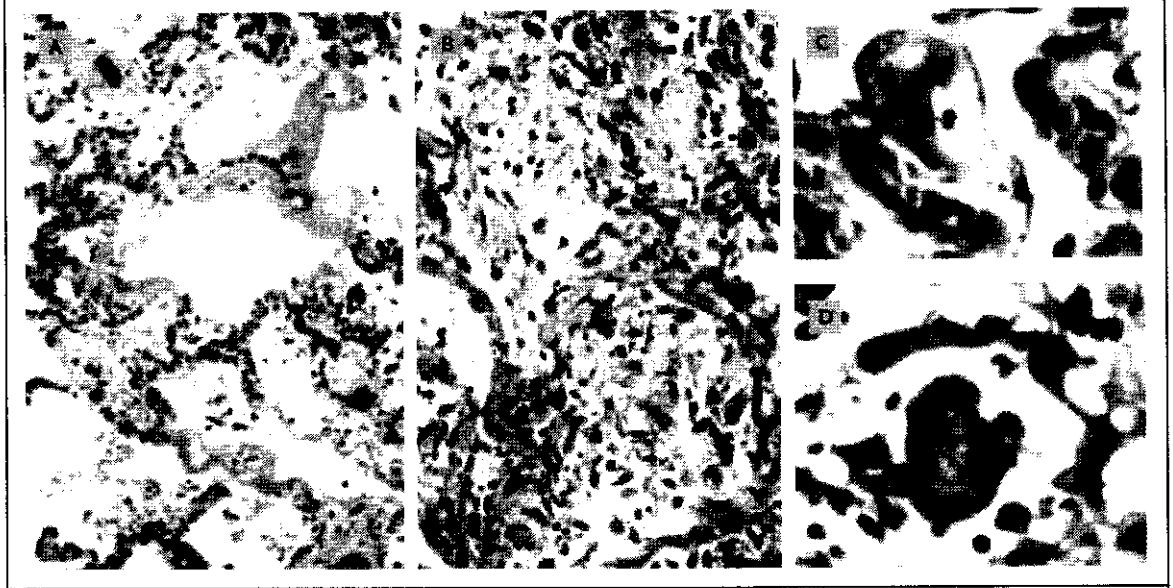


Figure 4. Lung-Biopsy Specimen Obtained at Autopsy.

Panel A shows diffuse alveolar damage with pulmonary congestion, edema, and formation of hyaline membrane (hematoxylin and eosin, ×100). Panel B shows the organizing phase of diffuse alveolar damage, with scanty interstitial inflammatory-cell infiltrates (hematoxylin and eosin, ×200). Panels C and D show vacuolated and multinucleated pneumocytes (hematoxylin and eosin, ×400).

to the initial antimicrobial treatment we provided led to the suspicion that we were dealing with a novel virus that causes lower respiratory tract infection. So far, there have been only preliminary data reported on the causative agent of SARS, and metapneumovirus and coronavirus have been implicated.[5] The relevance of histologic features such as vacuolated and multinucleated pneumocytes in the pathogenesis of SARS remains to be determined. As of this writing, no reliable diagnostic test is available. In the first 138 cases, we have identified several cardinal symptoms of SARS. Besides fever, chills, and rigor, which were present in more than 70 percent of cases, cough was present in more than 50 percent and dizziness in more than 40 percent of cases. Rigor may represent the viremic phase of the disease, which subsided gradually as the illness progressed. In addition, moderate lymphopenia and its subsequent progression, thrombocytopenia, a prolonged activated partial-thromboplastin time, elevated lactate dehydrogenase and creatine kinase levels, and elevated alanine aminotransferase levels were prevalent in the early phase of the illness in our cohort; all these findings are quite different from those associated with pneumonia caused by usual bacterial pathogens. Although these symptoms and laboratory findings are nonspecific, the constellation of these features should alert medical practitioners to the possibility of SARS.[9]

We have also found that the chest radiograph offers an important diagnostic clue to this condition. Typically, our patients presented with unilateral, predominantly peripheral areas of consolidation. After approximately one week, it progressed rapidly to bilateral patchy consolidation, and the extent of the lung opacities was correlated with the deterioration in respiratory function. In cases in which plain chest radiographs appeared normal in the presence of a high spiking fever and lymphopenia, CT of the thorax was a sensitive imaging approach for the diagnosis. The characteristic finding on CT was bilateral peripheral air-space ground-glass consolidation mimicking that in bronchiolitis obliterans with organizing pneumonia. In fact, the similarity of this radiographic picture to that of bronchiolitis obliterans with organizing pneumonia and the similarity of the histologic features to

those of early ARDS in postmortem studies have prompted us to use corticosteroids in combination with ribavirin for the treatment of SARS. In ARDS and particularly in bronchiolitis obliterans with organizing pneumonia, corticosteroid therapy has been used with some success.[7] The majority of our cohort appeared to have a response to corticosteroid therapy, in addition to ribavirin, with resolution of fever and lung opacities within two weeks.

In this study, we were able to identify some clinical and laboratory features on presentation that were associated with the adverse clinical outcome of respiratory failure requiring care in the ICU or death. Univariate analyses showed that advanced age, male sex, a high neutrophil count, a high peak creatine kinase level, high initial and peak lactate dehydrogenase levels, and a low serum sodium level were associated with an adverse outcome. Only advanced age, a high neutrophil count, and a high peak lactate dehydrogenase level were independent predictors. Since high lactate dehydrogenase levels are often seen in association with tissue damage, we propose that this finding indicates more extensive lung injury. The significant association between a high neutrophil count and an adverse outcome remains to be explained. All five patients who died had major coexisting disorders; however, in our analyses, coexisting illness was not correlated with a poor outcome, probably because of the small number of such patients.

SARS has already become a global health hazard, and its high infectivity is alarming. The discovery of the infective agent and studies of its behavior are crucial to an understanding of this new disease. A reliable, rapid diagnostic test, based on blood samples or nasopharyngeal aspirates, is of great importance in the future management of this disease. Until such a diagnostic test is available, a clear picture of its clinical presentation will help physicians be on the alert for this condition. Early recognition, prompt isolation, and appropriate therapy are the keys in combating this deadly infection.

We wish to dedicate this report to the patients we have described, many of whom are our colleagues and their family members, together with medical students from the Faculty of Medicine, Chinese University of Hong Kong. We are also indebted to the many members of the frontline medical and nursing staff who demonstrated selfless and heroic devotion to duty in the face of this outbreak, despite the potential threat to their own lives and those of their families.

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