Global outbreak of severe acute respiratory syndrome (SARS)

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INTRODUCTION

An outbreak of a novel respiratory infection causing atypical pneumonia occurred during late 2002 and continues in 2003. Spread of this infection from the initial cases in Guangdong Province in China has not only occurred in other areas within China, including the Hong Kong Special Administrative Region, but has also resulted in confirmed or probable cases in 26 other countries on four continents as of 26 April 2003.[1] Of particular concern is that there has been well-documented spread from patients to health care workers (HCWs), and subsequent secondary spread to contacts of these individuals. There have been 4836 probable cases of severe acute respiratory syndrome (SARS), resulting in 293 deaths that have been reported to the World Health Organization (WHO),[1] giving a case-mortality rate of 6.1%.

As the etiologic agent or agents were initially unknown, a syndromic definition was used for epidemiologic purposes in order to define cases. This definition, which has been modified over time, has most recently been updated for the USA as summarized in Table 1.[2] Early reports of the etiologic agent of the syndrome included a member of the genus *Chlamydia*, a paramyxovirus, and a *Mycoplasma* species. Most recently, a novel coronavirus has been identified as the etiologic agent of SARS,[3–5] although this agent has not been recovered in a significant fraction of the cases of SARS in Canada. Coronavirus infections, which are known to affect many vertebrates, have been identified, along with rhinoviruses, as common causes of upper respiratory tract infections. There is precedent for pneumonia due to coronaviral infections in humans. Human coronavirus OC43 strains have been shown to be present in lower respiratory tract infections, including cases of pneumonia and bronchiolitis in Normandy, France, and, in a number of cases in both children and adults, it was the only etiologic agent identified.[6]

On 14 March 2003, the WHO issued a global health alert for authorities to be aware of a new atypical pneumonia (SARS) reported in several countries in Southeast Asia. This was the first global alert from the WHO in more than a decade. The international dimension of the SARS outbreak, which is regarded as being beyond the control of any single government, has resulted in a great deal of work in a short period of time, although, as of this date, there is no known effective therapy.

Table 1. Case definition for SARS (U.S. Centers for Disease Control and Prevention)[2]

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

Measured temperature greater than 100.4°F (greater than 38°C) *and*

One or more clinical findings of respiratory illness (e.g. cough, shortness of breath, difficulty in breathing, or hypoxia) *and*

Travel[a] within 10 days of onset of symptoms to an area with documented or suspected community transmission of SARS (see list below; excludes areas with secondary cases limited to health care workers or direct household contacts) *or*

Close contact[b] within 10 days of onset of symptoms with a person known to be a suspect SARS case.

Probable case
A suspect case with one of the following:

Radiographic evidence of pneumonia or respiratory distress syndrome

Autopsy findings consistent with respiratory distress syndrome without an identifiable cause

[a]Travel includes transit in an airport in an area with documented or suspected community transmission of SARS.

Areas with documented or suspected community transmission of SARS: People's Republic of China (i.e. mainland China and Hong Kong Special Administrative Region); Hanoi, Vietnam; Singapore; and Toronto, Canada.

[b]Close contact is defined as having cared for, having lived with or having direct contact with respiratory secretions and/or body fluids of a patient known to be a suspect SARS case.

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EPIDEMIOLOGY

The impressive transmission within health care facilities of SARS is illustrated in Figure 1.[7] It is of note that this resulted not only in transmission of the infection to many hospitals within Hong Kong, but it also resulted in a multi-country spread of the infection, resulting in cases in Asia, Europe, and North America.

As noted in Morbidity Mortality Weekly Report,[7] the epidemiologic investigation of the cluster seen in Figure 1 suggested that, as of 25 March 2003 there was a cluster of 13 persons with suspected/probable SARS who are known to have stayed at hotel M. The index patient (patient A) had onset of symptoms on 15 February. He traveled from Guangdong Province, China to Hong Kong to visit his family, and stayed on the ninth floor of the hotel on 21 February. He was admitted to hospital 2 on 22 February, and died the next day. Four health care workers and two of his family members subsequently became ill; one family member died. Of the 12 other patients linked to hotel M, 10 were in the hotel on the same day as the index patient; the other two patients (patients L and M) stayed in the hotel during the time that three other symptomatic patients were

guests in the hotel. Nine of the 13 patients, including patient A, stayed on the ninth floor; one stayed on the 14th floor; one stayed on the 11th floor; and two stayed on both the ninth and 14th floors. Epidemiologic investigations have identified patients from this cluster as index patients in subsequent clusters in Hong Kong and other areas. Patient B is the index patient for the outbreak in Hanoi involving 59 HCWs and close contacts, and is also linked to one case in Thailand. Patients C, D and E are associated with 70 cases in Singapore and three cases in Germany. Patient F is linked with a cluster of 16 other cases in Toronto. Patients H and J are linked with outbreaks among HCWs in other hospitals in Hong Kong. Patient L appears to have become infected during his stay at hotel M, with subsequent transmission to his wife, patient M.

It is important to recognize that the current definition of a case of SARS is based on a clinical syndrome. It may well be that the range of illness due to the viral agent includes cases that do not fit the current case definition and, as a result, do not meet the criteria established for SARS. Thus, the number of clinically ill individuals is unknown, as the ratio of those who are infected by the coronaviral etiologic agent to those whose
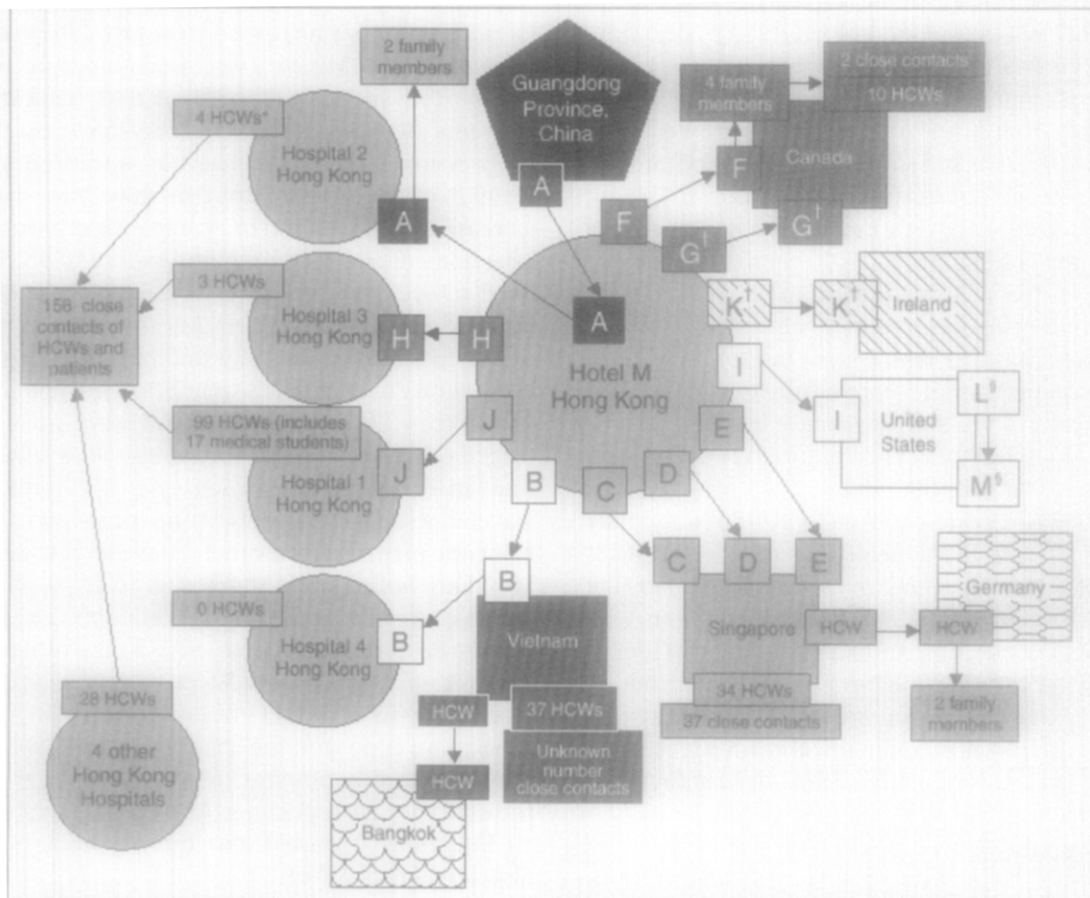
§Guests L and M (spouses) were not at Hotel M during the same time as Index Guest A but were at the hotel during the same times as Guests G, H, and I, who were ill during this period.

Figure 1. Chain of transmission of SARS at a hotel in Hong Kong.[7]

symptoms meet the case definition is not known. By contrast, as there are several infectious agents that can cause a clinically indistinguishable infection, there may well be individuals, especially within China, in whom the etiology of the illness is due to another agent. These cases of atypical pneumonia may meet the case definition of SARS, but are due to background noise.

SARS is mostly spread by exposure to respiratory droplets during close face-to-face contact. The initial cluster of patients from the index case in the Metropole Hotel in Hong Kong was probably infected in the elevator lobby. Increased spread by droplet infection by the use of nebulizers has been reported.[8]

There may be additional routes of transmission. The cluster of cases centered around the Amoy Gardens Housing Estate in Hong Kong has raised the possibility of transmission from an environmental source or the via the fecal–oral route. There appears to be no evidence among this group of patients for airborne transmission.

The survival time of the etiologic agent of SARS in the environment is critical in interpreting the epidemiology of SARS. Coronaviruses have lipid envelopes and, thus, are susceptible to inactivation by heat, desiccation, oxidizing agents, lipid solvents, non-ionic detergents, and ultraviolet irradiation. Survival time depends on the viral genotype, the composition of carrier and substrate, and the particular situation. Respiratory viruses transmitted in droplets or aerosols generally have a limited duration and range of infectivity, whereas other routes of transmission may be more protective (e.g. feces), and so would lead to contamination of the environment for longer periods.

Thus far, cases of SARS have tended to primarily involve healthy adults, aged 25–70 years. Rare cases have been reported in children. Most of the deaths in the Hong Kong outbreak occurred in those with a history of chronic diseases, or those who sought treatment late.[8] In this outbreak, a multivariate analysis identified advanced age, a high peak lactate dehydrogenase level and a high absolute neutrophil count at presentation as independent predictors of an adverse outcome.

The incubation period is usually 2–7 days, but may be as long as 10 days. In the health care setting, SARS is highly infectious, with some reported attack rates of greater than 50% among HCWs caring for patients with SARS. The WHO investigative team also found evidence of 'super-spreaders' in Guangdong, including one who is thought to have infected as many as 100 other persons. This could be due to poor infection control procedures, specific characteristics of a viral strain, or host factors.

GLOBAL UPDATE

By 26 April 2003, the cumulative number of reported probable cases of SARS was 4836.[1] The start of the surveillance period was extended back to 1 November 2002 to capture the cases of atypical pneumonia in Guangdong Province in China, which are now recog-

nized as being cases of SARS. China has reported a total of 2753 cases and an additional 1402 cases in the Special Administrative Region of Hong Kong. Other countries heavily affected include Singapore and Canada. Overall, almost 30 countries have reported cases of SARS, six of which were classified by the WHO as 'affected areas'. These 'affected areas' are those in which local chain(s) of transmission have been identified, and include Canada (Toronto); Singapore; China (Beijing, Guangdong, Hong Kong SAR, Inner Mongolia, Shanxi and the Province of Taiwan); USA (areas not reported); UK (London); and Vietnam (Hanoi). Note that, in Taiwan, London and some areas of the USA, the local transmission is limited: there is no evidence of international spread from the area since 15 March 2003, and no transmission other than close person-to-person contact.

In China, an outbreak of atypical pneumonia consisting of 305 cases began in Guangdong Province in November 2002. However, the Chinese authorities only informed the WHO on 11 February 2003. It transpired that this outbreak, which is now recognized as SARS, dates back to at least 16 November 2002, when an initial case was reported in Foshan City.

More recent data coming out of China have been problematic. By mid-April, Chinese health officials acknowledged only 37 cases of SARS in Beijing. A week later, this number increased to nearly 1200 cases, as the Chinese Health Ministry disclosed numerous previously unreported and new confirmed and suspected cases. It seems that the authorities may have been actively suppressing data. This possible underreporting and 'denial' of the disease burden may have resulted in increased transmission: for example, disregard of specific infection control measures, and failure to recognize the need to seek medical attention early to minimize the number of potential contacts. Another issue is the division of patients between regular and military hospitals, with suggestions that patients in military hospitals were not included in official figures. There were no restrictions placed on travel during the Chinese New Year celebrations in February 2003, when up to 100 million people traveled within China, permitting the spread of the virus from one province to another. However, the more recent May Day holiday was shortened, to try to prevent the massive movement of people. While this is encouraging, it may be too late, in that SARS has already spread to some of China's poorest provinces, many of which (according to a WHO investigative team) have less capacity to cope with the challenge posed by SARS. The unfortunate situation in China emphasizes the need for transparency in reporting (not just for SARS, but for all infectious diseases) and the need for coordinated disease-control efforts.

The outbreak at the Prince of Wales hospital in Hong Kong involved 138 patients who were ill between 11 and 25 March 2003, half of whom were HCWs and 16 of whom were medical students.[8] Overall, 32 patients were admitted to intensive care, and there were five

deaths. More recently, a cluster of 321 almost simultaneous cases has been recorded in residents of the Amoy Gardens housing estate. This large and sudden cluster has prompted many questions, such as whether transmission could be from an environmental source. Patients from the Amoy Gardens commonly presented with diarrhea, which is unusual, and their symptoms seemed more severe overall. There were also deaths in younger, previously healthy individuals. The severity may represent infection with high viral loads, following exposure to a concentrated environmental source, or infection with a virus that is of greater virulence.

By contrast, Vietnam appears to have controlled the SARS outbreak within its borders, but the government is considering closing its land border with China in an attempt to prevent the importation of SARS cases.

In Canada, there are currently 30 reported cases among approximately 500 members of a religious group in Toronto. The index case of this community cluster is linked to the first hospital cluster. Local health authorities have implemented isolation of all contacts of suspect and probable cases, including all 500 members of the religious group, to try to contain any further spread within and outside of this social network. The degree to which the outbreak has been controlled in Toronto has been the subject of some debate, as the WHO has included it in a list of sites to which travel should be restricted (www.who.int/csr/sars/travel). The United States Centers for Disease Control and Prevention, by contrast, does not recommend travel restrictions.

Epidemic curves and frequent updates on SARS, including maps, are available on the WHO website (www.who.int/csr/sars).

CLINICAL SYMPTOMS

The main symptoms and signs include high fever (>38°C), dry cough, and shortness of breath or breathing difficulties. The febrile prodrome may be associated with chills, rigors, headache, malaise and myalgia. At the onset of illness, some cases have mild respiratory symptoms, and some have reported diarrhea. After 3–7 days, the lower respiratory phase begins: dry cough or dyspnea that may be accompanied by or progress to hypoxia. A proportion of patients with SARS develop severe pneumonia; in one study, 19 of 138 patients (14%) of patients admitted to a hospital in Hong Kong required intubation and mechanical ventilation.[8]

Clinical findings may include chest X-rays (CXR) indicative of pneumonia; however, the CXR may be normal, especially during the prodrome. Subsequent findings may include early focal infiltrates progressing to more generalized patchy interstitial infiltrates. During the late stages of infection, CXR may demonstrate areas of consolidation.

Laboratory studies may be notable for the presence of low lymphocyte count early in the course of disease, with a normal or low total white blood cell count. At the peak of the respiratory illness, leukopenia and thrombocytopenia are common. Early in the course of the respiratory phase, increased levels of creatine phosphokinase, lactate dehydrogenase and hepatic transaminases have been noted.[8] Renal function is usually normal.

ETIOLOGIC AGENT OF SARS

The international medical and research communities responded with unprecedented speed, and identified the causative agent as a new coronavirus, now called the SARS virus, within 2 months. Genetic analysis indicates that the virus is only identical in 50–60% of nucleotide sequence to other known coronaviruses.[3] As it is an RNA virus, it is inherently highly mutable. Sequence comparisons of different isolates of the SARS virus show several variable sites, the biological significance of which has yet to be determined. Many aspects of the behavior of the SARS virus are currently poorly understood. Questions include the viral concentrations in different body fluids, and the stage of the illness in which viral shedding is highest. Survival time in the environment, on dry surfaces and in suspension (e.g. feces) is also being investigated. There are preliminary suggestions that viable virus could be cultured from surfaces after 24 h, which is longer than many similar viruses are expected to survive in the environment.

DIAGNOSTIC TESTS

The WHO appointed a network of 11 laboratories in nine countries to work together to try and develop fast and accurate laboratory tests for the SARS virus. There is considerable variation in viral shedding between and within individuals, and it is unclear when and where the virus is shed. It seems that there are different time periods for detection of the virus from different clinical samples—first from sputum, then from blood, and finally from stool. Guidelines on handling samples from suspected or probable SARS patients can be found on the WHO website (www.who.int/csr/sars/biosafety 2003_04_25).

Research is focusing on three main tests: PCR, enzyme-linked immunosorbent Assay (ELISA), and immunofluorescence (IF).

PCR can detect genetic material of the SARS virus in various specimens, such as blood, stool, respiratory secretions, and body tissue. It is useful in the early stages of the illness. Results are generally very specific, but may lack sensitivity, in that there are opportunities for false-negative results (e.g. if the sample was not collected when the virus or its genetic material was present). PCR also gives no information on whether the patient is infectious to others or not. Primers for the SARS virus have been developed and are publicly available on the WHO website at www.who.int/csr/sars/primers. A ready-to-use PCR test kit containing primers and positive and negative controls has also been developed, and its

performance is being evaluated by members of the WHO laboratory network.

ELISA detects the presence of antibodies in sera from about day 20 of the illness, by which time patients may have already spread the virus to others. If specimens are collected too early in the course of the illness (before antibodies are produced), this may produce a false-negative result.

IF is a reliable test that uses fixed SARS virus, an immunofluorescence microscope, and an experienced microscopist. It detects antibodies in sera reliably from day 10, so confirmation of the diagnosis is delayed. It is comparatively slow, and false-negative results are problematic.

The only means to show the existence of a live virus is cell culture. This is very demanding, but is considered the gold standard, as it is the only test that indicates (albeit in retrospect) the ability of an individual to transmit infection.

MANAGEMENT

Early diagnosis and prompt supportive care improve clinical prognosis. Management guidelines can be found at www.who.int/csr/sars/management, and are summarized as follows.

WHO Revised Guidelines: management of suspect and probable SARS cases

The patient should be admitted to the hospital according to the infection control policy (www.who.int/csr/sars/infectioncontrol). Ideally, potentially infected patients should be isolated in a negative pressure room, and HCWs and visitors accessing the unit should use the following personal protective equipment: N95 mask; gloves; goggles; disposable gown; footwear that can be decontaminated, and an apron. Clinical samples should be taken to exclude standard causes of pneumonia (including atypical pneumonia). The possibility of co-infection with SARS should be considered, and appropriate chest imaging performed. Tests to aid the clinical diagnosis of SARS should be done, including: white blood cell count, platelet count, creatine phosphokinase, liver function tests, blood urea nitrogen, electrolytes, and C-reactive protein. Paired sera should be stored for later. Antibiotics for the treatment of community-acquired pneumonia with atypical cover are recommended. Interventions that may cause aerosolization should be avoided (e.g. nebulizers, chest physiotherapy, bronchoscopy). If patients require the intervention, appropriate protective precautions should be taken.

The antiviral agent ribavirin (with or without corticosteroids) has been tried as treatment in an increasing number of patients. However, its effectiveness has not been proven. A coordinated multicenter approach to establish the effectiveness of ribavirin and other interventions has been proposed. There is no evidence for its use as prophylaxis, and many experts believe that it will be some years before an effective vaccine for the virus is available.

WHO Revised Guidelines: management of contacts of probable SARS cases

A SARS contact is a person who may be at greater risk of developing SARS because of exposure to a suspect or probable case of SARS (Table 1). A contact of a probable SARS case should be given information about SARS, and placed under active surveillance for 10 days in voluntary home isolation. The contact should record his temperature daily, and be visited or telephoned daily by a member of the public health care team. If the contact develops disease symptoms, they should be investigated locally at an appropriate health care facility.

WHO Revised Guidelines: management of contacts of suspect SARS cases

It is recommended that contacts of suspect cases should be given information on the clinical picture and transmission of SARS and placed under passive surveillance for 10 days. The contact is free to continue with his usual activities, but if he develops any symptoms, he should telephone the public health authority immediately.

CONCLUSION

As the work on the virus, its clinical manifestations, treatment and prevention proceed, there are many unanswered questions that will challenge scientists, clinicians, and public health workers. These include: how this new virus entered the human population and succeeded in spreading so rapidly from person-to-person, a phenomenon that is not always the case when respiratory viruses make the species jump to humans; what the variation at the molecular level means for the pathogenesis and epidemiology of this virus; and what will be the results over time of its co-evolution with the human host. As there are numerous as yet uncharacterized animal viruses that periodically enter the human population, this outbreak, although due to a viral infection with a relatively low mortality rate, should serve as a warning to the global public health community of the importance of openness in communicating health care threats at an early stage. To not do so because of political concerns could jeopardize human health due to pandemic influenza, a paramyxovirus that is able to establish human-to-human transmission, another coronavirus, or an unrecognized agent. The political will to ensure this openness must be universal, as a single area that does not cooperate with such a policy risks the health of all humankind.

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