SARS: A new infectious disease for a new century

BACKGROUND A new infectious disease swept the world in early 2003, causing restrictions on international travel and economic downturn in affected countries.
OBJECTIVE This article aims to provide an overview of the epidemic of severe acute respiratory syndrome (SARS).
DISCUSSION SARS is caused by a new coronavirus thought to be of animal origin. The virus induces symptoms of atypical pneumonia, clinically indistinguishable from similar syndromes. The severity is such that a 15% mortality rate has been reported. No treatment has yet been identified as reliably successful. Transmission is by droplet spread, requiring close contact. Stringent infection control precautions in health care institutions, broad isolation measures in affected communities and international surveillance with barrier restrictions to travel have led to termination of the epidemic. As of July 11, 2003, 8437 people in 32 countries have been affected, with 813 deaths reported.

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The term 'severe acute respiratory syndrome (SARS)' was coined by the World Health Organisation (WHO) in March 2003 following reports of cases of an undiagnosed atypical pneumonia in Vietnam, Hong Kong and in the Guangdong Province of China. The syndrome, as of July 11, 2003, has been diagnosed in 8437 people in 32 countries causing 813 deaths (Figure 1). The illness represents the first new major infectious disease of the 21st century.

Epidemiology and causation

Global spread

Initial cases of SARS were retrospectively identified in the Guangdong Province of Southern China in November, 2002. However, the diagnosis at the time was confused by isolation of Avian influenza strains and of Chlamydia pneumoniae from some infected patients. On February 21, 2003, a doctor from Guangdong Province travelled to Hong Kong. He was unwell at the time with respiratory symptoms and was subsequently admitted to, and later died in a Hong Kong hospital. This index patient infected his family and other guests on the floor of the hotel in which he stayed. These initial contacts subsequently spread the disease to other countries including Vietnam, Singapore and Toronto, Canada where local spread, both within the community and among health care workers, has occurred. Heightened case finding indicated local spread within mainland China particularly to Beijing and Huan Province, while spread within Taiwan occurred following contact with an initial patient from Hong Kong. The World Health Organisation termed those countries where local spread of the disease has occurred as being 'SARS affected'.

Stringent infection control regulation in all jurisdictions of SARS affected countries has led to control of the disease in Vietnam, Singapore, Hong Kong and Beijing, with falling case numbers in Toronto and in other areas of mainland China. A world free of SARS by August 2003 has been predicted.

Virology

SARS is a viral infection caused by an apparently unique coronavirus designated SARS Co-V.[1] (Figure 2). The virus was initially isolated in three laboratories in Germany, Hong Kong and the United States with all four of Kochs postulates subsequently being fulfilled.

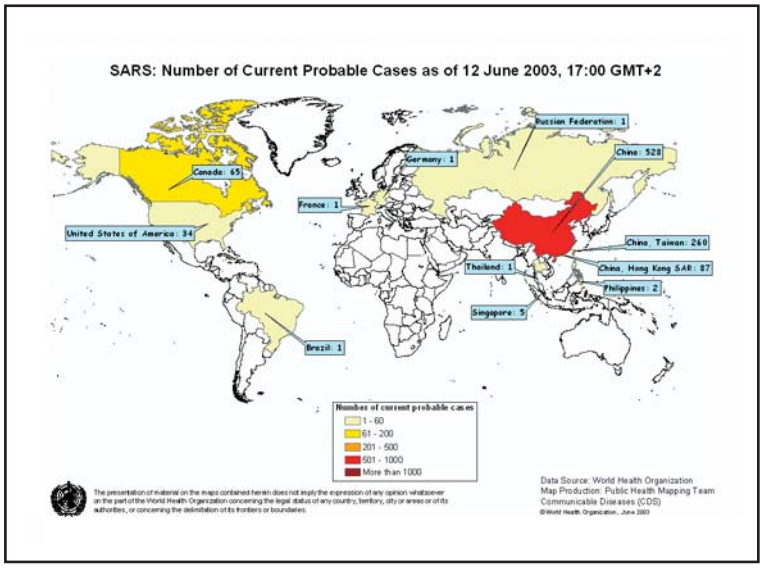

Figure 1. Prevalence SARS to mid June 2003 (after WHO)

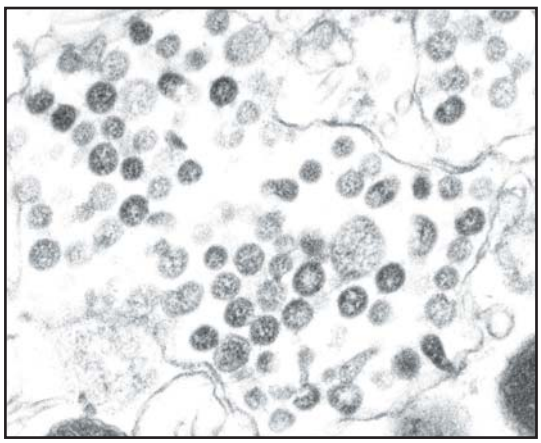

Figure 2. SARS Co-V (after CDC)

Coronaviruses are large enveloped, positive stranded RNA viruses that occur in a wide variety of animal hosts. There are three groups: groups 1 and 2 contain mammalian viruses, and group 3 contains only avian viruses. They induce a wide variety of respiratory and gastrointestinal diseases in their host species with coronaviruses being responsible for approximately 30% of upper respiratory tract infections in an Australian winter.

The genome of SARS Co-V has been determined and differs from the two major human coronaviruses. It appears to represent a new agent that may have derived from an animal virus that has crossed the species barrier to infect humans. Hong Kong researchers have identified the virus in a number of wild animal species in Guangdong Province including civet cats and have suggested these may be the virus's normal host. It is suggested that humans have become infected by ingesting civet meat, which is regarded as a delicacy in southern China. Proof of this hypothesis is yet to be forthcoming. It may be that like humans, these animals are not the normal virus host but are also infected. If SARS Co-V does have a natural animal host, then eradication of the virus is likely to be impossible.

Transmission

SARS Co-V has been detected in high concentrations in multiple tissues of affected patients, particularly in the lungs, sputum and broncho-alveolar specimens.[2] Plasma levels of virus are low, but renal tissue levels are high and the organism is found in the faeces in the convalescent phase following illness. The virus appears stable in faeces and urine at room temperature for at least 1–2 days, but is inactivated by heating to 56°C and is destroyed by commonly utilised antiviral disinfectants.

Attack rates, particularly among hospital workers, have in some circumstances exceeded 50%.[3] The majority of SARS infections have occurred in close contacts of patients such as hospital workers, close family members and household contacts as there are high levels of the virus in respiratory secretions. This suggests that the virus is spread either by direct contact or by droplets[4] consistent with known routes of transmission of other coronaviruses. The stability of the virus at room temperature implies the possibility of fomite spread. The presence of virus in faeces (in association with epidemiological evidence from a housing estate community outbreak in Hong Kong) implies that the faecal route may also be implicated.

Data from specific cluster outbreaks also suggests that some infected patients may excrete the virus in much higher concentrations than others ('superspreaders').[5] Airborne transmission does not seem to occur as evidenced by very localised transmission within the general population of affected countries, though the initial disease transmission on a single floor of a hotel in Hong Kong is not yet completely explained. A cluster of infected patients in one Hong Kong hospital has been attributed to airborne spread of the virus through the use of a nebuliser.

Clinical presentation

The clinical features of SARS are extremely nonspecific and in its most fulminant form can represent those of any of the atypical pneumonias. The incu-

bation period is generally thought to be less than 10 days. The clinical illness is triphasic with:

- an initial period of viral replication associated with nonspecific systemic toxicity
- a phase of immune response within the lung, and
- a final convalescent period when pulmonary fibrosis occurs.

The patient typically presents with fever of more than 38°C associated with a constellation of other possible symptoms including lethargy, myalgia, headache, serous rhinorrhoea, sore throat, cough and diarrhoea. Physical examination at this time is often unremarkable apart from raised temperature and possibly some inspiratory crepitations.

Clinical progress in patients is extremely variable.[6,7] Risk factors associated with a more severe course and higher mortality include older age and chronic hepatitis B infection, the latter common in southeast Asia. Respiratory illness is also highly variable, but progressive respiratory failure may induce the need for intensive care and ventilatory support in more than 20% of patients, 7–10 days after the onset of symptoms.

Mortality rates may be as high as 15% and appears to be age dependent. Children have a much less severe clinical course than adults, while mortality rates of more than 50% are seen in patients 65 years of age and older. Postmortem histopathological findings in the lung show alveolar damage consistent with the pathological manifestations of acute respiratory distress syndrome.

Investigations

Haematological and biochemical

Changes are often nonspecific. Leucopoenia due to decreasing lymphocyte counts is commonly reported as is thrombocytopenia. Elevated lactate dehydrogenase and aspartate may occur.

Radiological

Most pyrexial patients with SARS have an abnormal chest X-ray with airspace consolidation.[8] Initially an area of unilateral patchy shadowing occurs which may extend over a 24–48 hour period to bilateral interstitial infiltrates (Figure 3). Radiographically however, SARS is indistinguishable from other forms of severe pneumonia.

Serological

Sequencing of the genome of the virus permitted development of a number of serological tests many of which are available in reference laboratories in all states of Australia. However, the tests have variable sensitivity and specificity depending on both their intrinsic methodology and the stage of the illness (Table 1). While a positive test can be taken as evidence of SARS, a negative test does not exclude the diagnosis. Blood including convalescent specimens to 28 days should be taken.

Table 1. Serological tests for SARS

Method	Clinical specimens	Interpretation
PCR	Sputum, BAL throat serology, NPA blood	Positive day 1–15
IFA	Serum	Positive from day 10
ELISA	Serum	Positive from day 21

Figure 3. SARS pneumonia

Respiratory secretions

Tests include:

- viral culture, and
- polymerase chain reaction (PCR) methods.

Treatment

Current treatment is supportive with intensive ventilatory care in the event of continued deterioration. Ribavirin, a broad spectrum antiviral agent active against a variety of ribonucleic acid viruses, has been used in combination with high dose steroids.[9] Some reports from Hong Kong suggest this combination leads to a better outcome, but the number of patients studied is small and the results need verification in other centres. Canadian health officials have withdrawn ribavirin access from Canadian patients with SARS after studying outcome indices in treated patients, concluding that the risk of serious adverse events exceeded the benefits from the drug.

Prevention – two levels

International border precautions

SARS is a disease of international travel. Quarantine precautions, including dissemination of information to incoming travellers from SARS affected countries has been widely utilised both in Australia and elsewhere. Outgoing passengers in a number of SARS affected countries are subject to health screens, including self reporting of symptoms and estimation of tympanic membrane

Table 2. Case definition (after WHO)

Suspect case

A person presenting with:

- high fever (>38°C) AND
- cough or breathing difficulties AND
- one or more of the following:
  - close contact with SARS patient OR
  - travel to SARS affected area

temperature before embarkation.[10]

In June 2003, the Australian Government introduced a self reporting questionnaire for all incoming passengers to Australia. Such data does not detect those passengers in the incubation period of the disease, but does allow efficient contact tracing in the event that an incoming passenger does develop SARS while in Australia.

Local infection control precautions

In response to the number of health care workers infected by contact with patients, protective guidelines have been developed by a number of authorities. While some variation exists, in general, all recommend management of SARS patients, where possible, in negative pressure settings. Use by individual health care workers of N95 (Australian Standard P2) particulate masks (of higher filtration efficacy than a standard surgical mask), face shields, gloves, gowns and overshoes, together with stringent hand washing, provides protection but must be rigorously followed on all occasions.

The role of the GP

Without local transmission, the majority of SARS cases in Australia will derive from overseas contact and will be found in major population centres, close to large hospitals and to specialist medical care. However, suspected patients particularly overseas tourists may present in remote locations. It is therefore important that all general practitioners be familiar with the WHO definition of a possible SARS case and be aware of where to obtain expert advice. SARS is not a disease that can be distinguished from other similar conditions by clinical acumen. A provisional diagnosis is made on the basis of a patient's symptoms in association with their travel or contact history (Table 2). A patient with possible SARS should be immediately separated from others attending the practice and provided with a standard surgical mask, which is believed to provide adequate protection for a limited period. All staff attending the patient should also wear a mask. If a patient meets the WHO diagnostic criteria, they should be immediately referred to a local major hospital by private or ambulance transport while wearing the mask. Where this is not possible, advice should be obtained from either a public health physician, an infectious diseases physician or from the SARS Hotline (see Resources). Investigation of suspected cases should not begin without expert advice as this may unnecessarily induce the risk of exposure in others.

Where a patient is not particularly unwell or in a remote area, home isolation and management may be necessary and appropriate. Protocols for this circumstance are available.[10,11] Patients are regarded as no longer infectious once their clinical features have resolved. In some circumstances, GPs may be required to monitor the condition of contacts of SARS patients placed in home quarantine until the 10 day incubation period of the disease has elapsed.

The future

The international response to the SARS epidemic has provided some grounds for optimism. There has been significant co-operation with the WHO among the international community, in terms of both border protection and in the search for the causative agent. This along with local quarantine precautions has led to falling epidemic curves and the possibility of cessation of transmission of the virus in humans. However, heightened case surveillance, particularly in mainland China during the forthcoming northern winter will be essential. If SARS is a seasonal infection, and does have an animal reservoir, then eradication of the virus is highly unlikely and development of a protective vaccine will be critical.

Addendum

On July 5, 2003, the WHO declared Taiwan, the last SARS affected country, free of the disease as no local transmission had been recorded in the previous four weeks. The epidemic has thus come to a close. However, the WHO has recommended maintaining vigilance for a further 12 months.

SUMMARY OF IMPORTANT POINTS

- SARS is caused by a new coronavirus, of probable animal origin.
- 8437 people in 32 countries have been affected by the disease (July 11).
- The clinical presentation is usually indistinguishable from other forms of atypical pneumonia. Diagnostic serological tests have been developed and are available in Australia.
- 813 patients have died of SARS (July 11). Mortality rates of up to 15% have been described, with poorer prognosis in older patients.
- SARS is spread by droplets, thus requiring close contact. In a clinical situation, standard infection control precautions using gown, gloves and masks have proven effective.

Conflict of interest: none declared.

Resources

Commonwealth SARS Hotline: 1800 004 599
Victorian SARS Hotline: 1300 365 677
DHS (Vic) website: http://www.health.vic.gov.au/chiefhealthofficer/alerts/index.htm
World Health Organisation website: http://www.who.int/en/

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