Kamps - Hoffmann

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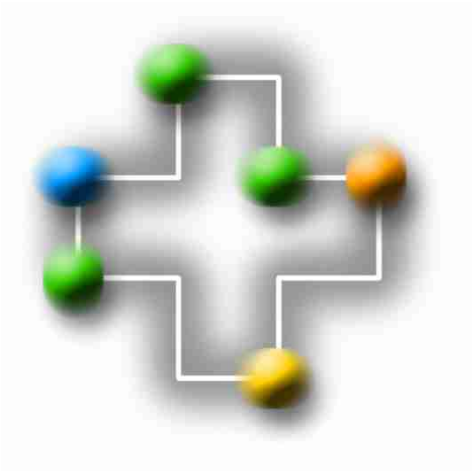

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La chronique est le témoignage pour

tous les hommes qui, ne pouvant être des saints et refusant d'admettre les fléaux, s'efforcent cependant d'être des médecins.

(Albert Camus, La Peste)

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Preface

First recognized in mid-March 2003, Severe Acute Respiratory Syndrome (SARS) was successfully contained in less than four months. On 5 July 2003, WHO reported that the last human chain of transmission of SARS had been broken.

Much has been learned about SARS, including its causation by a new coronavirus (SARS-CoV); however, our knowledge about the ecology of SARS coronavirus infection remains limited. In the post-outbreak period, all countries must remain vigilant for the recurrence of SARS and maintain their capacity to detect and respond to the re-emergence of SARS should it occur. Resurgence of SARS remains a distinct possibility and we need to be prepared.

For the third edition, most chapters have remained unchanged, with two exceptions: the Virology section has been updated and the chapter entitled SARS Treatment has been completely rewritten by Loletta So, Arthur Lau, and Loretta Yam from the Division of Respiratory and Critical Care Medicine, Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR, PR China. In the event of a new SARS outbreak, we shall have to rely on existing treatment modalities. These have now been brilliantly overviewed by our new colleagues.

Bernd Sebastian Kamps and Christian Hoffmann

www.HIVMedicine.com

October 17, 2003

Preface to the Second Edition

Just over five months ago, SARS started to spread around the world. It is the first major new infectious disease of this century, unusual in its high morbidity and mortality rates, and it is taking full advantage of the opportunities provided by a world of international travel. At the time of this writing, more than 8,000 persons with probable SARS have been diagnosed; 812 patients have died. Fortunately, one by one, the outbreaks in the initial waves of infection have been brought under control.

SARS demonstrates dramatically the global havoc that can be wreaked by a newly emerging infectious disease. SARS was capable of bringing the healthcare system of entire areas to a standstill, striking nurses, doctors and other medical personnel: human resources vital for disease control. Surgery and vital treatments for patients with serious conditions had to be postponed; care in emergency rooms was disrupted. A significant proportion of patients required intensive care, thus adding to the considerable strain on hospital and healthcare systems. Hospitals, schools, and borders were closed. The economic impact on individuals was profound, affecting tourism, education and employment.

The disease has several features that make it a special threat to international public health. There is no vaccine or treatment, and health authorities have to resort to control tools dating back to the earliest days of empirical microbiology: isolation, infection control and contact tracing.

The response of the scientific community to the new health threat was immediate and breath-taking. The etiologic relationship between a previously unknown coronavirus and SARS was established one month after the WHO issued a global alert and called upon 11 leading laboratories in 9 countries to join a network for multicenter research into the etiology of SARS and to simultaneously develop a diagnostic test. The early recognition of the etiologic agent has made the virus available for investigation of antiviral compounds and vaccines.

Experience with SARS has shown that, with strong global leadership by the WHO, scientific expertise from around the world can work in a very effective, collaborative manner to identify novel pathogens.

SARS has demonstrated how the world can come together in scientific collaboration, and what the power of the Internet is. This outstanding effort limited the potentially explosive spread of the outbreak.

Some hope exists that the disease might be contained, but much about SARS remains unknown. How important are animals in its transmission? Will SARS return with a stronger force next year? What are the host or virus factors responsible for the "superspreader" phenomenon, in which a single patient may infect many people through brief casual contact or possibly environmental contamination?

At this moment, a global epidemic of the magnitude of the 1918-19 influenza pandemic appears unlikely. However, development of effective drugs and vaccines for SARS is likely to take a long time. If SARS is not contained, the world will face a situation in which every case of atypical pneumonia, and every hospital-based cluster of febrile patients with respiratory systems will have the potential to rouse suspicions of SARS and spark widespread panic. The world will therefore anxiously watch if new outbreaks occur.

Bernd Sebastian Kamps and Christian Hoffmann

July 10, 2003

Preface to the First Edition

Just over three months ago, SARS started to spread around the world. It is the first major new infectious disease of this century and it is taking full advantage of the opportunities provided by a world of international travel. As of this writing (May 8), more than 7,000 persons have been infected in 29 countries. In China, the disease seems to be difficult to control. If not contained, SARS will change the way we live our lives.

The response of the scientific community to the new health threat has been breath-taking. The etiologic relationship between a previously unknown coronavirus and SARS was established just one month after the WHO issued a global alert and called upon 11 leading laboratories in 9 countries to join a network for multicenter research on the etiology of SARS and to simultaneously develop a diagnostic test. The early recognition of the etiologic agent has made the virus available for investigation of antiviral compounds and vaccines.

The WHO, the CDC, and national health agencies have disseminated up-to-the-minute information for clinicians, public health officials, and healthcare workers. The network of laboratories, created by the WHO, takes advantage of modern communication technologies (e-mail; secure website) so that the outcomes of investigations on clinical samples from SARS cases can be shared in real time. On the secure WHO website, network members share electron microscope pictures of viruses, sequences of genetic material for virus identification and characterization, virus isolates, and various samples from patients and postmortem tissues. Samples from one patient can be analysed in parallel by several laboratories and the results shared in real time.

But, as Julie Gerberding from the CDC stated: "Speed of scientific discovery and speed of communication are hallmarks of the response to SARS and reflect amazing achievements in science, technology, and international collaboration. However, despite these advances, a very sobering question remains —are we fast enough? Can we prevent a global pandemic of SARS?"

We don't know. It is the nature of epidemics to be unpredictable. What we do know is that unprecedented efforts will be needed to shape a world without SARS. SARSReference.com will accompany these efforts with monthly updates for the duration of the epidemic.

Bernd Sebastian Kamps and Christian Hoffmann

May 8, 2003

Summary

Severe Acute Respiratory Syndrome (SARS) is an acute respiratory illness caused by infection with the SARS virus. Fever followed by a rapidly progressive respiratory compromise is the key complex of signs and symptoms, which also include chills, muscular aches, headache and loss of appetite.

Mortality, initially believed to be around 3 %, may well be as high as 15 %. The WHO estimates that the case fatality ratio of SARS ranges from 0% to 50% depending on the age group affected: less than 1% in persons aged 24 years or younger; 6% in persons aged 25 to 44 years; 15% in persons aged 45 to 64 years; and greater than 50% in persons aged 65 years and older (WHO Update 49, http://www.who.int/csr/sarsarchive/2003_05_07a/en/).

The etiologic agent of SARS is a coronavirus which was identified in March 2003. The initial clusters of cases in hotel and apartment buildings in Hong Kong have shown that transmission of the SARS virus can be extremely efficient. Attack rates in excess of 50% have been reported. The virus is predominantly spread by droplets or by direct and indirect contact. Shedding in feces and urine also occurs. Medical personnel, physicians, nurses, and hospital workers are among those commonly infected.

In the absence of effective drugs or a vaccine for SARS, control of this disease relies on the rapid identification of cases and their appropriate management, including the isolation of suspect and probable cases and the management of their close contacts. In the great majority of countries, these measures have prevented imported cases from spreading the disease to others.

At present, the most efficacious treatment regimen for SARS is still subject to debate. For patients with progressive deterioration, intensive and supportive care is of primary importance. Immunomodulation by steroid treatment may be important.

Chapter 1: Timeline

November 16, 2002

The initial cases of SARS appear in the Guangdong Province, South China.

February 14, 2003

A small notice in the Weekly Epidemiological Record reports 305 cases and 5 deaths from an unknown acute respiratory syndrome which occurred between 16 November and 9 February 2003 in the Guangdong Province, China. (WHO WER 7/2003) The illness is spread to household members and healthcare workers. The Chinese Ministry of Health informs the WHO that the outbreak in Guangdong is clinically consistent with atypical pneumonia. Further investigations rule out anthrax, pulmonary plague, leptospirosis, and hemorrhagic fever.

Two weeks later, at the end of February, the Chinese Ministry of Health reports that the infective agent causing the outbreak of the atypical pneumonia was probably Chlamydia pneumoniae. (WHO WER 9/2003)

February 21

A 65-year-old medical doctor from Guangdong checks into the 9th floor of the Metropole hotel in Hong Kong. He had treated patients with atypical pneumonia prior to departure and is symptomatic upon arrival in Hong Kong. He infects at least 12 other guests and visitors to the 9th floor of the hotel (WHO. SARS: Status of the Outbreak).

February 28

Dr Carlo Urbani, a WHO official based in Vietnam, is alarmed by these cases of atypical pneumonia in the French Hospital, where he has been asked to assist. He is concerned it might be avian influenza, and notifies the WHO Regional Office for the Western Pacific.

March 7

New reports of outbreaks of a severe form of pneumonia come in from Vietnam. The outbreak traces back to a middle-aged man who was

admitted to hospital in Hanoi with a high fever, dry cough, myalgia and mild sore throat. Following his admission, approximately 20 hospital staff become sick with similar symptoms. In some cases, this is followed by bilateral pneumonia and progression to acute respiratory distress.

March 10

Eighteen healthcare workers on a medical ward in the Prince of Wales Hospital in Hong Kong report that they are ill. Within hours, more than 50 of the hospital's healthcare workers are identified as having had a febrile illness over the previous few days. On March 11, 23 of them are admitted to the hospital for observation as a precautionary measure. Eight develop early X-ray signs of pneumonia (Lee et al.) The outbreaks, both in Hanoi and Hong Kong, appear to be confined to the hospital environment. Hospital staff seem to be at highest risk.

The new syndrome is now designated "severe acute respiratory syndrome", or SARS.

March 12

The WHO issues a global alert about cases of severe atypical pneumonia following mounting reports of cases among staff in the Hanoi and Hong Kong hospitals.

March 14

The Ministry of Health in Singapore reports 3 cases of atypical pneumonia, including a former flight attendant who had stayed at the Hong Kong hotel. Contact tracing will subsequently link her illness to more than 100 SARS cases in Singapore (MMWR 52: 405-11).

March 15

The WHO issues a heightened global health alert about the mysterious pneumonia after cases are also identified in Singapore and Canada. The alert includes a rare emergency travel advisory to international travelers, healthcare professionals and health authorities, advising all individuals traveling to affected areas to be watchful for the development of symptoms for a period of 10 days after returning (http://www.who.int/csr/sarsarchive/2003_03_15/en/).

March 17

The WHO calls upon 11 leading laboratories in 9 countries to join a network for multicenter research into the etiology of SARS and to simultaneously develop a diagnostic test. The network takes advantage of modern communication technologies (e-mail; secure website) so that the outcomes of investigations on clinical samples from SARS cases can be shared in real time (http://www.who.int/csr/sars/project/en/). On the secure WHO website, network members share electron microscope pictures of viruses, sequences of genetic material for virus identification and characterization, virus isolates, various samples from patients, and postmortem tissues. Samples from one patient can be analyzed in parallel by several laboratories and the results shared in real time. The goal: detection of the causative agent for SARS and the development of a diagnostic test.

March 19

One week after the global alert, the WHO publishes an update on the situation, saying that the failure of all previous efforts to detect the presence of bacteria and viruses known to cause respiratory disease strongly suggests that the causative agent might be a novel pathogen.

March 21

The Center for Disease Control (CDC) publish a preliminary clinical description of SARS (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5212a5.htm).

March 24

Scientists at the CDC and in Hong Kong announce that a new coronavirus has been isolated from patients with SARS. (http://www.cdc.gov/od/oc/media/pressrel/r030324.htm)

Within days, sequences of the coronavirus polymerase gene are compared with those of previously characterized strains and scientists are able to demonstrate that this virus is distinct from all known human pathogens. In addition, serum from patients with SARS is evaluated to detect antibodies to the new coronavirus, and seroconversion is documented in several patients with acute- and convalescent-phase specimens.

March 26

The first global "grand round" on the clinical features and treatment of SARS is held by the WHO. The electronic meeting unites 80 clinicians from 13 countries; a summary of their discussions and conclusions is being made available on the SARS page of the WHO website, http://www.who.int/csr/sars/cliniciansconference/en/.

March 28

The CDC reports on the investigation into a cluster of 12 persons with suspected/probable SARS in Hong Kong which could be traced back to the medical doctor from southern China who arrived on 21 February 2003 and stayed in the Metropole hotel (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5212a1.htm).

March 30

In Hong Kong, a steep rise in the number of SARS cases is detected in Amoy Garden, a large housing estate consisting of ten 35-storey blocks, which are home to around 15,000 persons. The Hong Kong Department of Health issues an isolation order to prevent the further spread of SARS. The isolation order requires residents of Block E of Amoy Gardens to remain in their flats until midnight on 9 April (WHO Update 15). Residents of the building are subsequently moved to rural isolation camps for 10 days.

March 31

The New England Journal of Medicine publishes two articles about clusters of SARS patients in Hong Kong and in Toronto on its website (Tsang, Poutanen).

April 2

The WHO recommends that persons traveling to Hong Kong and the Guangdong Province of China consider postponing all but essential travel (http://www.who.int/csr/sarsarchive/2003_04_02/en/).

April 2

The WHO's Weekly Epidemiological Record publishes a new case definition, recommends measures to prevent the international spread of SARS, and proposes the implementation of a global surveillance

system (see http://www.who.int/wer/pdf/2003/wer7814.pdf, which includes a template of case reporting form).

The WHO recommends that airport and port health authorities in affected areas undertake screening of passengers presenting for international travel. In addition, the WHO issues guidance on the management of possible cases on international flights, disinfection of aircraft carrying suspect cases and surveillance of persons who have been in contact with suspect cases while undertaking international travel. Although this guidance is primarily directed at air travel, the same procedures are recommended for international travel by road, rail or sea from affected areas.

April 8-10

Three research groups publish results which suggest that a novel coronavirus might be the etiologic agent of SARS (Peiris, Drosten, Ksiazek).

Using serological tests and a reverse-transcriptase polymerase chain reaction (RT-PCR) specific for the new virus, one group of researchers found that 45 out of 50 patients with SARS, but none of the controls, had evidence of infection with the virus (Peiris). Electron-microscopic examination of cultures reveals ultrastructural features characteristic of coronaviruses. With specific diagnostic RT-PCR primers, several identical nucleotide sequences are identified in 12 patients from several locations; a finding which is consistent with a point source outbreak (Ksiazek). High concentrations of viral RNA of up to 100 million molecules per milliliter are found in sputum (Drosten).

April 12

Canadian researchers announce the first successful sequencing of the coronavirus genome believed to be responsible for the global epidemic of SARS. Scientists from the CDC confirm these reports. The new sequence has 29,727 nucleotides which fits well with the typical RNA boundaries of known coronaviruses. The results come just 12 days after a team of 10 scientists, supported by numerous technicians, began working around the clock to grow cells from a throat culture, taken from one of the SARS patients, in Vero cells (African green monkey kidney cells) in order to reproduce the ribonucleic acid

(RNA) of the disease-causing coronavirus (see press release http://www.cdc.gov/od/oc/media/pressrel/r030414.htm).

April 16

The WHO announces that a new pathogen, a member of the coronavirus family never before seen in humans, is the cause of SARS.

To prove the causal relationship between the virus and SARS, scientists had to meet Koch's postulates which stipulate that a pathogen must meet four conditions: it must be found in all cases of the disease, it must be isolated from the host and grown in pure culture, it must reproduce the original disease when introduced into a susceptible host, and it must be found in the experimental host that was so infected (http://www.who.int/csr/sarsarchive/2003_04_16/en/).

To confirm whether the new virus was indeed the cause of the illness, scientists at Erasmus University in Rotterdam, the Netherlands, infected monkeys with the pathogen. They found out that the virus caused similar symptoms – cough, fever, breathing difficulty – in the monkeys to that seen in humans with SARS, therefore providing strong scientific evidence that the pathogen is indeed the causative agent.

The unprecedented speed with which the causative agent of SARS was identified – just over a month since the WHO first became aware of the new illness – was made possible by an unprecedented collaboration of 13 laboratories in 10 countries.

April 20

The Chinese government discloses that the number of SARS cases is many times higher than previously reported. Beijing now has 339 confirmed cases of SARS and an additional 402 suspected cases. Ten days earlier, Health Minister Zhang Wenkang had admitted to only 22 confirmed SARS cases in Beijing.

The city closes down schools and imposes strict quarantine measures. Most worrying is the evidence that the virus is spreading in the Chinese interior, where medical resources might be inadequate.

April 20

After the identification of a cluster of illness among employees of a crowded wholesale market in Singapore, the market is closed for 15 days and the vendors placed in home quarantine.

April 23

The WHO extends its SARS-related travel advice to Beijing and the Shanxi Province in China and to Toronto, Canada, recommending that persons planning to travel to these destinations consider postponing all but essential travel. http://www.who.int/csr/sarsarchive/2003_04_23/en/

April 25

Outbreaks in Hanoi, Hong Kong, Singapore, and Toronto show signs of peaking.

April 27

Nearly 3,000 SARS cases have been identified in China. China closes theaters, Internet cafes, discos and other recreational activities and suspends the approval of marriages in an effort to prevent gatherings where SARS can be spread.

7,000 construction workers work around-the-clock to finish a new 1,000-bed hospital for SARS patients in Beijing.

April 29

The first report on SARS in children, published by the Lancet (Hon), suggests that young children develop a milder form of the disease with a less-aggressive clinical course than that seen in teenagers and adults.

May 1

The complete SARS virus genome sequence is published by two groups in Science (Marra, Rota).

May 2

The Xiaotangshan Hospital opens its doors for 156 SARS patients from 15 hospitals in urban areas in Beijing. The Xiaotangshan Hospital was built by 7,000 builders in just eight days.

Taiwan, which has a rapidly evolving outbreak, reports a cumulative total of 100 probable cases, with 11 new cases in 24 hours. Eight SARS deaths have occurred in Taiwan.

May 4

Scientists in the WHO network of collaborating laboratories report that the SARS virus can survive after drying on plastic surfaces for up to 48 hours; that it can survive in feces for at least 2 days, and in urine for at least 24 hours; and that the virus could survive for 4 days in feces taken from patients suffering from diarrhea (WHO Update 47).

May 7

The WHO revises its initial estimates of the case fatality ratio of SARS. It now estimates that the case fatality ratio of SARS ranges from 0% to 50% depending on the age group affected, with an overall estimate of case fatality of 14% to 15%. Based on new data, the case fatality ratio is estimated to be less than 1% in persons aged 24 years or younger, 6% in persons aged 25 to 44 years, 15% in persons aged 45 to 64 years, and greater than 50% in persons aged 65 years and older (Donnelly, WHO Update 49).

May 8

The WHO extends its SARS-related travel advice to the following areas of China: Tianjin, Inner Mongolia, and Taipei in Taiwan province ("postpone all but essential travel"; WHO Update 50).

May 9

Publication of the first prospective study on SARS (Peiris et al., http://image.thelancet.com/extras/03art4432web.pdf).

May 20

In Taiwan, more than 150 doctors and nurses quit various hospitals in one week, because of their fear of contracting SARS. Nine major hospitals have been fully or partly shut down.

May 22

Health authorities in Canada inform the WHO of a cluster of five cases of respiratory illness associated with a single hospital in Toronto. This is the second outbreak of SARS in Toronto.

May 23

The World Health Organization removes its recommendation that people should postpone all but essential travel to Hong Kong Special Administrative Region and the Guangdong province, China (http://www.who.int/csr/don/2003_05_23/en/).

May 23

Research teams in Hong Kong and Shenzhen announce that they have detected several coronaviruses closely related to the SARS coronavirus in animal species taken from a market in southern China. Masked palm civets, racoon-dogs, and Chinese ferret badgers are wild animals that are traditionally considered delicacies and are sold for human consumption in markets throughout southern China (http://www.who.int/csr/don/2003_05_23b/en/).

May 23

Two studies assess the epidemic potential of SARS, and the effectiveness of control measures. Their main message is that the SARS virus is sufficiently transmissible to be able to cause a very large epidemic if unchecked, but not so contagious as to be uncontrollable with good, basic public health measures (Lipsitch, Riley).

May 31

Singapore is removed from the list of areas with recent local transmission of SARS because 20 days (i.e., twice the maximum incubation period) have elapsed since the most recent case of locally acquired SARS was isolated or a SARS patient has died, suggesting that the chain of transmission had terminated.

May 31

Toronto is back on the WHO list of areas with local transmission after Canada reported new clusters of 26 suspected and eight probable cases of the disease linked to four Toronto hospitals.

June 6

82 cases are now being reported in the second outbreak of SARS in Ontario, Canada.

June 13

The World Health Organization removes its recommendation that people should postpone all but essential travel to Hebei, Inner Mongolia, Shanxi and Tianjin regions in China.

In addition, the WHO removes Guangdong, Hebei, Hubei, Inner Mongolia, Jilin, Jiangsu, Shaanxi, Shanxi and Tianjin from the list of areas with recent local transmission.

June 17

The WHO removes Taiwan from its list of areas to which travelers are advised to avoid all but essential travel. The move follows vast improvements in case detection, infection control, and the tracing and follow-up of contacts that led to a steep drop in the daily number of new cases.

June 21

A study by Rainer et al. suggests that the current WHO guidelines for diagnosing suspected SARS may not be sufficiently sensitive in assessing patients before admission to hospital. Daily follow-up, evaluation of non-respiratory, systemic symptoms, and chest radiography would be better screening tools (see Chapter 5: Prevention).

June 23

The WHO removes Hong Kong from its list of areas with recent local transmission of SARS (http://www.who.int/csr/don/2003_06_23/en/).

June 24

The WHO removes Beijing from its list of areas with recent local transmission and removes its travel recommendation (http://www.who.int/csr/don/2003_06_24/en/).

July 2

The WHO removes Toronto from its list of areas with recent local transmission (http://www.who.int/csr/don/2003_07_02/en/).

July 5

The WHO removes Taiwan from its list of areas with recent local transmission (http://www.who.int/csr/don/2003_07_05/en/).

The WHO reports that the last human chain of transmission of SARS has been broken.

August 14

WHO: Publication of " Alert, verification and public health management of SARS in the post-outbreak period". http://www.who.int/csr/sars/postoutbreak/en/

September 8

Singapore: A 27-year-old researcher is diagnosed with SARS.

September 24

The Singapore Ministry of Health releases the report of an investigation of the recent SARS case. The investigation concludes that the patient most likely acquired the infection in a laboratory as the result of accidental contamination. The patient was conducting research on the West Nile virus in a laboratory that was also conducting research using active SARS coronavirus (http://www.moh.gov.sg/sars/pdf/Report_SARS_Biosafety.pdf). The full report of the review panel is available at http://www.moh.gov.sg/sars/pdf/Report_SARS_Biosafety.pdf.

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Chapter 2: Virology

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The severe acute respiratory syndrome (SARS) is due to an infection with a novel coronavirus which was first identified by researchers in Hong Kong, the United States, and Germany (Ksiazek, Drosten, Peiris 2003a**,** Poutanen). The virus was provisionally termed SARS-associated coronavirus (SARS-CoV).

Discovery of the SARS Virus

Initial Research

The epidemic of severe atypical pneumonia which was observed in the Chinese province of Guangdong and reported internationally on February 11, 2003 (WHO, WER 11/2003), was initially suspected to be linked to a newly emerging influenza virus: on February 19, 2003, researchers isolated an avian influenza A (H5N1) virus from a child in Hong Kong. This virus was similar to the influenza virus originating from birds that caused an outbreak in humans in Hong Kong in 1997, and new outbreaks of similar strains were expected. However, bird 'flu', possibly of poultry origin, was soon ruled out as the cause of the newly-termed Severe Acute Respiratory Syndrome, or SARS.

Investigations then focused on members of the *Paramyxoviridae* family, after paramyxovirus-like particles were found by electron microscopy of respiratory samples from patients in Hong Kong and Frankfurt am Main. Further investigations showed that human metapneumovirus (hMPV; van den Hoogen) was present in a substantial number of, but not in all, SARS patients reported at the time.

At about the same time, China reported the detection, by electron microscopy, of Chlamydia-like organisms in patients who had died from atypical pneumonia during the Guangdong outbreak. Again, this finding could not be confirmed by other laboratories in SARS patients from outside China.

On March 17, 2003, the WHO called upon eleven laboratories in nine countries to join a network for multicenter research into the etiology of SARS and to simultaneously develop a diagnostic test (http://www.who.int/csr/sars/project/en/). The member institutions communicated through regular telephone conferences (initially held on a daily basis) and via a secure website and exchanged data, samples and reagents to facilitate and speed up research into the etiology of SARS (World Health Organization Multicentre Collaborative Network for Severe Acute Respiratory Syndrome (SARS) Diagnosis + WHO. WHO Multicentre Collaborative Networks for Severe Acute Respiratory Syndrome (SARS) diagnosis. http://www.who.int/wer/pdf/2003/wer7815.pdf).

The Breakthrough

The etiologic agent of SARS was identified in late March 2003, when laboratories in Hong Kong, the United States, and Germany found evidence of a novel coronavirus in patients with SARS. This evidence included isolation on cell culture, demonstration by electron microscopy, demonstration of specific genomic sequences by polymerase chain reaction (PCR) and by microarray technology, as well as indirect immunofluorescent antibody tests (Peiris, Drosten, Ksiazek).

Three weeks later, on April 16, 2003, following a meeting of the collaborating laboratories in Geneva, the WHO announced that this new coronavirus, never before seen in humans or animals, was the cause of SARS (Kuiken). This announcement came after research done by the then 13 participating laboratories from ten countries had demonstrated that the novel coronavirus met all four of Koch's postulates necessary to prove the causation of disease:

1. The pathogen must be found in all cases of the disease**;**
2. It must be isolated from the host and grown in pure culture**;**
3. It must reproduce the original disease when introduced into a susceptible host**;**
4. It must be found in the experimental host so infected.

Proof of the last two requirements was provided after inoculation of cynomolgus macaques (*Macaca fascicularis*) with Vero-cell cultured

virus that had previously been isolated from a SARS case. The infection caused interstitial pneumonia resembling SARS, and the virus was isolated from the nose and throat of the monkeys, as shown by polymerase chain reaction with reverse transcription (RT-PCR) and by virus isolation. The isolated virus was identical to that inoculated (Fouchier). A detailed account of the history of discovery of this novel agent can be found in Drosten 2003b.

Coronaviridae

The coronaviruses (order Nidovirales, family *Coronaviridae*, genus Coronavirus) are members of a family of large, enveloped, positive-sense single-stranded RNA viruses that replicate in the cytoplasm of animal host cells (Siddell).

The genomes of coronaviruses range in length from 27 to 32 kb, the largest of any of the RNA viruses. The virions measure between about 100 and 140 nanometers in diameter. Most but not all viral particles show the characteristic appearance of surface projections, giving rise to the virus' name (corona, Latin = crown). These spikes extend a further 20 nanometers from the surface.

The Coronaviridae family has been divided up into three groups, originally on the basis of serological cross-reactivity, but more recently on the basis of genomic sequence homology (see online database ICTVdB). Groups 1 (canine, feline infectious peritonitis, porcine transmissible gastroenteritis and porcine respiratory viruses, human coronavirus 229E) and 2 (bovine, murine hepatitis, rat sialodacryoadenitis viruses, human coronavirus OC43) contain mammalian viruses, while group 3 contains only avian viruses (avian infectious bronchitis, turkey coronavirus).

In animals, coronaviruses can lead to highly virulent respiratory, enteric, and neurological diseases, as well as hepatitis, causing epizootics of respiratory diseases and/or gastroenteritis with short incubation periods (2–7 days), such as those found in SARS (Holmes). Coronaviruses are generally highly species-specific. In immunocompetent hosts, infection elicits neutralizing antibodies and cell-mediated immune responses that kill infected cells.

Several coronaviruses can cause fatal systemic diseases in animals, including feline infectious peritonitis virus (FIPV), hemagglutinating encephalomyelitis virus (HEV) of swine, and some strains of avian infectious bronchitis virus (IBV) and mouse hepatitis virus (MHV). These coronaviruses can replicate in liver, lung, kidney, gut, spleen, brain, spinal cord, retina, and other tissues (Holmes). Coronaviruses cause economically important diseases in domestic animals.

Human coronaviruses (HCoVs) were previously only associated with mild diseases. They are found in both group 1 (HCoV-229E) and group 2 (HCoV-OC43) and are a major cause of normally mild respiratory illnesses (Makela). They can occasionally cause serious infections of the lower respiratory tract in children and adults and necrotizing enterocolitis in newborns (McIntosh, El-Sahly, Folz, Sizun). The known human coronaviruses are able to survive on environmental surfaces for up to 3 hours (Sizun). Coronaviruses may be transmitted from person-to-person by droplets, hand contamination, fomites, and small particle aerosols (Ijaz).

SARS-related CoV seems to be the first coronavirus that regularly causes severe disease in humans.

SARS Co-V

Genome Sequence

In April 2003, a Canadian group of researchers from the Michael Smith Genome Sciences Centre in Vancouver, British Columbia, and the National Microbiology Laboratory in Winnipeg, Manitoba, were the first to complete the genome sequencing of the new coronavirus (Marra), followed two days later by colleagues from the CDC (Rota).

The genome sequence data of SARS Co-V reveal that the novel agent does not belong to any of the known groups of coronaviruses, including two human coronaviruses, HCoV-OC43 and HCoV-229E (Drosten, Peiris, Marra, Rota), to which it is only moderately related. The SARS-CoV genome appears to be equidistant from those of all known coronaviruses. Its closest relatives are the murine, bovine, porcine, and human coronaviruses in group 2 and avian coronavirus IBV in group 1. For links to the most recent sequence data and publi

cations, see the NCBI web page http://www.ncbi.nlm.nih.gov/genomes/SARS/SARS.html.

It has been proposed that the new virus defines a fourth lineage of coronavirus (Group 4, Marra). The sequence analysis of SARS-CoV seems to be consistent with the hypothesis that it is an animal virus for which the normal host is still unknown and that has recently either developed the ability to productively infect humans or has been able to cross the species barrier (Ludwig). The genome shows that SARS-CoV is neither a mutant of a known coronavirus, nor a recombinant between known coronaviruses.

As the virus passes through human beings, SARS-CoV is apparently maintaining its consensus genotype and seems thus well-adapted to the human host (Ruan). However, genetic analysis is able to distinguish between different strains of SARS-CoV, which is of great value for epidemiological studies and may also have clinical implications (Tsui).

Morphology

Negative-stain transmission electron microscopy of patient samples and of cell culture supernatants reveals pleomorphic, enveloped coronavirus-like particles with diameters of between 60 and 130 nm. (Ksiazek, Peiris).

Examination of infected cells by thin-section electron microscopy shows coronavirus-like particles within cytoplasmic membrane-bound vacuoles and the cisternae of the rough endoplasmic reticulum. Extracellular particles accumulate in large clusters, and are frequently seen lining the surface of the plasma membrane (MMWR 2003; 52: 241-248).

Organization

The SARS-CoV genome contains five major open reading frames (ORFs) that encode the replicase polyprotein; the spike (S), envelope (E), and membrane (M) glycoproteins; and the nucleocapsid protein (N).

The main function of the S protein is to bind to species-specific host cell receptors and to trigger a fusion event between the viral envelope and a cellular membrane. Much of the species specificity of the initial infection depends upon specific receptor interactions. In addition, the spike protein has been shown to be a virulence factor in many different coronaviruses. Finally, the S protein is the principal viral antigen that elicits neutralizing antibody on behalf of the host.

The M protein is the major component of the virion envelope. It is the major determinant of virion morphogenesis, selecting S protein for incorporation into virions during viral assembly. There is evidence that suggests that the M protein also selects the genome for incorporation into the virion.

One remarkable feature about coronavirus RNA synthesis is the very high rate of RNA-RNA recombination.

Detection

SARS Co-V has been detected in multiple specimens including extracts of lung and kidney tissue by virus isolation or PCR; bronchoalveolar lavage specimens by virus isolation, electron microscopy and PCR; and sputum or upper respiratory tract swab, aspirate, or wash specimens by PCR (Ksiazek, Drosten).

High concentrations of viral RNA of up to 100 million molecules per milliliter were found in sputum (Drosten). SARS-associated coronavirus RNA was detected in nasopharyngeal aspirates by RT-PCR in 32% at initial presentation (mean 3.2 days after onset of illness) and in 68% at day 14 (Peiris 2003b). In stool samples, viral RNA was detected in 97% of patients two weeks after the onset of illness. 42% of urine samples were positive for viral RNA (Peiris 2003b).

Viral RNA was also detected at extremely low concentrations in plasma during the acute phase and in feces during the late convalescent phase, suggesting that the virus may be shed in feces for prolonged periods of time (Drosten).

Stability and Resistance

Work is on-going to evaluate the stability of SARS-CoV and its resistance against various environmental factors and disinfectants.

Preliminary results, obtained by members of the WHO multicenter collaborative network on SARS diagnosis (see: http://www.who.int/csr/sars/survival_2003_05_04/en/index.html), show that the virus is stable in feces and urine at room temperature for at least 1-2 days. The stability seems to be higher in stools from patients with diarrhea (the pH of which is higher than that of normal stool).

In supernatants of infected cell cultures, there is only a minimal reduction in the concentration of the virus after 21 days at 4°C and –80°C. After 48 hours at room temperature, the concentration of the virus is reduced by one log only, indicating that the virus is more stable than the other known human coronaviruses under these conditions. However, heating to 56°C inactivates SARS-CoV relatively quickly. Furthermore, the agent loses its infectivity after exposure to different commonly-used disinfectants and fixatives.

Natural Host

Research teams in Hong Kong and Shenzhen detected several coronaviruses that were closely related genetically to the SARS coronavirus in animals taken from a southern Chinese market that was selling wild animals for human consumption. They found the virus in masked palm civets (*Paguma larvata*) as well as some other species. All six of the civets included in the study were found to harbor SARS coronavirus, which was isolated in cell culture or detected by a PCR molecular technique. Serum from these animals also inhibited the growth of SARS coronavirus isolated from humans. Vice versa, human serum from SARS patients inhibited the growth of SARS isolates from these animals. Sequencing of viruses isolated from these animals demonstrated that, with the exception of a small additional sequence, the viruses are identical to the human SARS virus (Cyranoski; Enserink 2003a).

The study provides a first indication that the SARS virus exists outside a human host. However, at present, no evidence exists to suggest

that these wild animal species play a significant role in the epidemiology of SARS outbreaks. The civets sold on Chinese markets are born in the wild and then captured and raised on farms. They could therefore have acquired the virus from a wild animal or from other animals during captivity or even from humans. More research is needed before any firm conclusions can be reached (WHO Update 64, 23 May).

Antiviral Agents and Vaccines

Antiviral Drugs

Efforts are underway at various institutions to assess potential anti-SARS-CoV agents *in vitro*. According to the data available so far, Ribavirin, a "broad spectrum" agent, which is active against various RNA viruses (Tam) and which has been used extensively in SARS patients (Koren), seems to lack *in vitro* efficacy. Convalescent plasma and normal human immunoglobulin, not containing specific anti-SARS-CoV antibodies, have also been used in SARS patients (Wong). In addition, interferons may be promising candidate drugs (Cinatl 2003b).

In the light of the widespread utilization of traditional Chinese medicine in SARS patients in the Far East it is interesting that glycyrrhizin, a compound found in liquorice roots, was recently reported to have a good *in vitro* activity against SARS-CoV (Cinatl 2003a).

Further research includes detailed physico-chemical analysis of SARS-CoV proteins to allow the development of novel compounds based on targeted drug design (Anand**;** Thiel).

Vaccines

There are currently no commercial veterinary vaccines to prevent respiratory coronavirus infections, except for infectious bronchitis virus infections in chickens. Although an effective vaccine cannot be expected to be available soon, the relative ease with which SARS-CoV can be propagated *in vitro* and the availability of vaccines against animal coronaviruses, such as avian infectious bronchitis virus, transmissible gastroenteritis coronavirus of pigs, and feline infec

tious peritonitis virus, are encouraging. The S protein is generally thought to be a good target for vaccines because it will elicit neutralizing antibodies.

The apparent genetic stability of SARS-CoV is certainly encouraging with regard to the development of a vaccine (Brown). It should be noted, however, that in experimental infections with human coronavirus 229E, infection did not provide long-lasting immunity. Likewise, several animal coronaviruses can cause re-infections, so lasting immunity may be difficult to achieve. However, re-infections seem to be generally mild or sub-clinical. Before immunization strategies are devised, the immune pathogenesis of feline infectious peritonitis warrants careful investigation into whether immune enhancement also plays a role in SARS.

Outlook

The discovery of the SARS-associated coronavirus was the result of an unprecedented global collaborative exercise coordinated by the WHO (World Health Organization Multicentre Collaborative Network for Severe Acute Respiratory Syndrome (SARS) Diagnosis). The rapid success of this approach results from a collaborative effort – rather than a competitive approach – by high-level laboratory investigators making use of all available techniques, from cell culture through electron microscopy (Hazelton and Gelderblom) to molecular techniques, in order to identify a novel agent. It demonstrates how an extraordinarily well orchestrated effort may be able to address the threat of emerging infectious diseases in the 21st century (Hawkey). The SARS experience also sadly underlines that non-collaborative approaches may seriously impede scientific progress and sometimes have grave consequences (Enserink 2003b).

It may be surprising that despite the remarkable world-wide cooperative research efforts that allowed such significant progress in such a short time, the apparent success in ending the SARS outbreak (no new cases have been notified since 15 June 2003, suggesting that SARS-CoV no longer circulates within the human population) is undoubtedly due to "old-fashioned" infection control measures.

It is completely unclear at present (early September 2003) whether SARS will reappear. Clinically "silent" infections and long-term carriage can not be ruled out completely and may result in further outbreaks, perhaps in a season-dependent manner. Interestingly, the annual peak incidence of influenza virus infections is from March to July in southern China (Huang), which is similar to the epidemic curve of the 2003 SARS outbreak. It is also likely that SARS-CoV or a closely related coronavirus persist in an unidentified animal reservoir from where it may again spill over into the human population. Therefore, it is vital that vigilance for new SARS cases be maintained (see "Alert, verification and public health management of SARS in the post-outbreak period, http://www.who.int/csr/sars/postoutbreak/en/).

Sustained control of SARS will require the development of reliable diagnostic tests to diagnose patients in the early stages of illness and to monitor its spread, as well as of vaccines and antiviral compounds to prevent or treat the disease (Breiman). Vaccines are successful in preventing coronavirus infections in animals, and the development of an effective vaccine against this new coronavirus is a realistic possibility. As is the case for the development of any vaccine, time is needed. Suitable animal models must demonstrate efficacy, and time is necessary in order to be able to demonstrate the safety of the new vaccine in humans. While involvement by commercial enterprises is clearly wanted and necessary, it is to be hoped that patent issues will not stand in the way of scientific progress (Gold).

With the availability of different and improved laboratory methods, a number of important questions regarding the natural history of the SARS-associated coronavirus are now being addressed:

- What is the origin of SARS-CoV? What is the animal reservoir, if any? If SARS-CoV was present in an unknown animal species, did it jump to humans because of a unique combination of random mutations? Or can SARS-CoV now infect both its original host and humans?
- Which factors determine the period of time between infection and the onset of infectiousness?
- When, during the course of infection, is virus shedding highest? What is the concentration of the virus in various body compart

ments? In what way does the "viral load" relate to the severity of the illness or the likelihood of transmission?

- Do healthy virus carriers exist? If so, do they excrete the virus in amounts and concentrations sufficient to cause infection?
- Does virus shedding occur following clinical recovery? If so, for how long? Is this epidemiologically relevant?
- Why are children less likely to develop SARS ? Do they have a lower clinical manifestation index, or do they possess a (relative) (cross-?) immunity against SARS-CoV?
- What is the role of potential co-factors such as *Chlamydia spp.* and hMPV? Are they related to a clinically more severe illness or to a higher degree of infectiousness ("super-spreaders")?
- Are there environmental sources of SARS-CoV infection, such as foodstuff, water, sewage?
- How stable is SARS-CoV under different conditions? How can efficient disinfection be achieved? How long can the virus "survive" in the environment on both dry surfaces and in suspension, including in fecal matter?
- How important is genetic diversity among SARS-CoV strains?

Figure 1. Electron micrograph of coronavirus-like particles in cell culture, supernatant after ultracentrifugation and negative staining with uranyl acetate. (Source: Department of Virology, Bernhard Nocht Institute for Tropical Medicine; Director: H. Schmitz; full-size picture: http://SARSReference.com/archive/coronavirus_em.jpg)

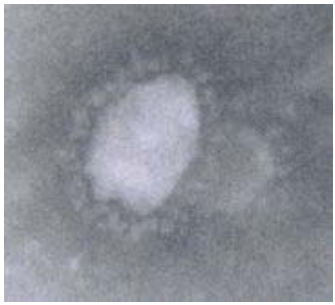
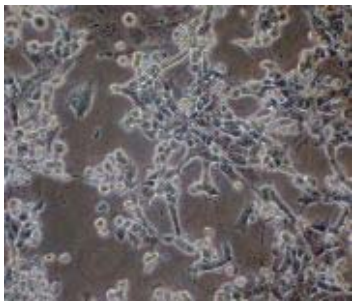


Figure 2. Cytopathic effect in Vero cell culture caused by SARS-associated coronavirus 24 hours post inoculation; for comparison: uninfected cell culture. (Source: Institute for Medical Virology, Director: H. W. Doerr; full-size picture: http://SARSReference.com/archive/cytopathiceffect.jpg, http://SARSReference.com/archive/uninfectedcells.jpg)



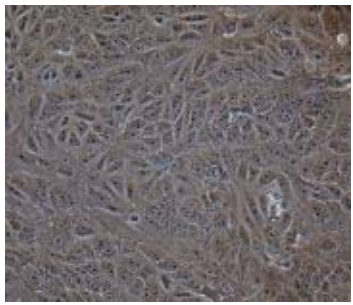
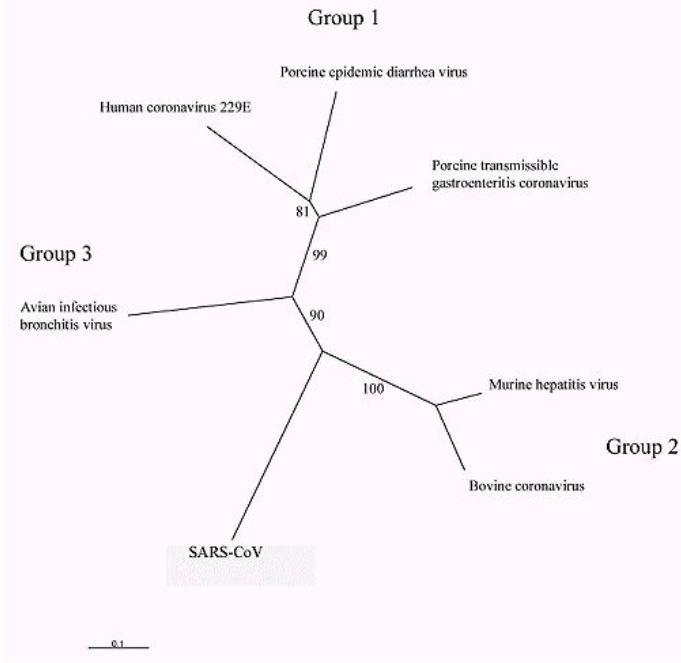


Figure 3. Phylogenetic tree of the SARS-associated coronavirus (Source: S. Günther, Department of Virology, Bernhard Nocht Institute for Tropical Medicine; Director: H. Schmitz; full-size picture: http://SARSReference.com/archive/phylogenetictree.jpg)



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Chapter 3: Transmission

Bernd Sebastian Kamps, Christian Hoffmann

The SARS coronavirus (SARS Co-V) is predominantly spread in droplets that are shed from the respiratory secretions of infected persons. Fecal or airborne transmission seem to be less frequent.

There is growing evidence that a majority of patients might not effectively transmit the virus to other individuals: in Singapore, 162 individuals (81%) of all probable SARS cases had no evidence of transmission of a clinically identifiable illness to other persons (MMWR 52: 405-11). This is in accordance with results from epidemiological studies which indicate that SARS is moderately rather than highly transmissible (Riley).

In some instances, however, so-called "superspreader" patients are able to transmit the SARS virus to a large number of individuals. Superspreaders and nosocomial amplification were the driving factors behind the early 2003 outbreaks.

Routes of Transmission

The fact that the majority of new infections occurred in close contacts of patients, such as household members, healthcare workers, or other patients who were not protected with contact or respiratory precautions, indicates that the virus is predominantly spread by droplets or by direct and indirect contact (CDC, Seto).

The presence of virus in the stool suggests the possibility of oral-fecal transmission (Drosten, Peiris 2003b). This is reminiscent of characteristics of other coronaviruses (Cho), and feces are therefore potentially an additional route of transmission. In the Amoy Gardens outbreak (see Chapter 4: Epidemiology, Hong Kong), the SARS virus may have been spread through the sewage systems of the buildings (for details, see Government of Hong Kong Special Administrative Region).

The airborne spread of SARS does not seem to be a major route of transmission. However, the apparent ease of transmission in some instances is of concern. In particular, the cases in the original Hong Kong cluster that originated at the Metropole hotel (MMWR 52:241-8) and in the Amoy Gardens Outbreak (Government of Hong Kong Special Administrative Region) indicate that the possibility of airborne transmission of the SARS virus, although probably a rare event, cannot be ruled out. Clusters among healthcare workers exposed during high-risk activities (i.e., endotracheal intubation, bronchoscopy, sputum induction) seem to confirm airborne transmission via a contaminated environment (i.e., re-aerosolization when removing protective equipment, etc.)

There are currently no indications that any goods, products or animals arriving from areas with SARS outbreaks pose a risk to public health. The WHO does not recommend any restrictions in this regard (http://www.who.int/csr/sars/goods2003_04_10).

Factors Influencing Transmission

Whether the transmission of a viral pathogen leads to the manifestation of the disease is determined by the intricate interplay of a multitude of still largely undefined viral and host factors.

As in other infectious diseases, the size of the inoculum, i.e., the number of infectious particles that are transmitted from one person to another, is probably of major importance. The size of the inoculum is determined by

- the viral load in the secretion of the index patient, and
- the distance to the index patient (face-to-face contact, crowded locations, i.e., a sneeze in the elevator)

Surprisingly, in the first few days after the onset of SARS-related symptoms, the amount of virus detected in secretion from the respiratory tract seems to be relatively low. Findings from sequential quantitative RT-PCR analyses of nasopharyngeal aspirates suggest that the viral load might peak only at around day 10 after the onset of symptoms and then decrease to the levels obtained on admission at day 15

(Peiris 2003b). In the stool, the virus appears to peak at day 13-14 (Peiris 2003b).

Infectivity might therefore be variable over time, even during the symptomatic phase of the disease, and transmission more likely to happen in the later phase of the illness.

In one study, severe disease was associated with acquisition of the disease through household contact. People infected in this way may have a higher dose or duration of viral exposure than people exposed through social contact (Peiris 2003a).

Patient Factors in Transmission

The most important factor is probably the viral load in infectious body secretions; so far, there is no indication that strains with different virulence are responsible for various degrees of infectivity.

Asymptomatic Patients

There are currently few data as to whether individuals can be infected with the SARS virus but remain asymptomatic, and if so, whether asymptomatic persons can transmit infection.

Preliminary findings suggest that some individuals that only developed mild symptoms may have antibodies to the SARS virus, although they did not develop SARS. Seroconversion without any disease has also been documented.

There is no direct evidence of transmission from an asymptomatic person. Indirect evidence that it may occur rarely includes a report that contact tracing in Hong Kong failed to identify a known symptomatic SARS contact in a small percentage of reported cases (WHO, Update 53).

Symptomatic Patients

It is now generally believed that only symptomatic patients may spread the SARS virus efficiently. However, transmission appears not to proceed in an explosive way. As stated above, 81% of all probable SARS cases in Singapore had no evidence of transmission of a clinically identifiable illness to other persons (MMWR 52: 405-11).

This is consistent with observations from the early Toronto outbreak, when suspected cases without pneumonia were initially sent home to spend their time in isolation. Some patients did not respect the isolation requirements and had interaction with the community. Despite that, apart from an outbreak in a religious group, no disease was seen in the community.

Another study, by Avendano et al., reports that 14 infected healthcare workers, who spent a mean of 4.5 days at home after the onset of symptoms, infected 2 out of 33 household contacts, in spite of unprotected contact within the home environment.

Finally, a report from the Philippines describes a patient who became symptomatic on April 6, had close contact with 254 family members and friends, traveled extensively in the Philippines and attended a prayer meeting and a wedding before becoming hospitalized on April 12. The contacts were placed under home quarantine for 9 days, with twice-daily temperature monitoring by health workers. Only two individuals (and questionably a third person) developed SARS, which represents an infection rate of less than 1% for the non-hospital contacts (WER 22/2003).

In comparison with other infectious diseases that are spread via the respiratory route (i.e., influenza), SARS seems therefore moderately transmissible.

Superspreaders

The term "superspreading" has been used to describe situations in which a single individual has directly infected a large number of other people (MMWR 52: 405-11). In the Singapore epidemic, of the first 201 probable cases reported, 103 were infected by just five source cases (Table 1).

A common feature of superspreading is nosocomial transmission, with hospitals serving as sources for disease amplification (MMWR 52: 405-11). However, some superspreaders may spread disease among social contacts (MMWR 52: 461-5), and the initial index patient and superspreader reported from Hong Kong spread the virus in the Metropole hotel (MMWR 52: 241-8).

The most probable explanation for the phenomenon of superspreading is extensive viral shedding by the patients. This may be due to advanced disease or possibly co-morbidities that result in high viral loads. However, additional data on the natural history of SARS are needed to understand other factors that might be associated, i.e., other transmission routes or inadequate infection control measures. In some circumstances, transmission of the SARS virus is therefore highly efficient.

Table 1: Superspreaders: Number of infected persons and outcome

Age	City	O→H*	Co-morbid conditions	Infected persons**	Outcome	Reference
64	Hong Kong	7	n.a.	13 p+s	dead	MMWR 52: 241-8
47	Hanoi	3	none	20 p	dead	WER 78: 73-4
26	Hong Kong	>5	none	112	alive	Lee, NEJM
22	Singapore	4	none	21 p, 3 s	alive	MMWR 52: 405-11
27	Singapore	3	none	23 p, 5 s	alive	MMWR 52: 405-11
53	Singapore	n.a.	Diabetes, ischemic heart disease	23 p, 8 s	dead	MMWR 52: 405-11
60	Singapore	n.a.	Chronic kidney disease, diabetes	62 p+s	alive	MMWR 52: 405-11
64	Singapore	3	Ischemic heart disease, left ventricular failure	12 p, 3 s	alive	MMWR 52: 405-11
n.a.	Toronto	6	Congestive heart failure	44 p	dead	Donald Low
43	Taiwan	6	Diabetes, peripheral vascular disease	137 p	dead	MMWR 52: 461-6

* Days between onset of illness and hospitalization

** p = probable case; s = suspected case

n.a. = not available

The Unsuspected Patients

SARS patients with chronic illnesses occurring concurrently with fever and/or pneumonia and who have a plausible diagnosis are the most challenging to the public health and healthcare systems (MMWR 52: 405-11).

Unrecognized cases of SARS have been implicated in recent outbreaks in Singapore (MMWR 52: 405-11), Taiwan (MMWR 52: 461-5), and Toronto. Despite efforts to implement extensive control measures, these cases led to nosocomial clusters and subsequent spread to other healthcare facilities and/or community settings. Several factors might contribute to difficulties in recognizing cases of SARS. Early symptoms of SARS are non-specific and are associated with other more common illnesses. Patients with SARS who are immunocompromised or who have chronic conditions (e.g., diabetes mellitus or chronic renal insufficiency) might not have fever when acutely ill or have symptoms attributable to the underlying disease, delaying the diagnosis of SARS (MMWR 52: 405-11). Finally, some patients might not reveal useful contact information (e.g., exposure to an implicated healthcare facility) for fear of being stigmatized by the local community or causing their friends and families to be quarantined (MMWR 52: 405-11).

These experiences demonstrate that spread among health care workers can occur despite knowledge about the epidemiology and transmission of SARS. To reduce the number of unrecognized cases, the Singapore Ministry of Health recommends a strategy to quickly identify febrile or symptomatic persons with chronic illnesses or any recent healthcare facility contact as suspected cases for isolation (MMWR 52: 405-11; see also Chapter 5: Prevention).

High-Risk Activities

The rapid spread of SARS among healthcare workers in Hanoi, Vietnam, and in hospitals in Hong Kong confirmed the potentially highly contagious nature of the virus. Medical personnel, physicians, nurses, and hospital workers are among those commonly infected. Attack rates in access of 50% have been reported (MMWR 52:226-8). SARS

infection of health care workers is probably related to increased contact with respiratory secretions, contact with patients during a more contagious phase of critical illness, contact with particular patients at increased likelihood of spreading SARS (i.e. superspreaders), or exposure to aerosol-generating patient care procedures (MMWR 52: 433-6).

In particular, diagnostic and therapeutic procedures inside the hospitals, such as diagnostic sputum induction, bronchoscopy, endotracheal intubation, and airway suction are potent aerosol-generating procedures, and are now being recognized as high-risk activities situations. Other potentially aerosol-generating procedures include BiPAP, during which air might be forced out around the facemask and thereby aerosolize secretions, and HFOV, during which exhaust from the ventilator tubing is more likely to escape without passing through an antibacterial/antiviral filter (MMWR 52: 433-6).

In Canada, a cluster of SARS cases occurred among health care workers despite apparent compliance with recommended infection control precautions. The probable transmission event was an endotracheal intubation of a patient who was in his second week of illness with clinical deterioration and a severe cough (MMWR 52: 433-6).

Another serious outbreak in a public hospital in Hong Kong could have been magnified by the use of a nebulized bronchodilator (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), causing atomization of the infected secretions (Lee).

Transmission during Quarantine

There has been at least one report of SARS Co-V transmission during quarantine (WER 22/2003). Three family contacts of a SARS patients became infected during hospital quarantine because strict isolation was not observed. This illustrates the fundamental principle of not "cohorting" suspect cases. Patients diagnosed with SARS may or may not be infected with the SARS virus, but they are at risk of contracting the infection if they are grouped with infected patients.

Transmission after Recovery

How long patients should remain in isolation depends on whether, and to what extent, patients continue to shed virus from the respiratory tract or from feces after overt clinical symptoms have stopped. Currently, at least 14 days of home quarantine are recommended following discharge. There have thus far been no reports of transmission after discharge.

Animal Reservoirs

There is limited data regarding the role of animals in the origin, transmission and reservoir of SARS CoV. Available data suggest that (Field)

- Early SARS cases were associated with animal markets
- SARS-like viruses were detected in apparently healthy animals in at least 2 wild animal species in one market place
- Preliminary experimental studies in pigs and poultry suggest these species are not likely to play a role in the spread of the SARS coronavirus
- Several coronaviruses infect multiple host species
- Antibody studies in people working in markets show a higher antibody prevalence among market workers in comparison to the general population

Conclusion

The SARS virus is not easily transmissible outside of certain settings. For a major local outbreak to occur there needs to be

- an infectious patient, and
- a close community or "tribe", i.e., healthcare workers, military populations, travel groups, religious gatherings, or funerals, with close interactions (kissing, hugging).

This gives some hope that SARS will not spread in a totally uncontrolled manner in the community.

The "ideal" conditions for efficient transmission of the SARS virus seem to be:

- The patient is highly infectious, shedding great quantities of infectious virus
- The patient has co-morbidities that mask the symptoms and signs of SARS
- The patient is admitted to a hospital with contact to multiple persons because of the diagnostic work-up, possibly including high-risk procedures such as bronchoscopy, endotracheal intubation, use of nebulizers, etc.

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Chapter 4: Epidemiology

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Introduction

Severe acute respiratory syndrome (SARS) is a new infectious disease which was first recognized in late February 2003, when cases of an atypical pneumonia of unknown cause began appearing among staff at a hospital in Hanoi. Within two weeks, similar outbreaks occurred in various hospitals in Hong Kong, Singapore and Toronto.

On March 15, the World Health Organization (WHO) issued emergency travel recommendations to alert health authorities, physicians and the traveling public to what was perceived to be a worldwide threat to health. The travel recommendations marked a turning point in the early course of the SARS outbreak. Areas with cases detected before the recommendations were issued, namely Vietnam, Hong Kong, Singapore and Toronto, experienced the largest and most severe outbreaks, all characterized by chains of secondary transmission outside the healthcare setting. After the recommendations had been issued, all countries with imported cases, with the exception of provinces in China, were able, through prompt detection of cases and isolation of patients, either to prevent further transmission or to keep the number of additional cases very low (WHO. SARS: Status of the Outbreak).

After the disease had moved out of southern China, Hanoi, Hong Kong, Singapore, and Toronto became the initial "hot zones" of SARS, characterized by rapid increases in the number of cases, especially in healthcare workers and their close contacts. In these areas, SARS first took root in hospital settings, where staff, unaware that a new disease had surfaced, exposed themselves to the infectious agent without barrier protection. All of these initial outbreaks were subsequently characterized by chains of secondary transmission outside the healthcare environment (WHO. SARS: Status of the Outbreak).

Now, at the beginning of July, SARS appears to be under control. It might not be all over, though. Toronto, after having had no new cases for more than 20 days, experienced a second outbreak with cases

linked to at least four hospitals, originating probably from a 96 year old man who had a pneumonia that was misinterpreted as a post-operative complication.

It is probably the "unsuspected SARS patients" that will be a major medical challenge if SARS cannot be eradicated. In Singapore, early in the epidemic (MMWR 52: 405-11), and later in Taiwan (MMWR 52: 461-6), the epidemic was driven partly by cases that either had atypical clinical presentations masking their infections, or were otherwise not rapidly identified because of lack of an initial history of direct contact with a known SARS case – despite efforts to implement extensive control measures. These patients became hidden reservoirs, and the subsequent transmission of the SARS virus resulted in substantial morbidity and mortality and the closure of several large healthcare facilities. Health authorities in Singapore subsequently defined an extended case definition that picked up virtually every person with symptoms that might possibly indicate SARS for investigation and monitoring, regardless of whether the person has been in contact with a SARS patient (see Chapter 5: Prevention).

The number of worldwide cases exceeded 4000 on 23 April and then rapidly soared to 5000 on 28 April, 6000 on 2 May, and 7000 on 8 May, when cases were reported from 30 countries. During the peak of the global outbreak, near the start of May, more than 200 new cases were being reported each day.

As of July 3, 2003, severe acute respiratory syndrome (SARS) had been diagnosed in more than 8,000 patients. The first SARS epidemic can be summarized as follows (Oxford):

1. The epidemiological observation that SARS was first detected in the Guangdong province in November 2002 and took three months to spread even to the immediately neighboring Hong Kong, despite easy exchange of family members between the two areas, does suggest, fortunately, a virus with a low infectiousness.

2. Outbreaks to date have been restricted to families, often living in high-density accommodation, and to hotels and hospitals. This limited spread is the hallmark of a virus with low communicability.

3. A truly global respiratory virus like influenza rather quickly emerged to infect millions of persons worldwide. Given the remarkable extent of air travel today, the SARS virus is not spreading rapidly, at least to date.

Modeling the Epidemic

Two major epidemiological studies have been published on the possible consequences of introduction of the SARS virus into a susceptible population (Lipsitch, Riley). Both calculate that the "basic case reproduction number" – the fundamental epidemiological quantity that determines the potential for disease spread – is of the order of 2 to 4 for the Hong Kong epidemic. They draw the conclusion that the SARS coronavirus, if uncontrolled, would infect the majority of people wherever it was introduced, but that it is not so contagious as to be uncontrollable with good, basic public health measures: improved control measures in hospitals, quarantine of contacts of cases, and voluntary reduction in contacts in the population (Dye).

Riley et al. estimate that in Hong Kong, 2.7 secondary infections were generated on average per case at the start of the epidemic, with a substantial contribution from hospital transmission. Transmission rates fell during the epidemic, primarily due to

- reductions in population contact rates
- improved hospital infection control
- more rapid hospital attendance by symptomatic individuals.

Starting Point

In November 2002, cases of a highly contagious and severe atypical pneumonia were noted in the Guangdong Province of southern China. The condition appeared to be particularly prevalent among healthcare workers and members of their household. Many cases were rapidly fatal. During the first week of February there was growing concern among the public about a mysterious respiratory illness, which apparently had a very high mortality and which caused death within hours (Rosling).

Local health officials reported 305 cases of the unknown disease to the WHO (WER 7/2003), as well as 5 resulting deaths.

Global Spread

SARS was carried out of the Guangdong Province on February 21, 2003, when an infected medical doctor spent a single night on the 9th floor of a Hong Kong hotel when he visited his family (Hotel M). He had become unwell a few days earlier and was now seriously ill. He was admitted to a hospital on February 22 and died ten days later (Tsang).

Before the end of February, guests and visitors to the hotel's ninth floor had seeded outbreaks of cases in the hospital systems of Hong Kong, Vietnam, and Singapore. Simultaneously, the disease began spreading around the world along international air travel routes as guests at the hotel flew home to Toronto and other cities around the world (WHO. SARS: Status of the Outbreak).

SARS, the first severe infectious disease to emerge in the twenty-first century, has taken advantage of opportunities for rapid international spread made possible by the unprecedented volume and speed of air travel. SARS has also shown how, in a closely interconnected and interdependent world, a new and poorly understood infectious disease can adversely affect economic growth, trade, tourism, business and industrial performance, and social stability as well as public health.

Hong Kong

The Hong Kong index patient (the physician from Guangdong) infected 12 other persons who had been staying at the same hotel (MMWR 2003;52:241-248). Two of these individuals were subsequently responsible for outbreaks in two local hospitals.

The Hong Kong health authorities immediately implemented enhanced infection-control procedures in all hospitals in Hong Kong, including stringent barrier and respiratory protection for healthcare workers, daily environmental disinfection of affected wards, and cohorting of SARS patients.

Towards the end of March 2003, a further SARS outbreak occurred among residents of Amoy Gardens, Hong Kong, with a total of 320 SARS cases in less than three weeks. The probable index patient was a patient suffering from chronic renal failure; in addition to person-to-person spread and to the use of communal facilities such as lifts and staircases, the SARS virus may have been spread through the sewage systems of the buildings (for details, see Government of Hong Kong Special Administrative Region).

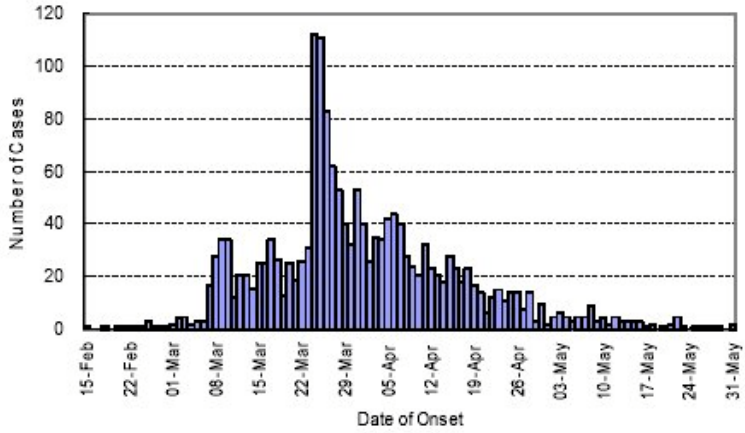

Figure 1. Epidemic curve, Hong Kong; June 16 (from Yeoh).

After the initial phase of exponential growth, the rate of confirmed SARS cases fell to less than 20 per day by April 28. The Hong Kong epidemic seems to have been under control even earlier, by early April 2003, in the sense that each case had, already by then, failed to replace itself (Riley). The main reason for this would have been the reduction in the contact rate between infectious individuals and the rest of the population.

At the beginning of June, public hospitals attempted to resume normal service, grappling with a backlog of an estimated 16 000 postponed operations because of the suspension of 30% of the medical services during the SARS crisis (Parry).

By June 16, 1755 cases of SARS had been diagnosed in Hong Kong. 295 patients (16.8%) had died. 1386 patients (79.0%) had recovered. Around 30% of cases occurred in healthcare workers. Among these, nurses were the most exposed category, accounting for about 55% of all infected healthcare workers. 15% were doctors, 27% support staff. Eight medical workers had died by June 2.

On June 23, the WHO removed Hong Kong from its list of areas with recent local transmission of SARS.

Vietnam

The outbreak in Vietnam began on February 26, when a 48-year-old Chinese-American businessman was admitted to the French hospital in Hanoi with a 3-day history of high fever, dry cough, myalgia and a mild sore throat. He had previously been in Hong Kong, where he visited an acquaintance staying on the 9th floor of the hotel where the Guangdong physician was a guest.

By March 5, secondary probable SARS cases were identified among health care workers in Hanoi, and subsequently 63 people were infected.

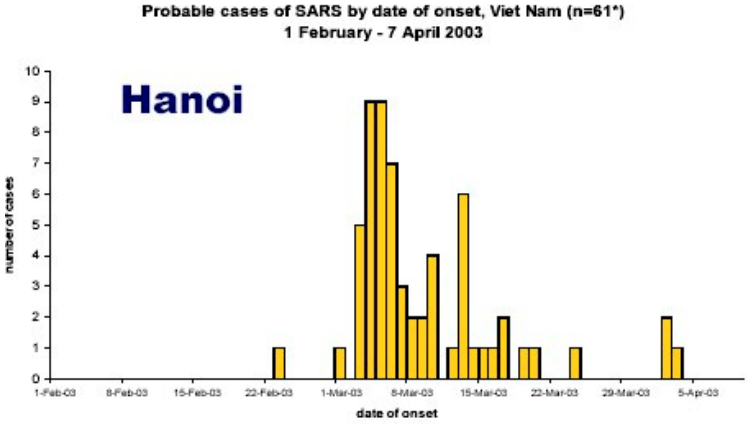

Figure 2. Epidemic curve, Hanoi (from Heymann).

On April 28, the WHO removed Vietnam from the list of affected areas, making it the first country to successfully contain its SARS outbreak. The absence of any new cases for a continuous 20-day period (the duration of two incubation periods) was an encouraging indicator that appropriate detection and protection measures, as recommended by the WHO, were able to contain outbreaks and prevent their further spread (WHO, WER 18/2003):

- prompt identification of persons with SARS, their movements and contacts;
- effective isolation of SARS patients in hospitals;
- appropriate protection of medical staff treating these patients;
- comprehensive identification and isolation of suspected SARS cases;
- exit screening of international travelers;
- timely and accurate reporting and sharing of information with other authorities and/or governments.

Toronto

SARS was introduced to Toronto by a woman of Hong Kong descent who had traveled home to visit relatives from February 13 to February 23, 2003. Whilst visiting their son in Hong Kong, she and her husband stayed at Hotel M from February 18 until February 21, at the same time and on the same floor as the Guangdong physician from whom the international outbreak originated. The woman and her husband only stayed in the hotel at night, and spent the days visiting their son. They returned to their apartment in Toronto, which they shared with two other sons, a daughter-in-law, and a five-month-old grandson on February 23, 2003. Two days later, the woman developed fever, anorexia, myalgia, a sore throat, and a mild non-productive cough. She died nine days after the onset of the illness. On March 8 and 9, five out of the six adult family members presented with symptoms of SARS (Poutanen).

By mid-May, the Toronto epidemic was thought to be over after the initial outbreak had mostly come under control. However, an undiag

nosed case at North York General Hospital led to a second outbreak among other patients, family members and healthcare workers.

The new outbreak spread from the SARS ward on the eighth floor of North York General Hospital, where a 96 year old man undergoing surgery for a fractured pelvis on 19 April is believed to have contracted the disease. The man developed pneumonia-like symptoms after his surgery but was not suspected of having SARS. He died on 1 May (Spurgeon).

A woman from the hospital's orthopedic ward, who was transferred to St John's Rehabilitation Hospital on 28 April, was later recognized as having a mild case of SARS, and five other SARS cases then appeared at St John's Hospital (Spurgeon).

The second Toronto outbreak (and the Taiwan outbreak, see below) demonstrate that spread among health care workers can occur despite knowledge about the epidemiology and transmission of SARS (see also Chapter 3: Transmission). SARS patients with chronic illnesses occurring concurrently with fever and/or pneumonia with a plausible diagnosis are extremely challenging to the public health and healthcare systems (MMWR 52: 405-11).

On July 2, the WHO removed Toronto from its list of areas with recent local transmission (WHO Update 93).

To date, 251 cases of SARS have been diagnosed in Canada, most of them in the Toronto area. 43 patients have died.

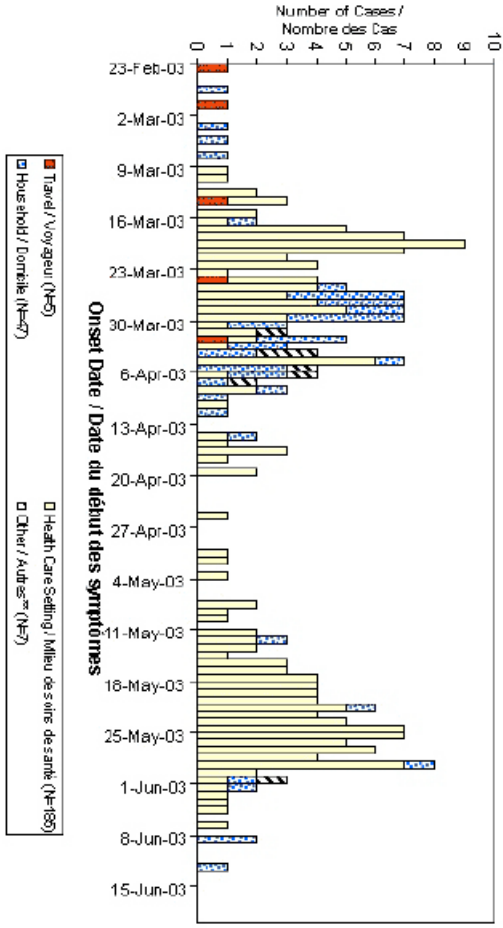

Figure 3. Canada, number of cases

Singapore, February 2003

The index case of SARS in Singapore was a previously healthy 23-year-old woman of Chinese ethnicity who had been staying on the 9th

floor of Hotel M during a vacation to Hong Kong from February 20–25, 2003 (Hsu). She developed fever and a headache on February 25 and a dry cough on February 28. She was admitted to a hospital in Singapore on March 1. At that time, SARS had not yet been recognized as a new disease easily spread in hospitals. As a result, hospital staff were unaware of the need to isolate patients and protect themselves. Over a period of several days, the index patient infected at least 20 other people. No further transmission from this patient was observed after strict infection control measures were implemented (Hsu).

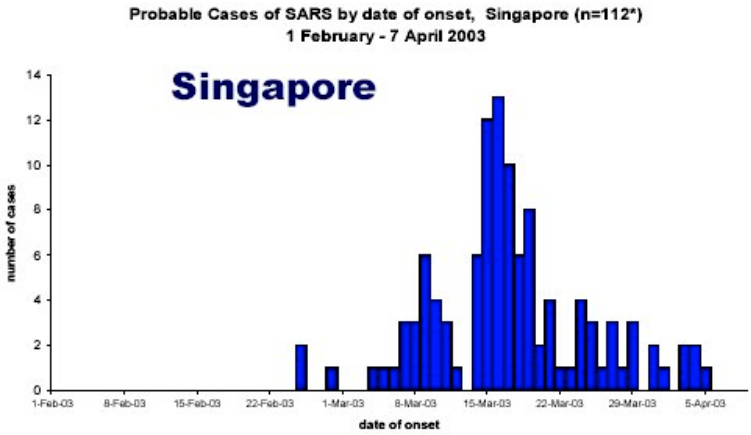

Figure 4. Epidemic curve, Singapore (from Yeoh).

The virus initially spread rapidly among hospital staff, patients, visitors, and their close family contacts. Later on, spread of infection between hospitals occurred when patients with underlying disease – which masked the symptoms of SARS – were transferred to other hospitals, placed in rooms with other patients, and managed without adequate protective equipment (WHO Update 70).

The outbreak in Singapore was amplified by several so-called "superspreaders" (see also chapter 3: Transmission). 144 of Singapore's 206 probable cases have been linked to contact with only 5 individuals (WHO Update 70; Figure 5).

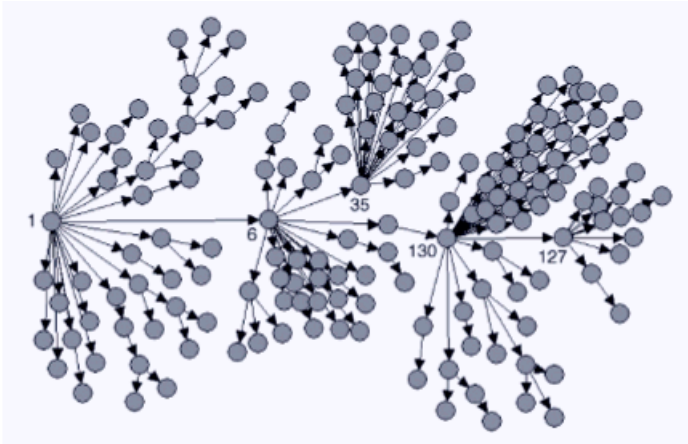

Figure 5. Probable cases of severe acute respiratory syndrome, by reported source of infection — Singapore, February 25–April 30, 2003 (from MMWR 52: 405-11)

On April 20, after the identification of a cluster of illness among employees at a crowded wholesale market, the market was closed for 15 days and more than 400 persons were placed in home quarantine. The spread of infection was limited to only 15 other persons.

In Singapore, 76% of infections were acquired in a healthcare facility; the remainder either had household, multiple, or unknown exposures. Due to rigorous contact tracing and isolation procedures, 81% of probable SARS cases had no evidence of transmission to other persons with a clinically identifiable illness (MMWR 2003; 52: 405-11).

Of the 84 (42%) healthcare workers with probable SARS, 49 were nurses; 13, physicians; and 22, persons with other occupations (attendants, radiographers, housekeepers, a porter, and a cleaning supervisor); no SARS cases have been reported among laboratory workers or pathologists (MMWR 2003; 52: 405-11).

238 cases of SARS were diagnosed in Singapore; 33 patients died.

On May 31, Singapore was removed from the list of areas with recent local transmission (WHO Update 70).

China

Up until mid-April, the Chinese authorities underestimated the magnitude of the epidemic in Beijing, with only 37 cases having been reported by April 19. In the following two days, the Chinese authorities announced more than 400 (WHO Update 35) new SARS cases. Additional reports (WHO Update 36) indicated that SARS had spread to other provinces, including western Guangxi, northern Gansu, and Inner Mongolia.

On April 23, the WHO extended its SARS-related travel advice (WHO Update 37) to Beijing and the Shanxi Province of China, recommending that persons planning to travel to these destinations consider postponing all but essential travel. Four days later, the Chinese Authorities closed theaters, Internet cafes, discos and other recreational activities and suspended the approval of marriages in an effort to prevent gatherings where SARS could be spread.

To date, the epidemic in China seems to be under control. 5,327 cases of SARS have been diagnosed, 349 patients have died.

On June 24, Beijing was removed from the list of areas with recent local transmission (WHO Update 87).

Taiwan

The first two suspected SARS cases were diagnosed in a couple on March 14. The man had a history of travel in February to the Guangdong Province and to Hong Kong. On March 26, a Taiwanese resident of Hong Kong's Amoy Gardens flew to Taiwan and took a train to Taichung to celebrate the traditional festival, Qing Ming. The man's brother became Taiwan's first SARS fatality, and a fellow passenger on the train was also infected.

Suddenly, in the last 10 days of April, the number of cases began to increase steadily, which would have made Taiwan's epidemic the third-worst in the world after China and Hong Kong. The origin of the outbreak was a laundry worker aged 42 years with diabetes mellitus and peripheral vascular disease who was employed at hospital A. On April 12, 14, and 15, he had a fever and diarrhea and was evaluated in the emergency department. The patient remained on duty and interacted frequently with patients, staff, and visitors. The patient had

sleeping quarters in the hospital's basement and spent off-duty time socializing in the emergency department. On April 16, because of worsening symptoms, the patient was admitted to the hospital with a diagnosis of infectious enteritis (MMWR 52;461-6). On April 18, the patient became short of breath. A chest radiograph showed bilateral infiltrates, and the patient was transferred to an isolation room in the intensive care unit with suspected SARS (MMWR 52;461-6).

Because the index patient had been symptomatic for 6 days before SARS was diagnosed, the number of potentially exposed persons was estimated at 10,000 patients and visitors and 930 staff. On April 24, hospital A was contained, and all patients, visitors, and staff were quarantined within the building (MMWR 52;461-6).

Healthcare worker clusters at eight additional hospitals in Taiwan have been linked to the initial outbreak at hospital A. Preliminary data suggest that many of these clusters occurred when pre-symptomatic patients or patients with SARS symptoms attributed to other causes were discharged or transferred to other healthcare facilities. SARS later extended to multiple cities and regions of Taiwan, including several university and private hospitals. Four of these hospitals, including a 2,300-bed facility in southern Taiwan, discontinued emergency and routine services. Sporadic community cases also were reported in Taipei and southern Taiwan (MMWR 52;461-6).

The April outbreak in Taiwan may serve as an example of the far-reaching consequences of one single unrecognized SARS case.

On July 5, Taiwan was removed from the list of areas with recent local transmission (WHO Update 96).

Other Countries

The number of probable SARS cases reported from other countries over the time period November 1, 2002 to July 2, 2003, is shown in the following table.

Country	Cumulative number of case(s)	Number of deaths	Case fatality ratio (%)
Australia	6	0	0
Canada	251	43	17
China	5327	349	7
France	7	1	14
Germany	9	0	0
Hong Kong	1755	299	17
India	3	0	0
Indonesia	2	0	0
Italy	4	0	0
Kuwait	1	0	0
Macao	1	0	0
Malaysia	5	2	40
Mongolia	9	0	0
New Zealand	1	0	0
Philippines	14	2	14
Republic of Ireland	1	0	0
Republic of Korea	3	0	0
Romania	1	0	0
Russian Federation	1	0	0
Singapore	238	33	14
South Africa	1	1	100
Spain	1	0	0
Sweden	5	0	0
Switzerland	1	0	0
Taiwan	346	37	11
Thailand	9	2	22
United Kingdom	4	0	0
United States	29	0	9
Vietnam	63	5	8
Total	**8098**	**774**	**9.6**

Notes:

The cumulative number of cases includes the number of deaths. Updated data are available at http://www.who.int/csr/sars/en/

Eradication

As the number of new cases continues to dwindle, one of the most important questions for the future is whether SARS can be eliminated or eradicated from its new human host. Experience with many other infectious diseases, including smallpox and poliomyelitis, has demonstrated that complete eradication of an infectious disease is possible only when three precise requirements can be met (WHO Update 84):

1) An effective intervention capable of interrupting transmission – ideally, a vaccine – must be available.

2) Easy-to-use diagnostic tools are needed, with sufficient sensitivity and specificity to detect levels of infection that can lead to transmission of the disease.

3) Finally, infection of humans must be essential to the life-cycle of the causative agent – if the chain of human-to-human transmission is broken, the agent cannot survive. Existence of an animal reservoir greatly complicates eradication, but does not preclude it, provided that interventions exist to break the chain of transmission in the animal species as well.

To achieve eradication at the global level, the control intervention must be safe, simple, and affordable. Current control measures for SARS, including case detection and isolation, tracing and follow-up of contacts, and quarantine, are effective but extremely time-intensive, costly, and socially disruptive. Few, if any, countries can sustain such efforts over time (WHO Update 84).

Outlook

During the first epidemic of SARS, most countries had to deal with a small number of imported cases. When these cases were promptly detected, isolated, and managed according to strict procedures of infection control, further spread to hospital staff and family members either did not occur at all or resulted in a very small number of secondary infections (Chan-Yeung).

In countries with significant transmission of the SARS virus, the local outbreaks of Spring 2003 have been controlled; however, second out

breaks, such as those in Taiwan and Toronto, teach that complacency must be avoided.

Many lessons have been learned:

- Only one individual is required for an outbreak. One single infected individual is sufficient to test the flexibility of modern healthcare systems to the limit;
- The SARS virus is sufficiently transmissible to cause a very large epidemic if unchecked, but not so contagious as to be uncontrollable with good, basic public health measures (Dye);
- The unsuspected SARS patients will be the greatest challenge in medicine if SARS cannot be eradicated

Many questions remain unsolved:

- Will SARS maintain itself, with new foci appearing here and there?
- Will SARS establish itself as an endemic illness, perhaps with seasonal patterns? (Holmes)
- Will SARS remain confined to the areas where it is currently located, or will it spread around the world?
- What would the virus do in the developing countries?
- Would the transmission patterns be different if the virus was introduced into populations with a high prevalence of immunocompromised patients, i.e., people living with HIV?

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Chapter 5: Prevention

Bernd Sebastian Kamps, Christian Hoffmann

Introduction

SARS, in contrast to diseases like flu or rubella, is only moderately transmissible. The number of secondary SARS cases per index case, ranging in one epidemiologic study from 2.2 to 3.6, are considerably lower than those estimated for most other diseases with respiratory transmission (Lipsitch). This indicates that a combination of control measures, including shortening the time from symptom onset to isolation of patients, effective contact tracing and quarantine of exposed persons, can be effective in containing SARS. Indeed, such measures have been successful and have contributed to the prevention of major outbreaks in other countries. On the other hand, in the absence of such effective measures, SARS has the potential to spread widely (Lipsitch).

In the absence of a vaccine, the most effective way to control a new viral disease such as SARS is to break the chain of transmission from infected to healthy persons. In almost all documented cases, SARS is spread through close face-to-face contact with infected droplets when a patient sneezes or coughs (WHO, WER 20/2003).

For SARS, three activities – case detection, patient isolation and contact tracing – can reduce the number of people exposed to each infectious case and eventually break the chain of transmission (WHO, WER 20/2003):

1. Case detection aims to identify SARS cases as soon after the onset of illness as possible.
2. Once cases are identified, the next step is to ensure their prompt isolation in a properly equipped facility, and management according to strict infection control procedures.
3. The third activity – the detective work – involves the identification of all close contacts of each case and assurance of their care

ful follow-up, including daily health checks and possible voluntary home isolation.

Together, these activities limit the daily number of contacts possible for each potentially infectious case. They also work to shorten the amount of time that lapses between the onset of illness and isolation of the patient, thus reducing the opportunities for the virus to spread to other patients (WHO WER 20/2003).

International Coordination

The World Health Organization (WHO) played a vital role in the containment of the first global outbreak of SARS.

After issuing a global alert about cases of severe atypical pneumonia following reports of cases among staff in the Hanoi and Hong Kong hospitals on March 12, the WHO received additional reports of more cases. Three days later, the WHO issued emergency travel recommendations to alert health authorities, physicians, and the traveling public to what was now perceived to be a worldwide threat to health. The alert included the first WHO emergency travel advisory to international travelers, healthcare professionals and health authorities, advising all individuals traveling to affected areas to be watchful for the development of symptoms for a period of 10 days after returning (http://www.who.int/csr/sarsarchive/2003_03_15/en/).

The decision was based on five different but related factors (WHO, Status of the Outbreak):

1. The causative agent, and therefore the potential for continued spread, of this new disease were not yet known.
2. The outbreaks appeared to pose a great risk to health workers who managed patients, and to the family members and other close contacts of patients.
3. Many different antibiotics and antiviral therapies had been tried empirically and did not seem to have an effect.
4. Though the numbers were initially small, a significant percentage of patients (25 of 26 hospital staff in Hanoi, and 24 of 39 hospital staff in Hong Kong) had rapidly progressed to respiratory failure,

requiring intensive care and causing some deaths in previously healthy persons.

5. The disease had moved out of its initial focus in Asia and appeared to have spread to North America and Europe.

Within less than two weeks, a collaborative network of laboratories set up by the WHO identified a novel coronavirus as the probable etiologic agent of SARS (see Chapter 2: Virology).

Early in April, travel advisories became more specific. On April 2, the WHO recommended that persons traveling to Hong Kong and the Guangdong Province of China consider postponing all but essential travel. (http://www.who.int/csr/sarsarchive/2003_04_02/en/). On April 23, the WHO extended its travel advice to Beijing and the Shanxi Province in China and to Toronto, Canada, http://www.who.int/csr/sarsarchive/2003_04_23/en/, and on May 8 to Tianjin, Inner Mongolia, and Taipei in Taiwan (WHO Update 50).

The global alert and the global effort coordinated by the WHO achieved its purpose. All countries with imported cases, with the exception of provinces in China, were able through

1. prompt detection of cases
2. immediate isolation, strict infection control, and
3. vigorous contact tracing

to either prevent further transmission or to keep the number of additional cases very low. The early management of the SARS epidemic may well serve as a model for the containment of future epidemics and pandemics.

At the beginning of July, all travel restrictions were lifted (WHO Update 96).

Advice to travelers

The most important message for international travelers concerning SARS is to be aware of the main symptoms of SARS: high fever (> 38° C or 100.4° F), dry cough, shortness of breath or breathing difficulties. Persons who experience these symptoms and who have been

in an area where there has been recent local transmission of SARS in the last 10 days are advised to contact a doctor (WHO WER 14/2003).

To further reduce the risk that travelers may carry the SARS virus to new areas, international travelers departing from areas with local transmission in the B or C categories (see "Areas with recent local transmission", http://www.who.int/csr/sarsareas/en/) should be screened for possible SARS at the time of departure. Such screening involves answering two or three questions and may include a temperature check. Travelers with one or more symptoms of SARS and who have a history of exposure, or who have fever, or who appear acutely ill should be assessed by a healthcare worker and may be advised to postpone their trip until they have recovered.

See also "Recommended procedures for prevention and management of probable cases of SARS on International Cruise Vessels", http://www.who.int/csr/sars/travel/vessels/en/.

Management of SARS in the post-outbreak period

A detailed document published by the WHO describes a SARS alert mechanism for the post-outbreak period. It provides guidance for managing a SARS "alert" through to laboratory confirmation or exclusion of persons under investigation as SARS cases and guidance to clinicans on the clinical presentation, laboratory and radiological findings to assist in diagnosis of SARS and in decisions to implement transmission-based infection control (WHO, August 14).

National Measures

The primary focus of SARS surveillance activities in countries without or with very few SARS cases is on the early identification and isolation of patients who have suspected SARS.

In contrast, countries which are affected by a severe SARS outbreak must immediately take a variety of sometimes unpopular measures to contain the epidemic. These measures generally include

1. the creation of an emergency operating center
2. the designation of one or more SARS hospitals

3. the institution of efficient quarantine measures, possibly based on an extended case definition (see below)
4. the rapid approval of pending legislation

In Singapore, the Tan Tock Seng Hospital, which is the second largest hospital in town (1500 beds) and site of the initial outbreak, was closed and designated to be the SARS hospital. Schools were closed and all public events postponed indefinitely (Mukherjee). Singapore used its military forces to assist in contact tracing and enforcement of home quarantine. All persons who were household, social, hospital, and occupational contacts during the 10 days before the onset of symptoms were traced to identify the source of infection. Persons identified as having had contact with a SARS patient from the onset of symptoms to the date of isolation were placed in home quarantine (WHO Update 70). Other measures included screening passengers at the airport and seaports, imposing a no-visitors rule on all public hospitals, and use of a dedicated private ambulance service to transport all possible cases to the SARS-designated hospital (WHO Update 70). Military forces were deployed to assist in contact tracing and to enforce quarantines. No visitors were allowed into any public hospital.

In Taiwan, the Department of Health efforts focused on limiting nosocomial transmission by designating dedicated SARS hospitals throughout the island. Approximately 100 “fever clinics” were also established to identify potential SARS patients and to minimize the risk of transmission in emergency departments. Patient care capacity was expanded by the construction of 1,000 additional negative pressure isolation rooms. Campsites and military facilities were identified to accommodate quarantined residents, and home quarantine was to be enforced through web-based cameras (MMWR 52; 461-6).

Legislation

On April 24, in Singapore, the Infectious Disease Act was amended with penalties for violations 1) to require persons who might have an infectious disease to go to a designated treatment center and to prohibit them from going to public places; 2) to prohibit breaking home quarantine with the possibility of electronic tagging and forced detention for violators; and 3) to permit contaminated areas to be quarantined and any suspected sources of infection to be destroyed. In addi

tion, persons throughout the country were requested to monitor body temperature and to stay home or seek medical care if any signs or symptoms suggestive of SARS appeared (MMWR 52: 405-11).

This legislation allowed mandatory home quarantine for 10 days, which was enforced by CISCO, a Singapore Security Agency. CISCO served the quarantine order and installed an electronic picture (ePIC) camera in the home of each contact (MMWR 52: 405-11).

The penalty for violating quarantine was raised to as much as $5,800 and six months in prison.

Extended Case Definition

Prevention aims at identifying and isolating all people suspected of being infected with the SARS virus. The main criteria in the current WHO case definition for suspected SARS are fever (> 38°C) and respiratory symptoms such as cough, shortness of breath, or breathing difficulty, and a history of exposure (see Chapter below "Case Definition"). This definition might not be wide enough when facing an outbreak.

In one study, in the early stages of SARS, the main discriminating symptoms were not cough and breathing difficulty but fever, chills, malaise, myalgia, rigors, and, possibly, abdominal pain and headache also occurred (Rainer). Documented fever (> 38°C) was uncommon in the early stages, and radiological evidence of pneumonic changes often preceded the fever. The authors calculated that the WHO case definition has a sensitivity of 26% and a negative predictive value of 85%. The case definition, which was initially based on patients who were already hospitalized, might therefore define the tip of the iceberg of an epidemic, and not be sufficiently sensitive in assessing patients before admission to hospital (Rainer).

In addition, patients presenting with overt symptoms suggestive of SARS, including fever, are unlikely to be the source of an outbreak; in contrast, unidentified SARS cases have, to date, been responsible for most of the sudden outbreaks. Several factors contribute to the difficulties in recognizing cases of SARS (MMWR 52; 461-6):

- Early symptoms are non-specific and may be associated with other more common illnesses

- Patients with SARS who are immunocompromised or who have chronic conditions (e.g., diabetes mellitus or chronic renal insufficiency) might not have fever when acutely ill or have symptoms attributable to underlying disease, delaying the diagnosis of SARS
- Some patients might not reveal useful contact information (e.g., exposure to an implicated healthcare facility) for fear of being stigmatized by the local community or causing their friends and families to be quarantined

These cases do not arise suspicion, are not isolated or managed according to strict procedures of infection control, have no restrictions on visitors, and are frequently transferred to other hospitals for further treatment or tests (WHO Update 83).

In order to prevent transmission from asymptomatic or mildly symptomatic and/or unrecognized patients, a "wide net" approach has been proposed by some national authorities.

Singapore changed the threshold criteria for initial isolation, picking up virtually every person with symptoms that might possibly indicate SARS for investigation and monitoring, regardless of whether the person had been in contact with a SARS patient (WHO Update 70). The "wide net" included all individuals with a low grade fever, chest radiograph abnormalities, or respiratory symptoms alone, leading to the admission to newly created "fever wards" of any patient with fever or respiratory symptoms or a chest x-ray abnormality which could not otherwise be explained. The rationale behind this approach is that a patient's likelihood of having SARS becomes clearer after 48 hours of monitoring respiratory symptoms, temperature, white cell count (for lymphopenia) and chest x-rays (Fisher).

In one hospital in Singapore, this policy led within three weeks to the admission to isolation wards of 275 individuals who did not meet the WHO criteria. 72 individuals were later referred to the SARS hospital. No secondary infections were caused (Fisher).

Quarantine

Unfortunately, tests to identify SARS patients at the earliest stages of disease are not expected to be widely available soon. Early introduc

tion of quarantine procedures for SARS should therefore be considered by health authorities. Isolation and quarantine procedures will be less effective as more cases accrue. Therefore, stringent measures implemented early in the course of the epidemic prevent the need for stricter measures as the epidemic spreads (Lipsitch).

During March, health officials in Singapore, Hong Kong, and Canada implemented quarantine and isolation measures to limit the spread of SARS. In Singapore, all primary contacts of these individuals were placed on home quarantine with financial penalties for violation; they were required to appear regularly before web cameras installed in their homes and to wear electronic bracelets if they failed to do so (Mukherjee).

On April 4, 2003, SARS was added to the list of quarantinable communicable diseases in the US. A presidential act provided the CDC with the legal authority to implement isolation and quarantine measures as part of transmissible disease-control measures, if necessary.

Quarantine does not always mean being confined to a hospital or military camp. If patients are not sick enough to warrant admission, the community may be best served by sending such patients home, provided patients can restrict their activities in a responsible manner until they are asymptomatic (Masur).

SARS Co-V may be transmitted in quarantine communities. There has been at least one report about SARS Co-V transmission during quarantine (WHO WER 22/2003). Putting patients with suspected or probable SARS and convalescent cases into isolation cubicles, each accommodating four to six patients (So), is therefore not the appropriate procedure to avoid infection. Don't "cohort" suspected cases! Patients diagnosed with SARS may or may not have the SARS virus, but they are at risk of contracting the infection if they are grouped with infected patients (Hon 2003b).

Reduce travel between districts

A recent analysis of the Hong Kong epidemic concluded that a complete ban on travel between districts could have the potential to reduce the transmission rate by 76% (Riley). This suggests that restrictions on longer-range population movement might represent a useful control measure in circumstances where it is not possible to substantially

reduce the average onset-to-hospitalization time – for example in resource-poor countries, or if a number of super-spreading events occur in close succession and hospital capacity is temporarily exceeded (Riley).

Quarantine after Discharge

There is little reliable information about the duration of quarantine after discharge. In Singapore, all inpatients who were discharged from a hospital with previous SARS cases were under telephone surveillance for 21 days; all probable SARS inpatients and selected suspect SARS inpatients who recovered and were discharged were on home quarantine for 14 days (MMWR 52; 405-11).

Infection Control in Healthcare Settings

General Measures

Hospital workers remain on the front lines in the global response to SARS. They are at considerable risk of contracting SARS when there is an opportunity for unprotected exposure. In order to protect healthcare workers and to prevent disease dissemination, strict infection control measures and public education are essential (Chan-Yeung).

In the SARS hospitals, all healthcare workers should have mandatory body temperature recording twice daily (Mukherjee).

In non-SARS hospitals, in order to minimize patient contact and deal with the potential increased workload from the SARS hospital, all elective surgery is cancelled, as are most outpatient clinics. In order to protect themselves, staff are required to wear an N95 mask, gloves and gown when in contact with all patients. Every attempt is made to streamline workflow to minimize the number of staff in contact with a patient and the time spent with a patient. Because of the potential risk of an individual healthcare worker contaminating a whole department of colleagues, medical units have been divided into small teams who do not have any contact with the other team. Some departments have mandated that one team must be at home to ensure that if another team

is quarantined because of exposure, there will still be a clean team available to continue emergency work (Mukherjee).

Other measures include stopping hospital visitations, except for pediatric, obstetric, and selected other patients. For these patients, visitors are limited to a single person who must wear a mask and pass a temperature check; all other visits are by video conference. An audit of infection control practices is ongoing (Mukherjee).

Eventually, appropriate respiratory precautions will be instituted when assessing patients with undifferentiated respiratory conditions and their family members, in order to prevent the introduction of SARS in the hospital setting (Booth).

Protective Measures

Droplet infection seems to be the primary route of spread for the SARS virus in the healthcare setting (Seto). In a case control study in five Hong Kong hospitals, with 241 non-infected and 13 infected staff with documented exposures to 11 index patients, no infection was observed among 69 healthcare workers who reported the use of mask, gloves, gowns, and hand washing. N95 masks provided the best protection for exposed healthcare workers, whereas paper masks did not significantly reduce the risk of infection (Seto).

Table 1 shows a summary of precautions for droplet infection. The implementation of aggressive infection control measures was effective in preventing the further transmission of SARS (Hsu).

Table 1: Precautions for SARS prevention in healthcare settings (from Chan-Yeung, Outbreak of severe acute respiratory syndrome in Hong Kong Special Administrative Region: case report.)

- Patients should wear N-95 masks once symptoms develop and be placed immediately in isolation facilities with negative pressure.
- Healthcare workers should wear similar masks together with head cover, goggles, gowns, and gloves when caring for these patients.
- Daily and terminal disinfection should be thorough, with careful washing and disinfection of the bed, handrails, bedside tables, floor, and equipment with hypochlorite solution (1000 ppm).
- For intubated patients, the use of a closed suction system is essential to avoid air leakage and enhanced disease transmission.

For detailed information, see the CDC guidelines further below.

As the SARS virus may be viable in the environment for several days, precautionary measures, including rigorous disinfection and hygiene procedures should provide the highest standard of protection.

Hand washing

It is essential to wash hands before touching faces or eyes.

Gloves

Health Canada advises double gloving when attending a suspected SARS patient. Hands must be washed after de-gloving.

Face Masks

The N95 respirator/mask has a filter efficiency level of 95% or greater against particulate aerosols free of oil when tested against a 0.3 micron particle. It is fluid resistant, disposable and may be worn in surgery. The "N" means "Not resistant to oil". The "95" refers to a 95% filter efficiency. The following points have to be kept in mind (Health Canada):

- An occlusive fit and a clean shave for men provide the best protection for the healthcare worker.

- Masks should be tested for fit according to the manufacturer's recommendations. In addition, masks should be fit-checked each time the mask is put on. To check the mask, the wearer takes a quick, forceful inspiration to determine if the mask seals tightly to the face.
- For instructions on how best to use the N95 mask or equivalent, refer to the handout provided by the manufacturer, or follow your provincial regulations.
- There are no published data on the length of time the mask is effective for the wearer. Health Canada recommends masks should be changed if they become wet, interfere with breathing, are damaged or visibly soiled.
- A respirator (mask) which has been exposed to a probable SARS case is considered contaminated and should be discarded.
- When discarding the mask: Wash hands prior to handling the mask. Carefully remove the mask using the straps. Discard. Wash hands after handling the mask.
- If re-using the mask: Place in a clean, dry location such as a paper bag. Do not mark the mask with a pen or marker. The name of the owner should be written on the outside of the paper bag to identify the mask. Hands should be washed after handling the mask.

Even for doctors in the community, it is advisable to wear a N95 mask when seeing any patient with respiratory symptoms (Chan-Yeung).

Additional protection

Theatre caps may reduce the risk of staff potentially contaminating their hands by touching their hair. The nature of the novel coronavirus is such that mucous membrane and eye spread is likely and therefore disposable fluid-resistant long sleeved gowns, goggles and disposable full-face shields are recommended for frontline medical staff at risk of exposure to SARS (Kamming).

Getting undressed

Getting undressed may seem easier than it is. The sequence that has to be followed – gloves first, gown next, wash your hands, take off your

face shield, then the mask, wash you hands again, etc. – requires previous exercise. Some healthcare workers have contracted the SARS virus although they had been using all recommended precautions.

Special Settings

Patients who are experiencing rapid clinical progression with a severe cough during the second week of illness should be considered particularly infectious. Procedures that might generate aerosols (e.g. nebulized medications, BiPAP, or HFOV) should be avoided if possible. When intubation is necessary, measures should be taken to reduce unnecessary exposure to health care workers, including reducing the number of health care workers present and adequately sedating or paralyzing the patient to reduce the cough (MMWR; 52: 433-6).

All high-risk procedures should be performed only by highly experienced staff.

Intensive Care Units

A brief summary of infection control measures in intensive care units (grouping critically ill patients with SARS in one ICU; transferring all pre-existing patients to other uncontaminated centers; the ICU restricted to patients with SARS; instructions to staff and visitors to put on gowns, gloves, caps, and masks in a designated area before they enter the unit; designation of "police nurses"; spot checks to ensure the correct fitting of masks; goggles and visors are worn during direct patient care, etc.) has been published by Li et al.

The use of nebulizer medications should be avoided in SARS patients (Dwosh).

Intubating a SARS Patient

In some high-risk instances (i.e., endotracheal intubation, bronchoscopy, sputum induction) airborne transmission may be possible, resulting in exposure to a particularly high viral load.

The best summary of the measures that need to be taken to minimize the risk to the anesthetist when intubating a suspected SARS patient, were recently published by Kamming, Gardam and Chung from the Toronto Western Hospital (Kamming et al.):

1. Plan ahead. It takes 5 min to fully apply all barrier precautions.

2. Apply N95 mask, goggles, disposable protective footwear, gown and gloves. Put on the belt-mounted AirMate™ and attach the respirator tubing and Tyvek© head cover. Then apply extra gown and gloves. All staff assisting to follow same precautions. If a powered respirator is unavailable, then apply N95 mask, goggles, disposable theatre cap, and a disposable full-face shield.

3. Most experienced anaesthetist available to perform intubation.

4. Standard monitoring, i.v. access, instruments, drugs, ventilator and suction checked.

5. Avoid awake fibreoptic intubation unless specific indication. Atomized local anaesthetic will aerosolize the virus.

6. Plan for rapid sequence induction (RSI) and ensure skilled assistant able to perform cricoid pressure. RSI may need to be modified if patient has very high A–a gradient and is unable to tolerate 30 s of apnoea, or has a contraindication to succinylcholine. If manual ventilation is anticipated, small tidal volumes should be applied.

7. Five minutes of preoxygenation with oxygen 100% and RSI in order to avoid manual ventilation of patient's lungs and potential aerosolization of virus from airways. Ensure high efficiency hydrophobic filter interposed between facemask and breathing circuit or between facemask and Laerdal bag.

8. Intubate and confirm correct position of tracheal tube.

9. Institute mechanical ventilation and stabilize patient. All airway equipment to be sealed in double zip-locked plastic bag and removed for decontamination and disinfection.

10. Assistant should then wipe down the Tyvek, head cover with disinfectant (accelerated hydrogen peroxide is most effective) after exiting the negative-pressure atmosphere. The protective barrier clothing is then removed paying close attention to avoid self-contamination. The outer gloves are used to remove the outer gown and protective overshoes. The outer gloves are then discarded and the inner gloves remove the disinfected head cover and the inner gown. The inner gloves are then removed. The head cover is discarded, the AirMate‘ tubing is pasteurized and the belt pack wiped down with disinfectant. The N95 mask and goggles are only removed after leaving the room.

11. After removing protective equipment, avoid touching hair or face before washing hands.

Anesthesia

As specialists in airway management, anesthetists are routinely exposed to patients' respiratory secretions and are at high risk of contracting SARS from infected patients (Kamming).

Any known or suspected SARS patient must be regarded as ultra high risk and the attending anesthetist should wear a N95 mask, goggles, face shield, double gown, double gloves, and protective overshoes. Removal and disposal of these items without contaminating oneself is critical. The use of a powered respirator by the anesthetist and assistant is strongly advised for high-risk aerosol-generating airway procedures in suspected SARS patients (Kamming).

Triage

Identifying persons who might be at risk of SARS on arrival at a medical facility or office is difficult and requires changes in the way medical evaluations are conducted. Revised interim guidelines for triage recommend that all patients in ambulatory-care settings be screened promptly for fever, respiratory symptoms, recent travel, and close contact with a suspected SARS patient:

- Updated Interim Domestic Guidelines for Triage and Disposition of Patients Who May Have Severe Acute Respiratory Syndrome (SARS) Guidance on triage screening to facilitate the identification of patients who may have SARS in the ambulatory setting: http://www.cdc.gov/ncidod/sars/triage_interim_guidance.htm

Internet Sources

Infection-control practitioners, clinicians providing medical care for patients with suspected SARS, and persons who might have contact with persons with suspected SARS should frequently consult the CDC's "SARS Infection Control and Exposure Management" guidelines (http://www.cdc.gov/ncidod/sars/ic.htm):

- Updated Interim Domestic Infection Control Guidance in the Healthcare and Community Setting for Patients with Suspected SARS Precautions are recommended until the epidemiology of the disease transmission is better understood (see details below); http://www.cdc.gov/ncidod/sars/infectioncontrol.htm

- Interim Domestic Guidance on the Use of Respirators to Prevent Transmission of SARS;
  http://www.cdc.gov/ncidod/sars/respirators.htm
- Infection Control Precautions for Aerosol-Generating Procedures on Patients who have Suspected SARS;
  http://www.cdc.gov/ncidod/sars/aerosolinfectioncontrol.htm
  Precautions for procedures such as aerosolized medication treatments (e.g., albuterol), diagnostic sputum induction, bronchoscopy, airway suctioning, & endotracheal intubation.
- Interim Laboratory Biosafety Guidelines for Handling and Processing Specimens Associated with SARS;
  http://www.cdc.gov/ncidod/sars/sarslabguide.htm

See also the article "Infection Control Guidance for Handling of Human Remains of Severe Acute Respiratory Syndrome (SARS) Decedents" published by Heath Canada at http://SARSReference.com/link.php?id=17

CDC: Updated Interim Domestic Infection Control Guidance in the Health-Care and Community Setting for Patients with Suspected SARS

Revised: May 1, 2003

Check regularly for updates:
http://www.cdc.gov/ncidod/sars/infectioncontrol.htm

For all contact with suspect SARS patients, careful hand hygiene is urged, including hand washing with soap and water; if hands are not visibly soiled, alcohol-based handrubs may be used as an alternative to hand washing.

Access www.cdc.gov/handhygiene for more information on hand hygiene.

For the inpatient setting:

If a suspect SARS patient is admitted to the hospital, infection control personnel should be notified immediately. Infection control measures

for inpatients (www.cdc.gov/ncidod/hip/isolat/isolat.htm) should include:

- Standard precautions (e.g., hand hygiene); in addition to routine standard precautions, health-care personnel should wear eye protection for all patient contact.
- Contact precautions (e.g., use of gown and gloves for contact with the patient or their environment)
- Airborne precautions (e.g., an isolation room with negative pressure relative to the surrounding area and use of an N-95 filtering disposable respirator for persons entering the room)

If airborne precautions cannot be fully implemented, patients should be placed in a private room, and all persons entering the room should wear N-95 respirators. Where possible, a qualitative fit test should be conducted for N-95 respirators; detailed information on fit testing can be accessed at http://SARSReference.com/link.php?id=4. If N-95 respirators are not available for health-care personnel, then surgical masks should be worn. Regardless of the availability of facilities for airborne precautions, standard and contact precautions should be implemented for all suspected SARS patients.

For the outpatient setting:

- Persons seeking medical care for an acute respiratory infection should be asked about possible exposure to someone with SARS or recent travel to a SARS-affected area. If SARS is suspected, provide and place a surgical mask over the patient's nose and mouth. If masking the patient is not feasible, the patient should be asked to cover his/her mouth with a disposable tissue when coughing, talking or sneezing. Separate the patient from others in the reception area as soon as possible, preferably in a private room with negative pressure relative to the surrounding area.
- All health-care personnel should wear N-95 respirators while taking care of patients with suspected SARS. In addition, health care personnel should follow standard precautions (e.g., hand hygiene), contact precautions (e.g., use of gown and gloves for contact with the patient or their environment) and wear eye protection for all patient contact.

For more information, see the triage guidelines (http://www.cdc.gov/ncidod/sars/triage_interim_guidance.htm).

For home or residential setting:

Placing a surgical mask on suspect SARS patients during contact with others at home is recommended. If the patient is unable to wear a surgical mask, it may be prudent for household members to wear surgical masks when in close contact with the patient. Household members in contact with the patient should be reminded of the need for careful hand hygiene including hand washing with soap and water; if hands are not visibly soiled, alcohol-based handrubs may be used as an alternative to hand washing. For more information, see the household guidelines, http://www.cdc.gov/ncidod/sars/ic-closecontacts.htm.

Case Definition for suspected Severe Acute Respiratory Syndrome (SARS)

Health-care personnel should apply appropriate infection control precautions for any contact with patients with suspected SARS. The case definition for suspected SARS is subject to change, particularly concerning travel history as transmission is reported in other geographic areas; the most current definition can be accessed at the Severe Acute Respiratory Syndrome (SARS) case definition web page, http://www.cdc.gov/ncidod/sars/casedefinition.htm.

Additional information

A power point file summarizing public health interventions has recently been presented at the WHO's Kuala Lumpur meeting:

"Severe Acute Respiratory Syndrome: Response from Hong", by Yeoh EK: http://SARSReference.com/link.php?id=14

Infection Control in Households

Healthcare workers should have a high index of suspicion if they or family members develop fever and features suggestive of severe acute respiratory syndrome. They should present themselves to hospitals

rather than treating themselves at home and putting their family members at risk (Chan-Yeung).

To prevent secondary transmission, close contacts of SARS patients should be vigilant for fever or respiratory symptoms. If such symptoms develop, exposed persons should avoid contact with others, seek immediate medical attention, and practice the infection control precautions that are recommended for SARS patients. Household members and other close contacts of SARS patients should be actively monitored by the local health department for illness.

Consult frequently CDC's "SARS Infection Control and Exposure Management" guidelines, http://www.cdc.gov/ncidod/sars/ic.htm:

- Interim Guidance on Infection Control Precautions for Patients with Suspected SARS and Close Contacts in Households (see below), http://www.cdc.gov/ncidod/sars/ic-closecontacts.htm
- Interim Domestic Guidance on Persons Who May Have Been Exposed to Patients with Suspected SARS, http://www.cdc.gov/ncidod/sars/exposuremanagement.htm
- Interim Domestic Guidance for Management of Exposures to SARS for Health-Care and Other Institutional Settings, http://www.cdc.gov/ncidod/sars/exposureguidance.htm

Contacts of proven cases should isolate themselves until the incubation period is over. After contact with patients with respiratory symptoms, careful hand hygiene is necessary, including washing with soap and water.

CDC: Interim Guidance on Infection Control Precautions for Patients with Suspected Severe Acute Respiratory Syndrome (SARS) and Close Contacts in Households

Revised: April 29

Check regularly for updates:

http://www.cdc.gov/ncidod/sars/ic-closecontacts.htm

Patients with SARS pose a risk of transmission to close household contacts and health care personnel in close contact. The duration of

time before or after onset of symptoms during which a patient with SARS can transmit the disease to others is unknown. The following infection control measures are recommended for patients with suspected SARS in households or residential settings. These recommendations are based on the experience in the United States to date and may be revised as more information becomes available.

1. SARS patients should limit interactions outside the home and should not go to work, school, out-of-home child care, or other public areas until 10 days after the resolution of fever, provided respiratory symptoms are absent or improving. During this time, infection control precautions should be used, as described below, to minimize the potential for transmission.

2. All members of a household with a SARS patient should carefully follow recommendations for hand hygiene (e.g., frequent hand washing or use of alcohol-based hand rubs), particularly after contact with body fluids (e.g., respiratory secretions, urine, or feces). See the "Guideline for Hand Hygiene in Health-Care Settings" at http://www.cdc.gov/handhygiene/ for more details on hand hygiene.

3. Use of disposable gloves should be considered for any direct contact with body fluids of a SARS patient. ***However, gloves are not intended to replace proper hand hygiene.*** Immediately after activities involving contact with body fluids, gloves should be removed and discarded and hands should be cleaned. Gloves must never be washed or reused.

4. Each patient with SARS should be advised to cover his or her mouth and nose with a facial tissue when coughing or sneezing. If possible, a SARS patient should wear a surgical mask during close contact with uninfected persons to prevent spread of infectious droplets. When a SARS patient is unable to wear a surgical mask, household members should wear surgical masks when in close contact with the patient.

5. Sharing of eating utensils, towels, and bedding between SARS patients and others should be avoided, although such items can be used by others after routine cleaning (e.g., washing with soap and hot water). Environmental surfaces soiled by body fluids should be cleaned with a household disinfectant according to

manufacturer's instructions; gloves should be worn during this activity.

6. Household waste soiled with body fluids of SARS patients, including facial tissues and surgical masks, may be discarded as normal waste.

7. Household members and other close contacts of SARS patients should be actively monitored by the local health department for illness.

8. Household members or other close contacts of SARS patients should be vigilant for the development of fever or respiratory symptoms and, if these develop, should seek healthcare evaluation. In advance of evaluation, healthcare providers should be informed that the individual is a close contact of a SARS patient so arrangements can be made, as necessary, to prevent transmission to others in the healthcare setting. Household members or other close contacts with symptoms of SARS should follow the same precautions recommended for SARS patients.

9. At this time, in the absence of fever or respiratory symptoms, household members or other close contacts of SARS patients need not limit their activities outside the home.

Related Links:

SARS Information for Patients and Their Close Contacts, http://www.cdc.gov/ncidod/sars/closecontacts.htm

Possible Transmission from Animals

SARS Co-V was found in three animal species taken from a market in Southern China (masked palm civet and racoon-dog, Chinese ferret badger). As a precautionary measure, persons who might come into contact with these species or their products, including body fluids and excretions, should be aware of the possible health risks, particularly

during close contact such as handling and slaughtering and possibly food processing and consumption (WHO Update 64).

After the Outbreak

When the Toronto epidemic was already thought to be over, an undiagnosed case at the North York General Hospital led to a second outbreak among other patients, family members and healthcare workers.

Infection control measures may have been lifted too early. During early and mid-May, as recommended by provincial SARS-control directives, hospitals discontinued SARS-expanded precautions (i.e., routine contact precautions with use of a N95 or equivalent respirator) for non-SARS patients without respiratory symptoms in all hospital areas other than the emergency department and the intensive care unit (ICU). In addition, staff were no longer required to wear masks or respirators routinely throughout the hospital or to maintain distance from one another while eating. In the hospital where the second outbreak originated, changes in policy were instituted on May 8; the number of persons allowed to visit a patient during a 4-hour period remained restricted to one, but the number of patients who were allowed to have visitors was increased (MMWR; 52:547-50).

Maintaining a high level of suspicion for SARS on the part of healthcare providers and infection-control staff is therefore critical, particularly after a decline in reported SARS cases. The prevention of healthcare-associated SARS infections must involve health care workers, patients, visitors, and the community (MMWR; 52:547-50).

Conclusion

One of the most important lessons learned to date is the decisive power of high-level political commitment to contain an outbreak even when sophisticated control tools are lacking. SARS has been brought close to defeat by the diligent and unrelenting application – on a monumental scale – of centuries-old control measures: isolation, contact tracing and follow-up, quarantine, and travel restrictions. Other successful measures include the designation of SARS-dedicated hospitals to minimize the risk of spread to other hospitals, mass media

campaigns to educate the public and encourage prompt reporting of symptoms, and the establishment of fever clinics to relieve pressure on emergency rooms, which have also been the setting for many new infections. Screening at airports and other border points and, thorough fever checks throughout selected population groups has also been effective (WHO Update 83).

All of these measures contributed to the prompt detection and isolation of new sources of infection – a key step on the way to breaking the chain of transmission. Given the importance of supportive public attitudes and actions, the single most important control "tool" in bringing SARS under control may very well be the thermometer (WHO Update 83).

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Chapter 6: Case Definition

WHO Case Definition

As defined by the World Health Organization (WHO), a suspected case is classified as being disease in a person with a documented fever (temperature >38 °C), lower respiratory tract symptoms, and contact with a person believed to have had SARS or a history of travel to a geographic area where there has been documented transmission of the illness.

A suspected case with 1) chest radiographic findings of pneumonia, 2) acute respiratory distress syndrome, or 3) an unexplained respiratory illness resulting in death with autopsy findings consistent with the pathology of ARDS without an identifiable cause is considered a probable case.

The WHO Case Definition is available at:
http://www.who.int/csr/sars/casedefinition/en/.

Clinicians are advised that patients should not have their case definition category downgraded while still awaiting results of laboratory testing or on the basis of negative results. See "Use of laboratory methods for SARS diagnosis", http://www.who.int/csr/sars/labmethods/

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 symptoms:

- 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 (http://www.who.int/entity/csr/sarsareas/en)
- residing in an area with recent local transmission of SARS

2. A person with an unexplained acute respiratory illness resulting in death after 1 November 2002[1], but on whom no autopsy has been performed

AND one or more of the following exposures during to 10 days prior to onset of symptoms:

- 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

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

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

Probable case

1. A suspect case with radiographic evidence of infiltrates consistent with pneumonia or respiratory 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. See "Use of laboratory methods for SARS diagnosis", http://www.who.int/csr/sars/labmethods/

3. A suspect case with autopsy findings consistent with the pathology of RDS without an identifiable 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 over time. A patient should always be managed as clinically appropriate, regardless of their case status.

- A case initially classified as suspect or probable, for whom an alternative diagnosis can fully explain 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 reclassified as "probable".
- A suspect case with a normal CXR should be treated, as deemed appropriate, and monitored for 7 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 explained by an alternative diagnosis should remain as "suspect".
- A suspect case who dies, on whom no autopsy is conducted, should remain classified as "suspect". However, if this case is identified as being part of a chain transmission of SARS, the case should be reclassified as "probable".
- If an autopsy is conducted and no pathological evidence of RDS is found, the case should be "discarded".

CDC Case Definition

The Centers for Disease Control and Prevention have added laboratory criteria for evidence of infection with the SARS-associated coronavirus (SARS-CoV) to the interim surveillance case definition.

Using the laboratory criteria, a SARS case is laboratory-confirmed if one of the following is met:

- Detection of antibody to SARS-associated coronavirus (SARS-CoV) in a serum sample, or

- Detection of SARS-CoV RNA by RT-PCR confirmed by a second PCR assay, by using a second aliquot of the specimen and a different set of PCR primers, or
- Isolation of SARS-CoV.

Negative laboratory results for PCR, viral culture, or antibody tests obtained within 28 days of illness do not rule out coronavirus infection. In these cases, an antibody test of a specimen obtained more than 28 days after the onset of illness is needed to determine infection.

The "Updated Interim Surveillance Case Definition for Severe Acute Respiratory Syndrome (SARS)", published July 18, 2003, is available on the Internet at http://www.cdc.gov/ncidod/sars/casedefinition.htm

Chapter 7: Diagnostic Tests

Wolfgang Preiser, Christian Drosten

Introduction

Despite the initial rapid progress in the discovery of the causative agent (see Chapter 2: Virology) and the early development of diagnostic tests, further progress in the establishment of laboratory tests for SARS has been slower than originally expected.

While various molecular (PCR-based) assays have been developed by different groups around the world, and although one such assay is available commercially, results of these tests should still not be used to rule out a suspected case of SARS, according to current WHO recommendations.

The continual lack of a rapid laboratory test to aid the diagnosis of suspected cases of SARS makes this area a priority for further research efforts (WHO, Update 71).

In many viral diseases, virus shedding is greatest during the early symptomatic phase, i.e. around, and immediately following the onset of symptoms. Unfortunately, virus excretion is comparatively low during the initial phase of SARS. It peaks in respiratory specimens and in stools at around day 10 after the onset of the clinical illness. In order to make an early diagnosis, it is therefore necessary to use highly sensitive tests that are able to detect the low levels of viral genome present during the first days of illness.

Because presently available tests are not generally able to detect the small amounts of SARS coronavirus (SARS-CoV) initially shed, they do not yet play a role in patient management and case control, as SARS patients may be capable of infecting others during the initial phase and therefore need to be reliably detected and quickly isolated (WHO, Update 71).

The results of the first clinical studies on SARS are now available and able to shed light on the clinical usefulness of various tests on different patient samples at different time points. In one series, IgG seroconversion was documented in 93% of patients at a mean of 20 days;

about 50 % of patients had seroconverted at around 15 days after the onset of symptoms (Peiris).

In the same study, SARS-associated coronavirus RNA was detected in nasopharyngeal aspirates by RT-PCR in 20 patients (32%) at initial presentation (mean 3.2 days after the onset of illness) and in 68% at day 14 (Peiris). Quantification revealed that the viral load peaked on day 10 with a mean geometric value of $1.9*10^7$ copies per ml, compared to values of $2.3*10^5$ copies per ml and $9.8*10^4$ copies per ml on days 5 and 15, respectively (Peiris).

Furthermore, viral RNA was detected in 97% of stool samples collected later in the illness (a mean of 14.2 days after onset). Similarly, viral RNA was detected in 42% of urine samples collected at a mean of 15.2 days after the onset of symptoms (Peiris).

The authors therefore conclude that although viral RNA detection in the nasopharyngeal aspirate has a sensitivity of only 32% at presentation, testing of multiple nasopharyngeal and fecal samples is able to increase the predictive value of the RT-PCR assay (Peiris).

Laboratory tests

Due to the efforts of the WHO-led international multi-center collaborative network of laboratories testing for SARS, tests for the novel coronavirus have been developed with unprecedented speed (SARS: Laboratory diagnostic tests – 29 April 2003; http://www.who.int/csr/sars/diagnostictests/en/). Samples from suspected and probable SARS cases have been tested for SARS-CoV for some time in several countries, including Canada, France, Germany, Hong Kong SAR, Italy, Japan, the Netherlands, Singapore, the United Kingdom and the United States of America.

Nevertheless, until standardized reagents for virus and antibody detection become available and methods have been adequately field tested, the diagnosis of SARS remains based on clinical and epidemiological findings. The revised case definition from May 1, 2003, (see: http://www.who.int/csr/sars/casedefinition/en/) includes laboratory results for the first time: a suspected case of SARS, that is positive for SARS-CoV in one or more assays, should be reclassified as a probable

case. At present there are no defined criteria for SARS-CoV test results to confirm or reject the diagnosis of SARS.

Positive laboratory test results for other known agents that are able to cause atypical pneumonia such as *Legionella pneumophila*, influenza and parainfluenza viruses, *Mycoplasma pneumoniae* etc. may serve as exclusion criteria: according to the case definition, a case should be excluded if an alternative diagnosis can fully explain the illness. However, the possibility of dual infection must not be ruled out completely.

Molecular tests

SARS-CoV-specific RNA can be detected in various clinical specimens such as blood, stool, respiratory secretions or body tissues by the polymerase chain reaction (PCR). A number of PCR protocols developed by members of the WHO laboratory network are available on the WHO website (http://www.who.int/csr/sars/primers/en/). Furthermore, a 5´-nuclease RT-PCR test kit containing primers and positive and negative controls, developed by the Bernhard Nocht Institute (http://www.bni-hamburg.de/; Drosten et al.), is available commercially (http://www.artus-biotech.de). An inactivated standard preparation is also available for diagnostic purposes through the European Network for Imported Viral Infections (ENIVD; http://www.enivd.de). ENIVD is also preparing an international external quality assessment scheme for SARS-CoV assays.

Despite their sometimes high sensitivity, the existing PCR tests cannot rule out, with certainty, the presence of the SARS virus in patients (Peiris, McIntosh, Poon). On the other hand, contamination of samples in laboratories might lead to false positive results. Stringent guidelines on laboratory quality control and confirmatory testing have therefore been issued by the WHO (http://www.who.int/csr/sars/labmethods/en/).

A valid positive PCR result indicates that there is genetic material (RNA) from the SARS-CoV in the sample. It does not mean, however, that the virus present is infectious, or that it is present in a large enough quantity to infect another person.

Negative PCR results do not exclude SARS. Besides the possibility of obtaining incorrect, false-negative test results (e.g. through lack of sensitivity), specimens may not have been collected at a time when the virus or its genetic material was present.

Currently, efforts are underway to improve the sensitivity of PCR assays to increase their clinical usefulness. One approach is to amplify another gene of SARS-CoV than the hitherto used polymerase gene; due to the unique transcription strategy of coronaviruses, a PCR targeting the nucleoprotein may have a higher sensitivity (Lai). While evaluations of such a PCR are ongoing, the protocol is already available from the Bernhard Nocht Institute.

Virus isolation

The presence of the infectious virus can be detected by inoculating suitable cell cultures (e.g., Vero cells) with patient specimens (such as respiratory secretions, blood or stool) and propagating the virus in vitro. Once isolated, the virus must be identified as SARS-CoV using further tests. Cell culture is a very demanding test, but currently (with the exception of animal trials) the only means to show the existence of a live virus. It has to be performed under at least biosafety safety level (BSL) 3 conditions (see below). Positive cell culture results indicate the presence of live SARS-CoV in the sample tested. Negative cell culture results do not exclude SARS (see negative PCR test result).

Antibody detection

Various methods provide a means for the detection of antibodies produced in response to infection with SARS-CoV. Different types of antibodies (IgM and IgG) appear and change in level during the course of infection. They can be undetectable in the early stages of infection. IgG usually remains detectable after resolution of the illness (Li).

The following test formats are being developed:

– Enzyme-linked immunosorbent assay (ELISA): a test which detects a mixture of IgM and IgG antibodies in the serum of SARS patients and reliably yields positive results at around day 21 after the onset of illness.

– Immunofluorescence assay (IFA): This requires the use of SARS-CoV-infected cells fixed on a microscope slide; patient antibodies bind to viral antigens and are in turn detected by immunofluorescent-labelled secondary antibodies against human IgG or IgM or both, using an immunofluorescence microscope. IFA typically yields a positive result after about day 10 after the onset of illness. Results may be quantified by using serial titrations of patient sera. A SARS-CoV IFA manufactured by Euroimmun AG (Seekamp 31, D-23560 Lübeck, Germany; http://www.euroimmun.de) is now available commercially for the detection of IgG and IgM antibodies against SARS-CoV.

– Neutralization test (NT): This test assesses and quantifies, by means of titration, the ability of patient sera to neutralize the infectivity of SARS-CoV on cell culture. NT is therefore likely to be the best correlate of immunity. However, due to the use of the infectious virus it is limited to institutions with BSL-3 facilities.

Interpretation

Positive antibody test results indicate previous infection with SARS-CoV. Seroconversion from negative to positive or a four-fold rise in the antibody titer from acute to convalescent serum indicates a recent infection. A negative antibody test result later than 21 days after the onset of illness is likely to indicate that no infection with SARS-CoV has taken place. There seems to be no background seroprevalence against SARS-CoV in the control populations screened so far. Antibody testing allows the indirect diagnosis of SARS-CoV infection and is unsuitable during the acute illness; it has the advantage of being rather independent of the sample type and timing, in contrast to other virus detection methods.

Limitations

All tests for SARS-CoV available so far have limitations. Extreme caution is therefore necessary when management decisions are to be based on virological test results. For more details, see the WHO Update 39, "Caution urged when using diagnostic tests": http://www.who.int/csr/sarsarchive/2003_04_25/en/. In particular, false negative test results (due to low sensitivity, unsuitable sample

type, or time of sampling, etc.) may give a false sense of security; in the worst case, they could allow persons carrying the SARS virus, and therefore capable of infecting others, to escape detection.

To aid in the better understanding of SARS, the WHO recommends that sequential samples be stored from patients with suspected or probable SARS – and also close contacts who are not ill themselves – for future use. This is particularly important for the first case(s) recognized in countries that have not previously reported SARS. Data on the clinical and contact history should also be collected in order to obtain a better understanding of the shedding pattern of the virus and the period of transmissibility. Such patient samples should be suitable for viral culture, PCR, antigen detection, immunostaining and/or serological antibody assays. For details, refer to "Sampling for Severe Acute Respiratory Syndrome (SARS) diagnostic tests", http://www.who.int/csr/sars/sampling/en/). The WHO also encourages each country to designate a reference laboratory for investigation and/or referral of specimens from possible SARS patients.

Biosafety considerations

So far, not a single case of a laboratory-associated SARS-CoV infection has been reported. Nevertheless, the WHO has issued biosafety guidelines for the handling of clinical specimens associated with SARS cases and materials derived from laboratory investigations of SARS (on April 25, 2003; see http://www.who.int/csr/sars/biosafety2003_04_25/en/). Suitable measures must be taken to prevent the potential spread by droplets, air, and/or contaminated surfaces and objects, with particular emphasis on avoiding the unguarded production of aerosols.

For routine diagnostic testing of serum and blood samples, manipulations involving known inactivated (lysed, fixed or otherwise treated) virus particles and/or incomplete, non-infectious portions of the viral genome, routine examination of mycotic and bacterial cultures, and final packaging of specimens (already in a sealed, decontaminated primary container) for transport to diagnostic laboratories for additional testing, BSL-2 facilities with appropriate BSL-2 work practices are deemed sufficient. Any procedure that may generate aerosols should be performed in a biological safety cabinet, and laboratory

workers should wear eye protection and a surgical mask in addition to standard protective equipment such as gloves, etc.

In vitro cell culture of the etiologic agent and manipulations involving growth or concentration of the etiologic agent require BSL-3 facilities and BSL-3 work practices.

The current Dangerous Goods Regulations (2003) of the International Air Transport Association (IATA) allow specimens known or suspected of containing the SARS agent to be transported as UN 3373 "Diagnostic Specimens" when they are transported for diagnostic or investigational purposes. Specimens transported for any other purpose, and cultures prepared for the deliberate generation of pathogens, must be transported as UN 2814, and marked as: "Infectious substance, affecting humans (Severe Acute Respiratory Syndrome virus)". All specimens that are to be transported (UN 3373 or UN 2814) must be packaged in triple packaging consisting of three packaging layers.

Further detailed information about containment facilities and biosafety practices can be found in the WHO Laboratory Biosafety Manual, 2nd revised edition, available from the WHO website (http://www.who.int/csr/resources/publications/biosafety/Labbiosafety.pdf).

Outlook

In addition to allowing the rapid diagnosis of SARS infection, the availability of diagnostic tests will help to address important questions such as the period of virus shedding (and communicability) during convalescence, the presence of virus in different body fluids and excreta, and the presence of virus shedding during the incubation period.

Until a certain degree of standardization and quality assurance has been achieved for the SARS-CoV laboratory tests, test results must be used with utmost caution in clinical situations. It is strongly advisable to closely check on updated recommendations by the WHO and relevant national organizations regarding the availability and use of such tests. If in doubt, advice should be sought from reference laboratories (see http://www.who.int/csr/sars/labmethods/en/).

Recent events in Canada once again demonstrated the urgent need for improved and standardized methods (Outbreak in British Columbia, Canada is not SARS, WHO press release); all laboratory test methods for SARS-CoV require careful evaluation before valid results can be issued. Because the previously recognized human coronaviruses received little attention in the past, much has to be learnt about their epidemiology and clinical relevance, and great care has to be taken in order not to be misguided by the insufficient specificity of available tests.

Table, Figures

Table 1: Currently (July 2003) available diagnostic tests for the SARS-associated coronavirus.

Detection method	Clinical material/ specimen	Technical details	Diagnostic significance
Virus detection			
Virus isolation on cell culture	Respiratory tract samples: sputum, BAL	Suitable cell lines: Vero; biosafety level 3 facility required	Indicates presence of infectious virus; negative result does not preclude SARS!
Polymerase chain reaction (PCR)	Respiratory tract samples: sputum, BAL, throat swab, throat washing, stool	Different primer sequences and protocols available from the WHO website *	Indicates presence of viral genome, not necessarily of infectious virus; negative result does not preclude SARS! *
Antibody detection			
Immunfluorescence assay (IFA)	Serum	For detection of specific IgG or IgM antibodies or both	IgM IFA usually positive from day 10 after the onset of symptoms
Enzyme-linked immunosorbent assay (ELISA)	Serum	May be designed to detect specific IgG or IgM antibodies or both	Usually positive from day 21 after the onset of symptoms
Neutralization test (NT)	Serum	Requires BSL-3 facility ("live" virus)	Under investigation; study use only

See also: "Severe Acute Respiratory Syndrome (SARS): Laboratory diagnostic tests" (http://www.who.int/csr/sars/diagnostictests/en/)

*see "PCR primers for SARS developed by the WHO Network Laboratories" (http://www.who.int/csr/sars/primers/en/) and "Recommendations for laboratories testing by PCR for presence of SARS coronavirus - RNA" (http://www.who.int/csr/sars/coronarecommendations/en/)

Figure 1. Immunofluorescence assay (IFA): SARS-CoV-infected Vero cells incubated with patient serum (1:50 dilution) obtained 11 days after the onset of symptoms, showing cytoplasmatic fluorescence. (Source: Source: Institute for Medical Virology, Director: W. Doerr)
http://www.sarsreference.com/archive/verocells_patientserum.jpg

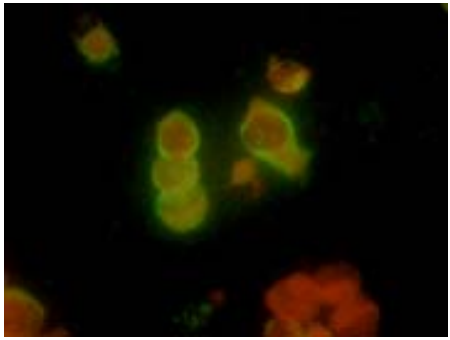
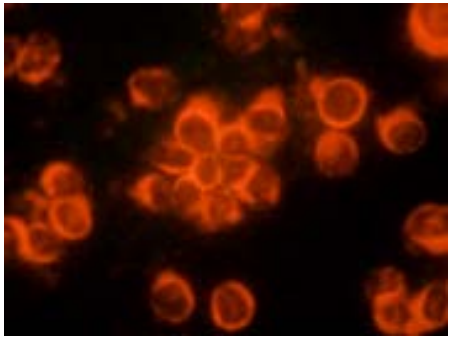


Figure 2. Immunofluorescence assay (IFA): SARS-CoV-infected Vero cells incubated with negative control serum. (Source: Source: Institute for Medical Virology, Director: W. Doerr)
http://www.sarsreference.com/archive/verocells_controlserum.jpg



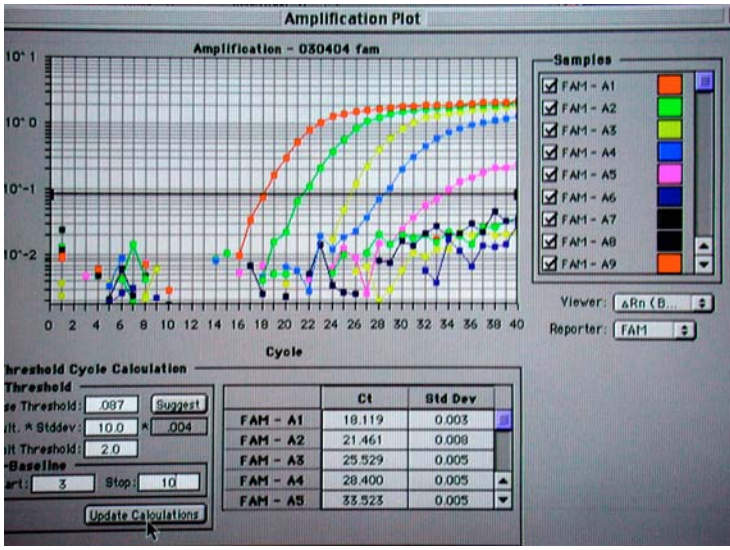


Figure 3. Amplification plot of "TaqMan" (5'nuclease) real-time PCR for the detection of SARS-CoV RNA in clinical specimens. This is a widely used assay, developed by BNI. Primers and fluorescence-labeled probe are located in the polymerase gene of SARS-CoV (Picture source: Institute for Medical Virology, Director: W. Doerr).

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Chapter 8:

Clinical Presentation and Diagnosis

Christian Hoffmann, Bernd Sebastian Kamps

There is no single test that can be used to diagnose SARS with a reasonable degree of accuracy. Diagnosis, therefore, continues to rely on the clinical examination, supported by case definitions that include a travel history. The initial symptoms of SARS are non-specific, complicating the differential diagnosis. Some features of the history, physical examination, radiological and laboratory findings, however, should alert clinicians to the possible diagnosis of SARS, even when the contact history is unreliable. These features are described below.

Clinical Presentation

The most common symptom in SARS patients is fever with a body temperature of > 38.0°C (100.4°F). Fever is therefore a main criteria in the current WHO case definition for suspected or probable SARS. However, fever may be absent during the early stages of the disease and in individuals with co-morbidities who may be impaired in their ability to mount a fever.

Fever is mostly associated with other symptoms including chills, rigors, headache, dizziness, malaise, and myalgia (CDC, Lee, Tsang, Peiris, Chan-Yeung, Donnelly, Booth). The frequency of these symptoms within different cohorts are shown in table 1. Thus, the initial symptoms may resemble those of other forms of "atypical pneumonia" which are usually caused by legionella, mycoplasma and chlamydia species.

Sputum production, sore throat, coryza, nausea, and vomiting are less common (Lee, Booth). Inspiratory crackles may be heard at the base of the lung. Wheezing is generally absent. Diarrhea only seemed to be a prominent symptom in the Amoy Gardens' outbreak in Hong Kong

(Peiris 2003b). Within the other cohorts published to date, diarrhea was less frequent.

Table 1 – Clinical symptoms at presentation (in %)

	Lee et al. n=138	Peiris et al. n=50	Donnelly et al. n > 1250	Booth et al. n=144
Fever	100	100	94	99
Chills or rigors	73	74	65*	28*
Cough	57	62	50	69
Myalgia	61	54	51	49
Malaise	n.a.	50	64	31
Runny nose	23	24	25	2
Sore throat	23.	20	23	12
Shortness of breath	n.a.	20	31	n.a.
Diarrhea	20	10	27	24
Headache	56	20	50	35

* chills

It is unknown to what degree asymptomatic infections can occur. A comprehensive description of the spectrum of the clinical illness of SARS is dependent on large serosurveys in populations to which the SARS virus has spread.

Hematological Manifestations

During the course of illness, abnormal hematological values are common. Early studies have shown lymphopenia and thrombocytopenia to be frequent in SARS patients (Tsang, Lee, Poutanen). There is now one study which analyzed the hematological changes during SARS in more detail (Wong R). Progressive lymphopenia was found in the peripheral blood of 153/157 (98 %) patients with SARS, reaching its lowest point in the second week. Lymphopenia was also shown in hemato-lymphoid organs at postmortem examination. The lymphocyte count commonly recovered in the third week, but about 30% of patients were still lymphopenic by the fifth week of SARS.

Most patients had reduced CD4 and CD8 T cell counts during the early phase of illness, with mean CD4 and CD8 T cell counts of 287 cells/µl (normal: 410 to 1590 cells/µl) and 242 cells/µl (normal: 62 to 559 cells/µl), respectively. Low CD4 and CD8 lymphocyte counts at presentation were associated with an adverse outcome in this study (Wong R).

Transient leucopenia was found in 64% of patients during their first week of illness. However, during the second and third week of illness, 61% developed leucocytosis. Neutrophilia (> 7.500/µl) developed in 82% of patients, possibly reflecting the wide use of corticosteroids.

In total, 55% of patients developed a self-limiting thrombocytopenia, possibly caused by an immune mechanism. With the exception of 2% of patients, the degree of thrombocytopenia was mild (platelet counts >50.000//µl), reaching a low point at the end of the first week. No patient had major bleeding or required platelet transfusion (Wong R).

Other Laboratory findings

Common electrolyte and biochemical abnormalities include elevated levels of lactate dehydrogenase (LDH), aspartate and alanine amino-transferases and creatine kinase (Lee, Tsang, Poutanen, Peiris, Booth; Table 2). Since high lactate dehydrogenase levels are often seen in association with tissue damage, some authors propose that this finding indicates extensive lung injury (Lee). However, it seems possible that elevated levels of lactate dehydrogenase and transaminases may be, at least partially, secondary to the hemolytic effect of ribavirin treatment (Booth). In a multivariate analysis, elevated LDH was an independent predictor for poor outcome in SARS patients (Lee).

A substantial proportion of patients demonstrate low calcium, phosphorus, magnesium, sodium and potassium levels (Lee, Peiris, Booth). These abnormalities tend to worsen during hospitalization. Again, it remains unclear whether these changes reflect the natural course of the infection or whether they are secondary to the effects of treatment with ribavirin or other agents that affect renal tubular function (Booth).

There is evidence that the clotting profile (prothrombin time, activated partial-thromboplastin time, international normalized ratio, and D-dimer) may be deranged in a substantial number of patients (Lee).

Table 2 – Laboratory findings at presentation (in %)

	Lee, et al. n=138	Peiris, et al. n=50
Leukopenia (< 3.5 x 10^9/l)	34	26
Lymphopenia (< 1.0 x 10^9/l)	70	68
Thrombocytopenia	45	40
Alanine aminotransferase ⇑	23	34
Creatine kinase ⇑	32	26
LDH ⇑	71	n.a.
Hyponatremia	20	n.a.
Hypokalemia	25	n.a.
D-dimer levels ⇑	45	n.a.
Prolonged activated partial-thromboplastin time	43	n.a.

n.a. = not available.

Atypical Presentation

Not recognized or misdiagnosed SARS patients, if not discovered within a reasonable lapse of time, may become sources for super-spreading events such as those reported from Hanoi, Singapore, Hong Kong, Toronto, and Taiwan (see also Chapter 3: Transmission and Chapter 4: Epidemiology).

There are several reports on atypical clinical presentations of SARS. Patients may present without fever, or with diarrhea but no pneumonia (Hon). Fisher et al. describe four patients with atypical presentations of disease who were later diagnosed with SARS, emphasizing the difficulties in identifying SARS without a reliable diagnostic test. On admission, the patients did not have the SARS-typical fever (>38º because of chronic co-morbidities (Table 3). This raises questions about the sensitivity of temperature monitoring as a screening tool. Only some time later, the patients became febrile with clinical and radiological deterioration, and eventually met the SARS criteria. However, the four patients all showed lymphopenia and raised serum concentrations of lactate dehydrogenase. These nonspecific abnormalities could alert doctors in affected areas to atypical presentations (Fisher).

Thus, atypical presentations of SARS are a threat to patients, staff, and visitors. The WHO case definition is a useful epidemiological device; however, it is no substitute for daily, thorough clinical, laboratory, and radiological assessment of patients with symptoms of SARS (Fisher).

Table 3: Characteristics of four patients with atypical presentations of SARS*

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	71	43	78	63
Time to isolation (h)	3	8	4	12
Temperature on admission (°C)	38.7	37.3	36.3	36.0
WBC (10^9/L)	4.5	19.3	11.2	9.3
Lymphocytes (10^9/L)	0.78	0.94	0.69	0.63
LDH (IU/L)	747	2513	1032	1770
Initial diagnosis	Possible congestive cardiac failure	Pneumonia bilateral, possibly bacterial	Exacerbation of chronic lung disease, possible congestive cardiac failure	Congestive cardiac failure
Co-morbidities	Diabetes, ischemic heart disease	Hypertension	Connective tissue disease on steroids, ischemic heart disease	Ischemic heart disease
Outcome	Survived	Died	Died	Died

* modified from Fisher et al.

Chest Radiographic Abnormalities

Imaging plays an important role in the diagnosis of SARS and monitoring of response to therapy. A predominant peripheral location, a progression pattern from unilateral focal air-space opacity to unilateral multifocal or bilateral involvement during treatment, and lack of cavitation, lymphadenopathy, and pleural effusion are the more distinctive radiographic findings (Wong 2003b).

Chest Radiographs

At the onset of fever, 70-80 % of the patients have abnormal chest radiographs (Booth, Wong 2003b, Peiris 2003b). It should be noted that, in a substantial proportion of cases, chest radiographs may be normal during the febrile prodrome, as well as throughout the course of illness. In other cases, radiological evidence of pneumonic changes may precede the fever (Rainer), particularly in individuals with co-morbidities who may be impaired in their ability to mount a fever (Fisher 2003a).

Chest X-ray findings typically begin with a small, unilateral, patchy shadowing, and progress over 1-2 days to become bilateral and generalized, with interstitial or confluent infiltrates. Air-space opacities eventually develop during the course of the disease. In patients who deteriorate clinically, the air-space opacities may increase in size, extent, and severity (Tsang, Lee).

In the first large cohort from Hong Kong, 55 % of the patients had unilateral focal involvement and 45 % had either unilateral multi-focal or bilateral involvement at the onset of fever (Lee). Within a prospective cohort, initial involvement was confined to one lung zone in 49% and was multi-zonal in 21% of the patients (Peiris 2003b).

The initial radiographic changes may be indistinguishable from those associated with other causes of bronchopneumonia. The research group from Hong Kong suggested that chest radiographs might offer important diagnostic clues, in particular when, after approximately one week, unilateral, predominantly peripheral areas of consolidation progress to bilateral patchy consolidation, and when the extent of the lung opacities is correlated with the deterioration in respiratory function (Lee).

There seems to be a predominant involvement of the peripheral-zone. Pleural effusions, cavitation, and hilar lymphadenopathy are usually absent. Respiratory symptoms and positive auscultatory findings are disproportionally mild compared with the chest radiographic findings (Lee).

One large study focused on radiographic appearances and the pattern of progression (Wong 2003b). Within this cohort of 138 patients, four patterns of radiographic progression were recognized: type 1 (initial

radiographic deterioration to a peak level, followed by radiographic improvement) in 70.3%, type 2 (fluctuating radiographic changes) in 17.4%, type 3 (static radiographic appearance) in 7.3%, and type 4 (progressive radiographic deterioration) in 5.1% of the patients. Findings during deterioration are compatible with the radiological features of acute respiratory distress syndrome.

CT Scans

The predominant abnormalities found on initial CT scans are areas of sub-pleural focal consolidation with air bronchograms and ground-glass opacities (Tsang). The lower lobes are preferentially affected, especially in the early stages. Patients with more advanced cases show a more bilateral involvement (Wong 2003a). The lesions tend to be peripheral and smaller in the less severely affected lungs, also suggesting an earlier stage of the disease. In patients with more advanced cases, there is involvement of the central, perihilar regions by larger (>3 cm) lesions. The majority of the lesions contained an area of ground-glass opacification with or without consolidation. Other findings include intralobular thickening, interlobular septal thickening, a crazy-paving pattern, and bronchiectasis (Wong 2003a). Obvious bronchial dilatation is generally not found (Lee).

Radiographically, SARS may be indistinguishable from other severe forms of pneumonia. It also shares CT features with other conditions that result in subpleural air-space disease, such as the pneumonia of bronchiolitis obliterans and acute interstitial pneumonia (Tsang).

Radiologists from the Prince of Wales Hospital, Hong Kong, recommend the following protocol for diagnostic imaging of suspected SARS patients (Wong 2003a):

a) Patients with symptoms and signs consistent with SARS and with abnormalities on chest radiographs are followed up with serial radiography. CT scanning is not required for diagnosis.

b) Patients with symptoms and signs consistent with SARS and with a normal chest radiograph undergo thin-section CT to confirm the diagnosis. They subsequently undergo serial radiography for follow-up.

Diagnosis

Identifying hospitalized patients with SARS is difficult, especially when no epidemiological link has been recognized and the presentation of symptoms is non-specific. Patients with SARS might develop symptoms common to hospitalized patients (e.g., fever or prodromal symptoms of headache, malaise, and myalgia), and diagnostic testing to detect cases is limited (MMWR 52: 547-50). Unless specific laboratory tests (PCR, detection of SARS antibodies; see Chapter 7: Diagnostic Tests) confirm the initial suspicion of SARS infection, the diagnosis of SARS is based on the clinical findings of an atypical pneumonia not attributed to any other cause, as well as a history of exposure to a suspect or probable case of SARS, or to their respiratory secretions or other body fluids.

As mentioned above, during the early stages, SARS may be difficult to differentiate from other viral infections, especially when symptoms are unspecific (Rainer). The initial diagnostic testing for suspected SARS patients should include chest radiography, pulse oximetry, bacterial cultures of blood, sputum, and urine, serology for mycoplasma, chlamydia, influenza, parainfluenza, respiratory syncytial and adenoviruses, nasopharyngeal aspirates for viral cell cultures, and direct sputum smear for *Pneumocystis jiroveci* by silver stain. A specimen for Legionella and pneumococcal urinary antigen testing should also be considered (CDC, http://www.cdc.gov/ncidod/sars/diagnosis.htm).

The radiographic appearance of peripheral air-space opacities is indistinguishable from other causes of atypical pneumonia, such as Mycoplasma, Chlamydia, and Legionella, and overlaps with other types of viral pneumonia. The presence of an air-space opacity on chest radiographs has been helpful in the confirmation of the diagnosis (Wong 2003b).

Clinicians should save any available clinical specimens (respiratory, blood, and serum) for additional testing until a specific diagnosis is made. Acute and convalescent (greater than 21 days after the onset of symptoms) serum samples should be collected from each patient who meets the definition criteria for SARS. Specific instructions for collecting specimens from suspected SARS patients are available on the Internet: http://SARSreference.com/link.php?id=19

Table 4: Features of SARS that may commonly help with clinical diagnosis. Source: WHO

SARS	Example	Caution
Clinical history	Sudden onset of flu-like prodrome, dry cough, non-respiratory symptoms e.g. diarrhoea common	Take a travel history, history of hospitalisation and history of contact with healthcare facility. The absence of such a history should not automatically exclude diagnosis of SARS.
Clinical examination	Does not correlate with chest radiology changes	Lack of respiratory signs particularly in groups such as the elderly
Bedside monitoring	Hypoxia	Temperature may not be elevated on admission, respiratory rate should be documented
Haematology investigations	Low lymphocyte count	
Biochemistry investigations	Raised LDH	Check profile for electrolytes and liver function
Radiology investigations	CXR changes poorly defined, patchy, progressive changes	May present as a lobar pneumonia, pneumothorax and pneumomediastinum may occur
Microbiology investigations	Investigate for community, and hospital acquired pneumonias including atypical pneumonias	Concurrent infections may occur
Virology investigations	Investigate for other causes of atypical pneumonia	Interpret SARS test results with caution
Treatment	As yet there is not proven treatment for SARS, supportive measures are recommended	Lack of response to treatment with standard antibiotics for community acquired pneumonia including atypical pneumonia may be indicative of SARS

Clinical Course

The incubation period of SARS is short. Two large studies consistently noted a median incubation period of six days (Lee, Booth). However, the time from exposure to the onset of symptoms may vary considerably, ranging from 2 to 16 days (Lee, Tsang). This may re

flect biases in reporting, different routes of transmission, or varying doses of the virus (Donnelly). The WHO continues to conclude that the current best estimate of the maximum incubation period is 10 days (WHO Update 49).

The clinical course of SARS is highly variable, ranging from mild symptoms to a severe disease process with respiratory failure and death. Clinical deterioration combined with oxygen desaturation, requiring intensive care and ventilatory support, generally occurs 7 to 10 days after the onset of symptoms (Lee, Peiris). In severe cases, SARS is a fulminant disease, progressing from being "comfortable" to respiratory failure requiring intubation within less than 24 hours (Tsang, Fisher).

The first prospective study on the clinical course was published on May 24, 2003, in the Lancet (Peiris 2003b). This 24-day study included 75 adult patients from Hong Kong. The clinical course of SARS was remarkably uniform in this cohort, following a tri-phasic pattern in most cases:

1. Week 1 was characterized by fever, myalgia, and other systemic symptoms that generally improved after a few days. In terms of disease progression, all except one patient became afebrile within 48h using the standard treatment protocol, consisting of intravenous amoxicillin-clavulanate, oral azithromycin, intravenous ribavirin and a tailing regimen of corticosteroids.

2. As the disease progressed into week 2, the patients frequently had recurrence of fever, onset of diarrhea, and oxygen desaturation. Fever recurred in 85% of the patients at a mean of 8.9 days. Radiological worsening was noted in 80% at a mean of 7.4 days: Nearly half the patients developed shifting of radiological lesions, evidenced by improvement of the original lesions followed by the appearance of new lesions. IgG seroconversion, apparently correlating with falls in viral load, could be detected from day 10 to 15. Severe clinical worsening also occurred at this time.

3. 20% of patients progressed to the third phase, characterized by ARDS necessitating ventilatory support. Several patients developed nosocomial sepsis during this phase of end-organ damage and severe lymphopenia.

In total, 32% of patients required intensive care at a mean of 11.0 days after onset of symptoms, among whom 79% had to be intubated at a mean of 12.9 days. The mean length of stay for 75 patients was 22.1 days, whereas for the 15 patients who developed ARDS, the mean length of stay was 26.8 days at the time of writing. In this cohort, the total mortality was 7%.

The two retrospective cohorts from Canada and Hong Kong demonstrated a comparable outcome (Booth, Lee). Within both cohorts, 20-23% of the patients were admitted to the intensive care unit, and 59-69% of these received mechanical ventilation. Mortality was lower in these studies, ranging from 3.6% (Lee) to 6.5% (Booth) within the first 21 days.

However, it should be mentioned that the WHO revised its initial estimates of the case fatality ratio of SARS on May 7 (WHO Update 49). The revision was based on an analysis of the latest data from Canada, China, Hong Kong SAR, Singapore, and Vietnam. On the basis of more detailed and complete data, and more reliable methods, the WHO estimates that the case fatality ratio of SARS ranges from 0% to 50% depending on the age group affected, with an overall estimate of case fatality of 14% to 15%. According to the WHO, estimates of the case fatality ratio range from 11% to 17% in Hong Kong, from 13% to 15% in Singapore, from 15% to 19% in Canada, and from 5% to 13% in China.

Several studies have demonstrated a number of risk factors for a poor outcome. In most studies, multivariate analysis revealed an older age and co-morbid conditions as being independent predictors (Table 4).

Table 5 – Risk factors associated with clinical deterioration

Authors	N	Risk factors
Lee et al.	138	Older age, high neutrophil count, high LDH peak
Peiris 2003a	50	Older age, severe lymphopenia, impaired alanine aminotransferase, delayed starting of ribavirin and steroids
Peiris 2003b	75	Older age, chronic hepatitis B infection
Booth et al.	144	Diabetes mellitus and other co-morbid conditions, (trend for older age)
Wong et al.	157	Older age, high LDH
Wong et al.	31	Low CD4 and CD8 counts at presentation

There is currently no information as to whether virulent mutants of SARS viruses are associated with fatal cases. Comparison of the genomes of SARS isolates from fatal versus milder cases will identify any virus mutations that may be associated with an increased virulence (Holmes).

In a small percentage of patients, various degrees of pulmonary fibrosis have been reported following recovery. The pathophysiological mechanism of this finding is unclear. It will be important to perform follow-up evaluation of these patients to determine the long-term repercussions of SARS.

Viral Load and Immunopathological Damage

Quantitative RT-PCR of nasopharyngeal aspirates have shown a peak viral load at day 10 and a decrease to admission levels at day 15 (Peiris 2003b).

The increasing viral load at the end of the first week of the disease suggests that the symptoms and signs (recurrent fever, diarrhea, worsening of radiographic findings) could be related to the effect of viral replication and cytolysis (Peiris 2003b).

However, further deterioration at the end of week 2, when some patients had severe clinical worsening, may not be related to uncontrolled viral replication, but may rather be caused by immunopathological damage (Peiris 2003b). This assumption is supported by the

progressive decrease in rates of viral shedding from the nasopharynx, stool, and urine from day 10 to 21 after the onset of symptoms. In addition, nearly half the patients had shifting radiographic shadows. If viral-induced damage was the primary pathological mechanism, such a flitting pattern of radiological change is difficult to explain (Peiris 2003b).

Taken together, these findings suggest that the lung damage at this phase is related to immunopathological damage as a result of an over-exuberant host response, rather than uncontrolled viral replication (Peiris 2003b).

Histopathology

Lung Biopsy

The histopathological examination of a lung biopsy specimen from a patient with SARS showed a mild interstitial inflammation with scattered alveolar pneumocytes showing cytomegaly, granular amphophilic cytoplasm, and enlarged nuclei with prominent nucleoli. No cells showed inclusions typical of herpes virus or adenovirus infection (Peiris 2003a).

Postmortem Findings

Postmortem histopathological evaluations of lung tissue from patients who died from SARS showed diffuse alveolar damage at various levels of progression and severity, consistent with the pathologic manifestations of acute respiratory distress syndrome (Ksiazek, Tsang, Poutanen).

The changes included hyaline membrane formation, interstitial mononuclear inflammatory infiltrates, and desquamation of pneumocytes in alveolar spaces (Ksiazek, Nicholls). There were also scattered foci of alveolar myxoid fibroblastic tissue, a finding consistent with the early organizational phase of progressive pneumonia. Interalveolar septa were mildly thickened, with a mild mononuclear infiltrate (Tsang). Bronchial epithelial denudation, loss of cilia, and squamous metaplasia were early features (Nicholls). The presence of hemophagocytosis

supports the contention that cytokine dysregulation may account, at least partly, for the severity of the clinical disease (Nicholls).

Examination of the liver revealed microvesicular fatty change, focal hemorrhages, and hepatocyte necrosis with scattered acidophilic bodies. The spleen showed large areas of probable ischemic necrosis and some atypical lymphocytes in the periarteriolar sheaths (Poutanen).

In one series, autopsy of hemato-lymphoid organs from four patients showed neither enlarged lymph nodes in the peripheral soft tissues or other body parts, nor reactive lymphoid hyperplasia or T zone reaction. The splenic white pulps appeared atrophic with lymphoid depletion, and the red pulp was congested. Bone marrow appeared active with the presence of three lineages. No features of hypoplastic marrow or reactive hemophagocytic syndrome were noted (Wong R).

Discharge and Follow-up

The duration of shedding of the SARS virus from respiratory secretions of SARS patients appears to be variable. Some animals can shed infectious coronavirus persistently from the enteric tract for weeks or months without signs of disease, transmitting the infectious virus to neonates and other susceptible animals (Holmes). Studies are being done to learn whether the SARS virus is shed persistently from the respiratory and/or enteric tracts of some humans without signs of disease (Holmes). In the meantime, all SARS patients should limit interactions outside the home and should not go to work, school, out-of-home childcare, or other public areas until 10 to 14 days after the fever and respiratory symptoms have resolved. During this time, the infection control precautions for SARS patients should be followed. In a small study of 14 patients, none reported secondary cases in their household following their discharge home (Avendano).

At a follow-up visit one week after discharge, all 14 patients in one series still felt weak and complained of dyspnea on exertion. They all reported significant weight loss during their acute illness (mean 7 kg). Two patients had had a low grade fever (up to 37.5°C) for 2–3 days following discharge. Only 2 patients had persistence of a slight dry cough. The chest radiograph was clear for 7 patients and, although

improved, abnormalities on the chest radiograph persisted for the remaining 7 (Avendano). Two weeks later, the patients were no longer as weak, but still complained of easy fatiguability and dyspnea on climbing stairs. The cough was no longer present. The chest radiograph had cleared for an additional 2 patients. 5 patients still had an abnormal chest radiograph, but improvement was noted (Avendano).

Psychosocial Issues

Most patients express complaints consistent with depression and anxiety regarding various aspects of their disease, hospitalization, and personal and family impact (Maunder). Other patients report insomnia and nightmares. The psychosocial aspects associated with this illness should not be underestimated and warrant further investigation. In addition to the effect on the patients, the psychological impact on staff and their families was also noted to be significant (Avendano).

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Appendix: Guidelines

A small number of guidelines on the management of SARS have been published so far (Ho, WHO).

The WHO guidelines outlined below are constantly reviewed and updated as new information becomes available. Check the CDC website regularly for new updates. http://www.who.int/csr/sars/management/en/

WHO: Management of Severe Acute Respiratory Syndrome (SARS)

Revised: April 11

Management of Suspect and Probable SARS Cases

- Hospitalize under isolation or cohort with other suspect or probable SARS cases (see Hospital Infection Control Guidance, http://www.who.int/entity/csr/sars/infectioncontrol/en)
- Take samples (sputum, blood, sera, urine,) to exclude standard causes of pneumonia (including atypical causes); consider possibility of co-infection with SARS and take appropriate chest radiographs.
- Take samples to aid clinical diagnosis of SARS including:
- White blood cell count, platelet count, creatine phosphokinase, liver function tests, urea and electrolytes, C reactive protein and paired sera. (Paired sera will be invaluable in the understanding of SARS, even if the patient is later not considered a SARS case)

- At the time of admission the use of antibiotics for the treatment of community-acquired pneumonia with atypical cover is recommended.
- Pay particular attention to therapies/interventions which may cause aerosolization such as the use of nebulisers with a bronchodilator, chest physiotherapy, bronchoscopy, gastroscopy, any procedure/intervention which may disrupt the respiratory tract. Take the appropriate precautions (isolation facility, gloves, goggles, mask, gown, etc.) if you feel that patients require the intervention/therapy.
- In SARS, numerous antibiotic therapies have been tried with no clear effect. Ribavirin with or without use of steroids has been used in an increasing number of patients. But, in the absence of clinical indicators, its effectiveness has not been proven. It has been proposed that a coordinated multicentre approach to establish the effectiveness of ribavirin therapy and other proposed interventions be examined.

Definition of a SARS Contact

A contact is a person who may be at greater risk of developing SARS because of exposure to a suspect or probable case of SARS. Information to date suggests that risky exposures include having cared for, lived with, or having had direct contact with the respiratory secretions, body fluids and/or excretion (e.g. feces) of a suspect or probable cases of SARS.

Management of Contacts of Probable SARS Cases

- Give information on the clinical picture, transmission, etc., of SARS to the contact
- Place under active surveillance for 10 days and recommend voluntary home isolation
- Ensure contact is visited or telephoned daily by a member of the public health care team
- Record temperature daily

- If the contact develops disease symptoms, the contact should be investigated locally at an appropriate healthcare facility
- The most consistent first symptom that is likely to appear is fever

Management of Contacts of Suspect SARS Cases

As a minimum the following follow-up is recommended:

- Give information on the clinical picture, transmission, etc., of SARS to the contact
- Place under passive surveillance for 10 days
- If the contact develops any symptoms, the contact should self report via the telephone to the public health authority
- Contact is free to continue with usual activities
- The most consistent first symptom which is likely to appear is fever
- Most national health authorities may wish to consider risk assessment on an individual basis and supplement the guidelines for the management of contacts of suspected SARS cases accordingly.

Removal from Follow-up

- If, as a result of investigations, suspected or probable cases of SARS are discarded (no longer meet suspect or probable case definitions) then contacts can be discharged from follow-up.

Chapter 9: SARS Treatment

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The treatment of coronavirus-associated SARS has been evolving and so far there is no consensus on an optimal regimen. This chapter reviews the diverse treatment experience and controversies to date, and aims to consolidate our current knowledge and prepare for a possible resurgence of the disease.

Treatment strategies for SARS were first developed on theoretical bases and from clinical observations and inferences. Prospective randomized controlled treatment trials were understandably lacking during the first epidemic of this novel disease. The mainstream therapeutic interventions for SARS involve broad-spectrum antibiotics and supportive care, as well as antiviral agents and immunomodulatory therapy. Assisted ventilation in a non-invasive or invasive form would be instituted in SARS patients complicated by respiratory failure.

Antibiotic therapy

Anti-bacterial agents are routinely prescribed for SARS because its presenting features are non-specific and rapid laboratory tests that can reliably diagnose the SARS-CoV virus in the first few days of infection are not yet available. Appropriate empirical antibiotics are thus necessary to cover against common respiratory pathogens as per national or local treatment guidelines for community-acquired or nosocomial pneumonia (Niederman et al 2001). Upon exclusion of other pathogens, antibiotic therapy can be withdrawn.

In addition to their antibacterial effects, some antibiotics are known to have immunomodulatory properties, notably the quinolones (Dalhoff & Shalit 2003) and macrolides (Labro & Abdelghaffar 2001). Their effect on the course of SARS is undetermined.

SARS can present with a spectrum of disease severity. A minority of patients with a mild illness recover either without any specific form of treatment or on antibiotic therapy alone (Li G et al 2003; So et al 2003).

Antiviral therapy

Various antiviral agents were prescribed empirically from the outset of the epidemic and their use was continued despite lack of evidence about their effectiveness. With the discovery of the SARS-CoV as the etiologic agent, scientific institutions worldwide have been vigorously identifying or developing an efficacious antiviral agent. Intensive *in vitro* susceptibility tests are underway.

Ribavirin

Ribavirin, a nucleoside analog, was widely chosen as an empirical therapy for SARS because of its broad-spectrum antiviral activity against many DNA and RNA viruses. It was commonly used with corticosteroids and has since become the most frequently administered antiviral agent for SARS (Peiris et al 2003a, 2003b; So et al 2003; Tsang KW et al 2003; Poutanen et al 2003; Chan-Yeung & Yu 2003; Koren et al 2003; Lee et al 2003; Booth et al 2003; Tsang & Lam 2003; Chan et al 2003; Tsui et al 2003; Ho JC et al 2003).

The use of ribavirin has attracted a lot of criticism due to its unproven efficacy and undue side effects (Cyranoski 2003). Ribavirin at non-toxic concentrations has no direct *in vitro* activity against SARS-CoV (Huggins 2003; Cinatl et al 2003a; Health Canada July 2, 2003). Clinical experience so far, including quantitative reverse transcriptase polymerase chain reaction (RT-PCR) monitoring the nasopharyngeal viral load, has also not been able to suggest any substantial *in vivo* antiviral effect from this drug (Peiris et al 2003b). It is still a moot point as to whether or not the immunomodulatory actions of ribavirin, as found in other conditions (Ning et al 1998; Hultgren et al 1998), could also play a role in the treatment of SARS (Peiris et al 2003b; Lau & So 2003).

The prevalence of side effects from ribavirin is dose-related. High doses often result in more adverse effects, such as hemolytic anemia,

elevated transaminase levels and bradycardia (Booth et al 2003). However, lower doses of ribavirin did not result in clinically significant adverse effects (So et al 2003). Side effects have also been observed more frequently in the elderly (Kong et al 2003).

Neuraminidase inhibitor

Oseltamivir phosphate (Tamiflu®, Roche Laboratories Inc., USA) is a neuraminidase inhibitor for the treatment of both influenza A and B viruses. It was commonly prescribed together with other forms of therapy to SARS patients in some Chinese centers. Since there is no evidence that this drug has any efficacy against SARS-CoV, it is generally not a recommended treatment apart from in its role as an empirical therapy to cover possible influenza.

Protease inhibitor

Lopinavir-ritonavir co-formulation (Kaletra®, Abbott Laboratories, USA) is a protease inhibitor preparation used to treat human immunodeficiency virus (HIV) infection. It has been used in combination with ribavirin in several Hong Kong hospitals, in the hope that it may inhibit the coronaviral proteases, thus blocking the processing of the viral replicase polyprotein and preventing the replication of viral RNA.

Preliminary results suggest that the addition of lopinavir-ritonavir to the contemporary use of ribavirin and corticosteroids might reduce intubation and mortality rates, especially when administered early (Sung 2003). It thus appears worthwhile to conduct controlled studies on this promising class of drugs.

Human interferons

Interferons are a family of cytokines important in the cellular immune response. They are classified into type I (interferon α and β, sharing components of the same receptor) and type II (interferon γ which binds to a separate receptor system) with different antiviral potentials and immunomodulatory activities.

So far, the use of interferons in the treatment of SARS has been limited to interferon α, as reported from China (Zhao Z et al 2003; Wu et al 2003; Gao et al 2003) and Canada (Loutfy et al 2003). The Chinese experiences were mostly in combining the use of interferons with immunoglobulins or thymosin, from which the efficacy could not be ascertained. Faster recovery was observed anecdotally in the small Canadian series using interferon alfacon-1 (Infergen®, InterMune Inc., USA), also known as consensus interferon, which shares 88% homology with interferon α-2b and about 30% homology with interferon β.

In vitro testing of recombinant interferons against SARS-CoV was recently carried out in Germany (Cinatl et al 2003b) using interferon α-2b (Intron A®, Essex Pharma), interferon β-1b (Betaferon®, Schering AG) and interferon γ-1b (Imukin®, Boehringer Ingelheim). Interferon β was found to be far more potent than interferon α or γ, and remained effective after viral infection. Although interferon α could also effectively inhibit SARS-CoV replication in cell cultures, its selectivity index was 50-90 times lower than that of interferon β. These *in vitro* results suggested that interferon β is promising and should be the interferon of choice in future treatment trials.

Human immunoglobulins

Human gamma immunoglobulins were used in some hospitals in China and Hong Kong (Wu et al 2003; Zhao Z et al 2003). In particular, an IgM-enriched immunoglobulin product (Pentaglobin®, Biotest Pharma GmbH, Germany) was tried in selected SARS patients who were deteriorating despite treatment (Tsang & Lam 2003). However, as there was often concomitant use of other therapies such as corticosteroids, their effectiveness in SARS remains uncertain.

Convalescent plasma, collected from recovered patients, was also an experimental treatment tried in Hong Kong. It is believed that the neutralizing immunoglobulins in convalescent plasma can curb increases in the viral load. Preliminary experience of its use in a small number of patients suggests some clinical benefits and requires further evaluation (Wong et al 2003).

Alternative medicine

In China, traditional herbal medicine has been frequently used in conjunction with Western medicine to treat SARS, and is believed to be effective (Zhong & Zeng 2003; Xiao et al 2003; Lin L et al 2003; Zhao CH et al 2003).

Recently, glycyrrhizin, an active component derived from liquorice roots, was tested against SARS-CoV *in vitro* (Cinatl et al 2003a). It has previously been used in the treatment of HIV and hepatitis C virus infections, and was found to be relatively non-toxic with infrequent side effects (e.g. hypertension; hypokalemia). In Vero cell cultures, it could inhibit the adsorption, penetration and replication of SARS-CoV, and was most effective when administered both during and after viral adsorption. It has been postulated that the mechanisms are mediated through the nitrous oxide pathway (Cinatl et al 2003a). However, as glycyrrhizin can only act against SARS-CoV at very high concentrations, its clinical dosing and utility remain uncertain. It could perhaps be explored as an adjunct therapy for SARS, or continued as an ingredient or base in herbal preparations.

Immunomodulatory therapy

The rationale for using immunomodulatory therapy in SARS is based on the fact that acute infections in general can stimulate the release of proinflammatory cytokines. In SARS, there may be an excessive host response or cytokine dysregulation. This hypothesis may be substantiated from the observation that clinical deterioration can paradoxically occur despite a fall in the viral load as IgG seroconversion takes place (Peiris et al 2003b), as well as from autopsy findings which demonstrate a prominent increase in alveolar macrophages with hemophagocytosis (Nicholls et al 2003). A tri-phasic model of pathogenesis comprising viral replicative, immune hyperactive and pulmonary destructive phases was thereafter proposed (Peiris et al 2003b; Sung 2003). Intuitively, immunomodulatory therapy carefully applied during the hyper-immune phase may be an important treatment component in SARS.

Corticosteroids

Corticosteroids have been the mainstay of immunomodulatory therapy for SARS. Their timely use often led to early improvement in terms of subsidence of fever, resolution of radiographic infiltrates and better oxygenation, as described in many Chinese and Hong Kong reports (Zhong & Zeng 2003; Xiao et al 2003; Wu et al 2003; Zhao Z et al 2003; Meng et al 2003; So et al 2003; Lau & So 2003; Lee et al 2003; Tsang & Lam 2003; Ho JC et al 2003). However, there is much scepticism and controversy about the use of corticosteroids, centering on their effectiveness, adverse immunosuppressive effects and impact on final patient outcomes.

An early Singaporean report on five patients on mechanical ventilation indicated that corticosteroids showed no benefits (Hsu et al 2003). A retrospective series of over 320 patients from a regional hospital in Hong Kong concluded that two-thirds progressed after early use of ribavirin and corticosteroids, but only about half of these subsequently responded to pulsed doses of methylprednisolone (Tsui et al 2003). A cohort study also noted that about 80% of patients had recurrence of fever and radiological worsening (Peiris et al 2003b). This contrasted with another paper which described four patient stereotypes for pulsed methylprednisolone therapy, namely the good responder, good responder with early relapse, fair responder and poor responder. The good responders were the most common group (Tsang & Lam 2003). There was also a comparative study showing the efficacy and safety of pulsed methylprednisolone as an initial therapy compared with a lower dosage regimen (Ho JC et al 2003). On the contrary, pulsed methylprednisolone was identified as a major independent predictor for mortality (Tsang OTY et al 2003).

The inconsistencies of treatment outcomes in SARS (or other illnesses) could be due to differences in the timing, dosing and duration of corticosteroid use (Lau & So 2003; Meduri & Chrousos 1998). The following points have been emphasized (So et al 2003; Lau & So 2003):

1. The timing of initiating corticosteroids should coincide with the onset of a truly excessive immune response, which may be best represented by a combination of clinico-radiographic surrogate criteria. Too early use of corticosteroids may theoretically pro

long the viral replicative phase and increase the viral burden, whereas delayed administration may not be able to halt the cytokine storm and prevent immunopathological lung damage.

2. The dosage of corticosteroids should be chosen to sufficiently counterbalance the degree of hyper-immunity. It should be adjusted to individual body weight and disease severity, with the latter reflected by surrogate criteria before the immunological profile of SARS is fully understood.

3. The duration of corticosteroids should be adequate to maintain the optimized immune balance. Too short a course may result in a rebound of cytokine storm with lung damage, whereas protracted usage will put the patient at risk of various corticosteroid complications.

The ultimate aim should theoretically be to strike an optimal immune balance so that the patient can mount a sufficient adaptive immune response to eradicate the virus, but without the sequelae of irreversible lung damage from immune over-reactivity. A published protocol (Appendix 1) based on the above rationale was reported to have achieved satisfactory clinical outcomes (So et al 2003; Lau & So 2003).

Although corticosteroids can be beneficial, their use is not without risk. Profound immunosuppression, resulting from needlessly high doses or protracted usage of corticosteroids, not only facilitates coronaviral replication in the absence of an effective antiviral agent, but also invites bacterial sepsis and opportunistic infections. There has been one report of a SARS patient who died from systemic fungal infection (Wang et al 2003).

The common phenomenon of "radiological lag" (radiological resolution lagging behind clinical improvement) must be recognized. As long as the patient remains clinically stable, it is likely that an optimal immune balance has been reached, and most radiological infiltrates will resolve gradually on a diminishing course of corticosteroids over 2-3 weeks. No additional corticosteroids are necessary to hasten radiological resolution under such circumstances (Lau & So 2003; Yao et al 2003). Radiographic abnormalities arising from a superimposed bacterial pneumonia must also be differentiated from the progressive immunopathological lung damage of SARS, since the latter would result in adding further corticosteroids.

As superimposing infections add to the morbidity and mortality and offset the beneficial effects of corticosteroids in SARS, it is of vital importance that strict control of hyperglycemia during corticosteroid administration is implemented to reduce the chance of septic complications (Van den Berghe et al 2001) and measures are taken to prevent ventilator-associated pneumonia (Collard et al 2003). Successful control of superimposing infections also demands a judicious use of empirical and culture-directed antimicrobials.

In summary, corticosteroids must not be indiscriminately prescribed for SARS, but should only be used according to the above principles and by exercising good clinical judgment.

Other immunomodulators

Thymosin alpha 1 (Zadaxin®, SciClone Pharmaceuticals Inc., USA) is used in the treatment of chronic viral hepatitis B and C, and has also been administered to SARS patients in some Chinese hospitals (Zhao Z et al 2003; Gao et al 2003). It is a relatively safe product and may augment T-cell function. The role and effectiveness of this agent in SARS has not yet been determined.

Other immunomodulatory agents in anecdotal use included tumor necrosis factor blocking agents, namely etanercept (Enbrel®, Immunex Corporation, USA) and infliximab (Remicade®, Centocor Inc., USA), and some other compounds like cyclophosphamide, azathioprine, cyclosporin and thalidomide.

Assisted ventilation

Despite treatment efforts, some SARS patients still develop acute hypoxemic respiratory failure. According to the current literature, 20-30% of SARS warranted admission into intensive care units, and 10-20% eventually required intubation and mechanical ventilation.

The initial management of SARS-related respiratory failure is oxygen supplementation. If the oxygen saturation remains low or dyspnea persists, assisted ventilation, either through non-invasive or invasive means, has to be considered.

Non-invasive ventilation

Non-invasive ventilation (NIV) is instituted via a face or nasal mask, as distinguished from invasive ventilation which necessitates endotracheal intubation. It is a valuable treatment for acute respiratory failure of various causes, and can avoid complications associated with intubation and invasive ventilation (Baudouin et al 2002; Peter et al 2002). Its application in SARS may be of particular benefit since SARS patients are frequently treated with high dose corticosteroids, which predispose them to infections including ventilator-associated pneumonia.

NIV, as either continuous positive airway pressure (CPAP) or bi-level pressure support, was commonly employed in many Chinese hospitals (Zhong & Zeng 2003; Luo & Qian 2003; Liu et al 2003; Xiao et al 2003; Zhao Z et al 2003; Wu et al 2003; Li H et al 2003) and in one hospital in Hong Kong (So et al 2003). Its use can improve oxygenation and tachypnea within an hour, and this may help to prevent adding further corticosteroids for respiratory failure (Liu et al 2003). In general, NIV was found to be able to avoid intubation and invasive ventilation in up to two-thirds of SARS patients with deterioration (Xiao et al 2003; Zhao Z et al 2003; Unpublished data from Hong Kong).

NIV can be given using a CPAP of 4-10 cm H_2O or bi-level pressure support with an inspiratory positive airway pressure (IPAP) of <10 cm H_2O and an expiratory positive airway pressure (EPAP) of 4-6 cm H_2O. Contrary to the scenarios for non-SARS-related acute respiratory distress syndrome, higher pressures were generally not necessary and should be avoided whenever possible, because not only was there usually no additional clinical improvement observed, but it can also add to the risk of pneumothorax and pneumomediastinum. The latter conditions are known complications of SARS, even without assisted positive pressure ventilation (Peiris et al 2003b).

Although NIV can improve patient outcome, the infective risks associated with aerosol generation have hampered its use in many hospitals. Nevertheless, centers with experience have reported the use of NIV to be safe, if the necessary precautions are taken (Li H et al 2003; Zhao Z et al 2003; Unpublished data from Hong Kong). In addition to the recommended standard infection control measures for aerosol-

generating procedures (Centers for Disease Prevention and Control [CDC] May 6, September 23, 2003; World Health Organization [WHO] April 24, 2003), the use of exhalation ports which generate round-the-tube laminar airflow (e.g. Whisper Swivel II, Respironics Inc., USA) and viral-bacterial filters interposed between the mask and exhalation port may further reduce the infective risk.

Invasive mechanical ventilation

Patients with SARS-related respiratory failure who continue to deteriorate while on NIV, or in whom NIV is contraindicated, should be promptly intubated and mechanically ventilated. The actual endotracheal intubation procedure bears a high infective risk and healthcare workers must strictly adhere to all infection control measures. To minimize the risk, the procedure is best performed by highly skilled personnel (Lapinsky & Hawryluck 2003) using rapid sequence induction. Other approaches like a "modified awake" intubation technique and elective intubation upon recognizing signs of imminent need for airway management have been recommended (Cooper et al 2003).

Most centers (Lew et al 2003; Gomersall & Joynt 2003) used ventilation method and settings with reference to the strategies for acute respiratory distress syndrome (ARDS) (The ARDS network 2000). Both pressure and volume control ventilation can be employed. The tidal volume should be kept low at 5-6 ml per Kg of the predicted body weight, and plateau pressures be kept less than 30 cm H_2O. Positive end-expiratory pressure (PEEP) should also be titrated to as low as possible to maintain the oxygenation, since a high rate (34%) of barotraumas have been reported (Fowler et al 2003). Mechanically ventilated patients should be adequately sedated and a short-term neuromuscular blockade may be required for permissive hypercapnia.

Clinical outcomes

In this SARS epidemic, which eventually involved 8098 probable cases worldwide, the overall case-fatality ratio has been updated to 9.6%. Significant regional differences were seen. China had the greatest number (5327) of cases, but its case-fatality ratio was reported as being only 7%. Hong Kong came second with 1755 cases, of whom

17% died. Taiwan, Canada and Singapore followed, and their ratios were 11%, 17%, and 14% respectively (WHO September 23, 2003). Age-stratified ratios were estimated to be <1% in patients ≤24 years old, 6% in 25-44 years old, 15% in 45-64 years old, and >50% in elderly ≥65 years old (WHO May 7, 2003). The estimates in Hong Kong were 13% in patients <60 years old, and 43% in those ≥60 (Donnelly et al 2003).

In addition to age, death rates may be affected by other patient factors such as genetic predispositions, the immune status, pre-existing co-morbidities and cardiopulmonary reserve, and by the disease severity which depends theoretically on the viral strain's virulence, viral load and magnitude of the host's immune response. The rates may also be related to other factors such as case selection and volume, facilities and manpower, treatment strategies and regimens.

A multi-center study comparing four treatment regimens in Guangzhou, China, found that a regimen (Appendix 2) of early use of higher dose corticosteroids, coupled with nasal continuous positive airway pressure (CPAP) ventilation, produced the least mortality. All 60 clinically-defined SARS patients (mean age 30.5 years) treated with this regimen survived, 40% of them used CPAP and none required mechanical ventilation. Only a small number of deaths were recorded out of a further 160 cases treated with the same regimen (Zhao Z et al 2003).

Favorable protocol-driven treatment outcomes were also reported from a center in Hong Kong. The protocol (Appendix 1) was applied to 88 consecutively admitted SARS patients (mean age 42), of whom 97% were laboratory-proven cases. The overall mortality was 3.4% (3/88) occurring in patients aged ≥65 only, out of which two died from co-morbidities instead. 24% required intensive care unit admission, 14% received non-invasive ventilation (bi-level pressure support) and 10% invasive mechanical ventilation. High-resolution computed tomography performed 50 days after the commencement of treatment showed that most survivors did not have clinically significant lung scarring, and none required any form of pulmonary rehabilitation (Lau & So 2003).

Based on the treatment experiences of the above and other centers with similar outcomes, suffice it to say that SARS may not be a dis

ease of high mortality, at least in non-elderly patients. Even though a substantial portion may require a period of assisted ventilation, the mortality rate could be kept down to just a few percent by using appropriate management and therapeutic strategies.

Outlook

We have gained much experience in the treatment of SARS. Without being complacent, scientists and clinicians alike are striving for more effective treatment aiming to lower mortality and transmission rates as much as possible. This can only be achieved together with an increased understanding of the viral structure and processes (Holmes 2003; Thiel et al 2003) and by defining the potential targets for drug and vaccine development.

The development of vaccines and new drugs for human use usually take many years. To expedite the development, the collaborative efforts around the world that unraveled the etiologic agent of SARS will be continued. Previous knowledge obtained from the HIV may give us a lead (Ho D 2003; Kliger & Levanon 2003; De Groot 2003), as well as the information known about the existing vaccines for animal coronaviruses (Clarke 2003). Three-dimensional computer modeling of key viral proteins may also facilitate the search and design of antivirals (Anand et al 2003). On the other hand, massive random screening and targeted searching of potential compounds by various institutions have already tested hundreds of thousands of compounds *in vitro*, and have had several hits which could be targets for further research (Abbott 2003).

In addition to the antiviral studies, research on the gene expression profiles (Cameron et al 2003; Lin M et al 2003) and the disease immune profiles (Li Z et al 2003; Beijing Group of National Research Project for SARS 2003) are in progress. In the future, they may facilitate the diagnosis, monitoring and tailoring of specific immunotherapies.

While awaiting research breakthroughs, we have to rely on the existing treatment modalities, which have been overviewed in this chapter. It is envisaged that with the early use of efficacious antiviral agents singly or in combination, the necessity for high dose immunomodula

tory therapy may be decreased. Well-conducted randomized controlled trials on a sufficient number of cases are necessary to clarify the effectiveness of and controversies surrounding existing treatment regimens; however, these may not be feasible since large-scale outbreak will hopefully never be seen again with our heightened preparedness.

Appendix 1

A standardized treatment protocol for adult SARS in Hong Kong

From: So, et al. Lancet 2003;361:1615-6

(1) Antibacterial treatment

- Start levofloxacin 500 mg once daily intravenously or orally
- Or clarithromycin 500 mg twice daily orally plus amoxicillin and clavulanic acid 375 mg three times daily orally if patient <18 years, pregnant, or suspected to have tuberculosis

(2) Ribavirin and methylprednisolone

Add combination treatment with ribavirin and methylprednisolone when:

- Extensive or bilateral chest radiographic involvement
- Or persistent chest radiographic involvement and persistent high fever for 2 days
- Or clinical, chest radiographic, or laboratory findings suggestive of worsening
- Or oxygen saturation <95% in room air

Standard corticosteroid regimen for 21 days

- Methylprednisolone 1 mg/kg every 8 h (3 mg/kg daily) intravenously for 5 days
- Then methylprednisolone 1 mg/kg every 12 h (2 mg/kg daily) intravenously for 5 days
- Then prednisolone 0.5 mg/kg twice daily (1 mg/kg daily) orally for 5 days
- Then prednisolone 0.5 mg/kg daily orally for 3 days
- Then prednisolone 0.25 mg/kg daily orally for 3 days
- Then off

Ribavirin regimen for 10–14 days

- Ribavirin 400 mg every 8 h (1200 mg daily) intravenously for at least 3 days (or until condition becomes stable)
- Then ribavirin 1200 mg twice daily (2400 mg daily) orally

(3) Pulsed methylprednisolone

- Give pulsed methylprednisolone if clinical condition, chest radiograph, or oxygen saturation worsens (at least two of these), and lymphopenia persists
- Give as methylprednisolone 500 mg twice daily intravenously for 2 days, then back to standard corticosteroid regimen

(4) Ventilation

- Consider non-invasive ventilation or mechanical ventilation if oxygen saturation <96% while on >6 L per min oxygen or if patient complains of increasing shortness of breath

Appendix 2

A treatment regimen for SARS in Guangzhou, China

Extracted & modified from Zhao Z, et al. J Med Microbiol 2003; 52: 715-20

- Levofloxacin 200 mg twice daily plus azithromycin 600 mg daily intravenously.
- Recombinant interferon α 3.000.000 U daily intramuscularly (for 75% of their cases).
- If patients failed to respond (continuing high fever), with pulmonary infiltrates involving more than one pulmonary segment, or an expanding area of consolidation was observed, they were treated with high-dose methylprednisolone for 5-14 days (160-1000 mg daily depending on symptoms and X-ray results: 160 mg daily if one lobe was involved; 320 mg daily if >1 lobe; 25% needed an increase in dosage from 160 to 320-720 mg daily to maintain respiratory physiological parameters and to control temperature).
- Oxygen 3-5 L per min was given by mask if SaO2 <95% or, if patients felt short of breath, non-invasive continuous positive airway pressure (CPAP) ventilation was used.
- If CPAP failed (SaO2 <90%), mechanical ventilation was used.
- Immunoglobulins, thymic peptides or recombinant human thymus proteins were given to some critically ill patients.

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Chapter 10: Pediatric SARS

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Clinical Manifestation

Two studies have so far reported on SARS among children. In one study, persistent fever, cough, progressive chest radiograph changes and lymphopenia were noted in all 10 patients (Hon). Teenage patients presented with symptoms of malaise, myalgia, chill, and rigor similar to those seen in adults, whereas the younger children presented mainly with a cough and runny nose, and none had chills, rigor, or myalgia.

In the second study, fever was the presenting symptom in 19 of 21 children. Other prodromal symptoms reported included malaise, loss of appetite, chills, dizziness, and rhinorrhea. Headache, myalgia, diarrhea, sore throat, and skin rash were relatively uncommon (Chiu; Table 1). During the lower respiratory phase of the illness, approximately one half of the children had coughing, one third of which was productive. Dyspnea or tachypnea was uncommon (Chiu).

At presentation, all 21 children had normal hemoglobin values. The total white cell count was low in five children (23.8%). All neutrophil counts were normal. Twelve children (57.1%) had lymphopenia, and five (23.8%) had thrombocytopenia (Chiu). Subsequently, during the course of the disease, 19 children (90.5%) developed lymphopenia and ten of them (47.6%) had mild thrombocytopenia. All elevated activated partial thromboplastin time levels during the acute phase in six children (28.6%) subsequently returned to normal levels. D-dimer was abnormal in three children (14.3%). All children had normal renal function. Abnormal ALT levels were found in two children (9.5%) at admission. Mild biochemical hepatitis, defined as an elevation three times that of a normal ALT level with a normal bilirubin level, was observed in five children (23.8%). Fifteen children (71.4%) had a raised LDH level, and nine children (42.9%) had a raised CPK level (Chiu).

Table 1. Clinical features of children with severe acute respiratory syndrome*

Features	No. of Children (%)
Fever	19 (90.5)
Malaise	13 (61.9)
Loss of appetite	12 (57.1)
Chills	10 (47.6)
Cough	9 (42.9)
Dizziness	8 (38.1)
Rhinorrhea	7 (33.3)
Sputum	3 (14.3)
Dyspnea/tachypnea	3 (14.3)
Headache	3 (14.3)
Myalgia	2 (9.5)
Diarrhea	2 (9.5)
Sore throat	1 (4.8)
Rash	1 (4.8)

* from Chiu: Severe acute respiratory syndrome in children: experience in a regional hospital in Hong Kong

When comparing the 11 children below 12 years with the ten children 12 years and older, the older group had less cough. However, these children had higher temperatures, a longer duration of fever, and more constitutional upset in terms of malaise and dizziness. They had more derangement in laboratory variables, including platelet counts, ALT, LDH, and CPK. All of them received steroid treatment. The changes in their chest radiographs took a longer time to resolve (Chiu).

Radiologic Features

In the same series (Chiu), pneumonic changes on chest radiographs were present in ten children (47.6%) at admission, but all 21 children developed abnormal chest radiographs during the course of the disease. The primary radiological abnormality was airspace opacity. Unilateral focal opacity was the most common presentation and was found in 18 children (85.7%). Two children (9.5%) had unilateral multi-focal opacities, and one child (4.8%) had bilateral involvement. There was no particular distribution pattern. Peripheral zone involvement was found in six children (28.6%). The opacities found in the

chest radiographs of the children showed evidence of progression, with an increase in the size or involvement of multiple areas in 18 children (85.7%). Bilateral involvement was observed in ten children (47.6%). Chest radiographic abnormalities were worst on day 6.5 +/- 2.7 days after admission. Two children (9.5%) had high-resolution computerized tomography of the thorax done because of a high clinical suspicion of SARS, although chest radiographs were initially negative. Both tomographs were abnormal and showed the characteristic ground-glass opacities, as described previously in adults (Chiu).

Treatment

The treatment protocol proposed by Hon et al. is shown in Table 2. In this series, four teenagers required oxygen therapy and two needed assisted ventilation, whereas none of the younger children required oxygen supplementation (Hon). Among the 21 children reported by Chiu, only two children (9.5%) required supplemental oxygen. None of them required mechanical ventilation.

Table 2. Treatment of children with SARS*

Diagnosis of SARS suspected on admission	Intravenous cefotaxime, oral clarithromycin, and oral ribavirin** (40 mg/kg daily, given in two or three doses)
Fever persists >48 h	Oral prednisolone** (0·5 mg/kg daily to 2·0 mg/kg daily)
Patients with moderate symptoms of high fluctuating fever and notable malaise	Intravenous ribavirin** (20 mg/kg daily, given in three doses) and hydrocortisone** (2 mg/kg every 6 h) immediately after admission
Persistent fever and progressive worsening clinically or radiologically	Pulse intravenous methylprednisolone (10–20 mg/kg)

* from Hon: Clinical presentations and outcome of severe acute respiratory syndrome in children.

** Ribavirin was administered for 1–2 weeks and corticosteroid dose was tapered over 2–4 weeks.

Clinical Course

The clinical course seems to be much milder and shorter among patients less than 12 years of age (Hon, Chiu). In addition, the radiological changes are milder and generally resolve more quickly than in teenagers. Compared with adults and teenagers, SARS seems to have a less aggressive clinical course in younger children (Hon, Chiu). The reason why children with SARS fare better than adults and adolescents infected with the disease is unclear.

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