Kamps - Hoffmann

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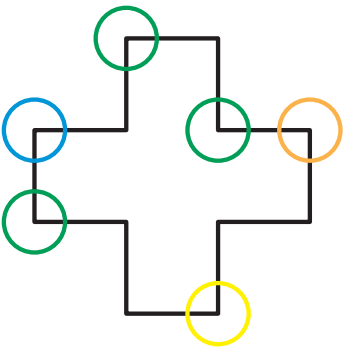

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Kamps and Hoffmann (eds.)

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Preface

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?"

8 Summary

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

www.HIVMedicine.com

May 8, 2003

Chapter 1: Summary

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

Mortalitiy, initially believed to be around 3 %, may well be as high as 15 %. The WHO now 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 access 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, if any, is unknown. For patients with progressive deterioration, intensive and supportive care is of primary importance. Immunomodulation by steroid treatment may be important.

Chapter 2: 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. (WER 7/2003) The illness is spread to household members and healthcare workers. 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. (WER 9/2003)

February 26

New reports of outbreaks of a severe form of pneumonia come in from Hong Kong, and Vietnam. The outbreak in Vietnam 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 became sick with similar symptoms. In some cases, this was 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, followed three days later by 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 travelling 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 on 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 rounds" 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 web site, http://www.who.int/csr/sars/cliniciansconference/en/.

So far, a total of 1,323 suspected and/or probable SARS cases, 49 of whom have died, have been reported from eight countries. Local transmission of SARS has been confirmed in Canada, Hong Kong, Singapore, Taiwan and Vietnam.

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 a doctor from southern China who arrived on 21 February 2003 and stayed in a local hotel (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5212a1.htm)

March 30

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 Garden 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 Guangdong Province of China consider postponing all but essential travel. (http://www.who.int/csr/sarsarchive/2003_04_02/en/). 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).

This updated travel advice comes as a result of new developments, particularly in Hong Kong, where a continued steep rise in the number of SARS cases is detected in a large housing estate consisting of ten 35-storey blocks, which are home to around 15,000 persons.

The WHO recommends that airport and port health authorities in affected areas undertake screening of passengers presenting for international travel. In addition, the WHO is issuing 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-microscopical 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 has now 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 worrisome is the evidence that the virus is spreading in the Chinese interior, where medical resources might be inadequate.

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 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.

Taiwan's government imposes a 10-day mandatory quarantine on all people arriving from China, Hong Kong, Singapore, Vietnam and the Canadian city of Toronto.

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.

April 30

In Beijing, rumors are circulating that the Chinese authorities might be ready to impose authoritarian measures to control SARS. The mayor still denies that Beijing, with a population of 13 million people, will soon be closed off from the rest of the world.

Hong Kong reports that a small number of people ("less than 10 out of more than 700, according to a Hospital Authority spokeswoman) who had previously been diagnosed as having recovered from SARS have become stricken again. In some cases, the illness returned more than two weeks after discharge.

May 1

The head of the WHO's clinical network, Mark Salter, says current death rates are at 6 percent, but could reach 10 percent.

May 2

The Xiaotangshan Hospital opened 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, today reported a cumulative total of 100 probable cases, with 11 new cases compared with yesterday. 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 diarrhoea (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).

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Chapter 3: Virology

Wolfgang Preiser, Christian Drosten

The search for the causative agent of SARS

The epidemic of severe atypical pneumonia which was observed in the Chinese province of Guangdong and reported internationally on February 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 focussed 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. Further tests did not confirm these findings.

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, although a concurrent *Chlamydia pneumoniae* infection was also found in the index patient from the outbreak in Frankfurt am Main (Drosten).

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.

Discovery of SARS Co-V

The etiologic agent of severe acute respiratory syndrome (SARS) is a coronavirus which was identified during the third week of March 2003, when laboratories in Hong Kong, Germany, and the United States 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 (Ksiazek, Drosten, Peiris).

The discovery of the novel agent was made less than two weeks after the WHO-led laboratory network came into existence. Three weeks later, on April 16, 2003, following a meeting of collaborating laboratories in Geneva, the WHO officially announced that this new coronavirus, never before seen in humans or animals, was the cause of SARS. 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: the pathogen 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 so infected.

The new virus was provisionally termed SARS-associated coronavirus (SARS-CoV). Shortly thereafter, complete genome sequences of the new coronavirus (Marra, Rota) were published by a Canadian laboratory and the CDC. The genome sequence data available so far from several SARS-CoV strains 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. 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).

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. Most but not all viral particles display the characteristic appearance of surface projections, giving rise to the virus' name (corona, Latin = crown) (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).

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 electron microscopy and PCR; and sputum or upper respiratory tract swab, aspirate, or wash specimens by PCR or isolation. (Ksiazek, Drosten)

High concentrations of viral RNA of up to 100 million molecules per milliliter were found in sputum. 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 virus may be shed in feces for prolonged periods of time. (Drosten)

Coronaviridae

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

There are three groups of coronaviruses; groups 1 and 2 contain mammalian viruses, while group 3 contains only avian viruses. The viruses are associated with a variety of diseases in humans and domestic animals, including gastroenteritis and disease of the upper and lower respiratory tract. Whereas animal coronaviruses may cause

severe disease in animals (i.e., porcine transmissible gastroenteritis virus, murine hepatitis virus, feline infectious peritonitis virus, and avian infectious bronchitis virus), human strains were previously associated only with mild diseases.

Human coronaviruses (HCoVs) are found in both group 1 (HCoV-229E) and group 2 (HCoV-OC43) and are a major cause of 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.

Stability and resistance

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

The preliminary results, obtained by members of the WHO multi-center 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 faeces and urine at room temperature for at least 1-2 days. The stability seems to be higher in stools from patients with diarrhoea (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.

Antiviral agents and vaccines

Efforts are underway at various institutions to assess potential anti-SARS-CoV agents in vitro. Ribavirin, a "broad spectrum" agent, which is active against various RNA viruses (Tam) has also been used clinically in SARS patients, but seems to lack the in vitro efficacy.

Likewise, efforts are underway to develop a vaccine that offers protection against SARS-CoV infection and/or disease. Although an effective vaccine cannot be expected to be available within less than at least one to two years, both 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 infectious peritonitis virus, are encouraging.

Outlook

The discovery of the SARS-associated coronavirus was the result of an unprecedented global collaborative exercise co-ordinated by the WHO. 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.

Control of the SARS epidemic will require the development of reliable diagnostic tests to diagnose patients and to monitor its spread, as well as of vaccines and antiviral compounds to prevent or treat this disease. Vaccines are successful in preventing coronavirus infections in animals, and the development of an effective vaccine against this new coronavirus is a realistic possibility. However, vaccination against coronaviruses in animal diseases is not uniformly successful. 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.

With the availability of different laboratory methods, a number of highly important questions regarding the natural history of the SARS-

associated coronavirus are now being addressed as a matter of urgency:

- When during the course of infection is virus shedding highest? What is the concentration of the virus in various body compartments? 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 the 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")?
- What is the origin of SARS-CoV? What is the animal reservoir, if any? Has this cross-species transmission to humans been a singular event or is there constant re-introduction?
- Are there environmental sources of SARS-CoV infection, such as food items, 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 ultrazentrifugation 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)

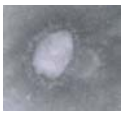
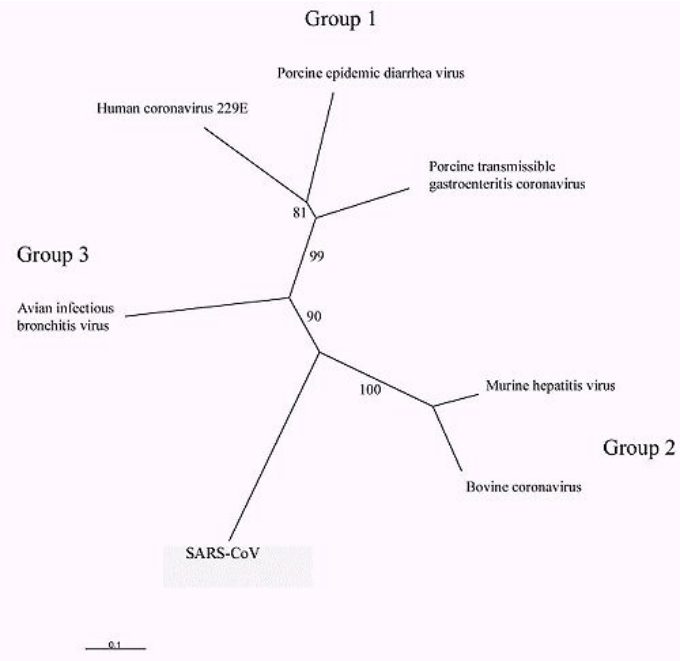


Figure 2. Cytopathic effect in Vero cell culture caused by SARS-associated coronavirus 24 hours post inoculation; for comparison: uninfected cell culture. (Source: Institute for Medical Virology, Director: H. W. Doerr; full-size picture: http://SARSReference.com/archive/cytopathiceffect.jpg, http://SARSReference.com/archive/uninfectedcells.jpg)

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 4: Transmission and Prevention

The initial clusters of cases in hotels and apartment buildings in Hong Kong have demonstrated that transmission of the SARS virus can be extremely efficient. The rapid spread of the disease among healthcare workers in Hanoi, Vietnam, and in hospitals in Hong Kong confirmed the highly contagious nature of the virus. Medical personnel, physicians, nurses, and hospital workers are among those commonly infected. As attack rates in access of 50 % have been reported (CDC, MMWR 2003;52:226-8), SARS might well evolve into the first global health crisis of the 21st century.

Routes of transmission

The mechanisms of transmission of the SARS virus are not yet fully understood. 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, seems to suggest that the virus is predominantly spread by droplets or by direct and indirect contact. (CDC, Seto). The infectious virus is present at very high concentrations in the respiratory tract of patients (Drosten). Low amounts of viral RNA have also been detected in the stools of patients late in their convalescence period (Drosten). This is reminiscent of characteristics of other coronaviruses (Cho), and feces are therefore potentially an additional route of transmission.

The airborne spread of SARS does not seem to be a major transmission route. 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 hotel M (CDC, MMWR 2003;52:241-248) 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.

WHO does not at present conclude that any goods, products or animals arriving from areas with SARS outbreaks pose a risk to public health. No restrictions in this regard are recommended. Information to

Member States regarding goods and animals arriving from SARS-affected areas (http://www.who.int/csr/sars/goods2003_04_10).

Amoy Gardens

Towards the end of March 2003, an outbreak of SARS occurred among residents of Amoy Gardens, Hong Kong, Within less than three weeks, there were a total of 320 SARS cases. The outbreak raised the possibility of an environmental source of infection. Preliminary findings suggest that the probable index patient of the outbreak was a patient suffering from chronic renal failure and that, in addition to person-to-person spread and 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). These findings were subsequently corroborated by results from studies which indicate that the SARS virus may not be killed by all commonly used detergents and that it may survive for at least 24 hours on a plastic surface at room temperature, and for up to four days in diarrheal stool (WHO). Interestingly, around 66% of Amoy Gardens SARS patients presented with diarrhoea as a symptom, compared with 2% to 7% of cases in other outbreaks.

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.

Viral factors

To date, there is no information as to whether different SARS virus strains may have different degrees of virulence.

Viral load

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.

Infectivity might therefore be variable over time, even during the symptomatic phase of the disease. Indeed, preliminary findings from sequential quantitative RT-PCR analyses of nasopharyngeal aspirates suggest that the viral load might peak at around day 10 after the onset of symptoms and then decrease to the levels obtained on admission at day 15 (Peiris II).

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, for example, through social contact (Peiris).

Diagnostic and therapeutic procedures

Diagnostic and therapeutic procedures inside the hospitals, such as diagnostic sputum induction, bronchoscopy, endotracheal intubation, and airway suction are potent aerosol-generating procedures. In these situations, standard droplets precautions have never been recognized as an effective infection control measure (Seto).

At least one serious outbreak in a public hospital in Hong Kong could have been due to 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).

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

Host factors

There is growing evidence that SARS has a less aggressive clinical course in younger children when compared with adults and teenagers (Hon). In addition, in one study, eight children had been attending school at the time of onset of the illness, and there was no evidence that they had spread the infection to their classmates. This finding is in sharp contrast to a very high infectivity rate of SARS among adults (Peiris, Lee). It has yet to be proven that a less aggressive clinical course is associated with a lower amount of viral shedding from the respiratory tract and therefore a minor degree of infectivity.

Prevention

National Response

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 countries with a high number of SARS cases, key epidemiological determinants of the magnitude and timescale of the epidemic include the interval between infection and onset of symptoms and between onset and hospital admission, the degree and duration of the infectiousness of the agent, and the extent of contact and mixing between infectious and susceptible people enabling transmission of the virus (Donnelly). Shortening the time from clinical onset to admission expedites isolation and reduces the effective infectious period and, thus, the risk of onward transmission (Donnelly).

The early introduction of quarantine procedures for SARS should be considered by health authorities. During March, health officials in Singapore, Hong Kong, and Canada implemented quarantine and isolation measures to limit the spread of SARS. 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.

Infection Control in Healthcare Settings

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. To protect healthcare workers and to prevent disease dissemination, strict infection control measures, and public education are essential (Chan-Yeung).

One study suggests that droplet infection with SARS might be the primary route of spread for the SARS virus (Seto) in the healthcare setting. 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. Surgical and N95 masks provided the best protection for exposed healthcare workers, whereas paper masks did not significantly reduce the risk of infection (Seto).

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

Table 1 shows a summary of precautions for droplet infection. For detailed information, see the CDC guidelines below.

Table 1: Precautions for droplet infection (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.

The implementation of aggressive infection control measures may be very effective in preventing the further transmission of SARS. In one hospital, no further transmission from a patient was observed after strict infection control measures involving the use of N95 masks, gown, gloves, and handwashing before and after patient contact were implemented (Hsu).

For doctors in the community, it is advisable to wear a N-95 mask when seeing any patient with respiratory symptoms (Chan-Yeung).

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:

- 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)
- Interim Domestic Guidance on the Use of Respirators to Prevent Transmission of SARS
- Infection Control Precautions for Aerosol-Generating Procedures on Patients who have Suspected SARS
  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

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 centres; 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.

Triage

Identifying persons who might be at risk of SARS on arrival to 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.

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 on this website.

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 on this website.

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.

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:

- Interim Guidance on Infection Control Precautions for Patients with Suspected SARS and Close Contacts in Households (see below)
- Interim Domestic Guidance on Persons Who May Have Been Exposed to Patients with Suspected SARS
- Interim Domestic Guidance for Management of Exposures to SARS for Health-Care and Other Institutional Settings

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, with 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 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

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Chapter 5: Epidemiology

As of May 5, 2003, severe acute respiratory syndrome (SARS) has been diagnosed in more than 6,000 patients from 29 countries.

Local Spread

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. Symptoms included cough, fever, and difficulty breathing (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

The global spread of SARS started in Hong Kong on February 21, 2003, when a doctor from the Guangdong province travelled to Hong Kong to visit his family and stayed on the 9th floor of a local hotel (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 the next day.

Hong Kong, February 2003

By the time he died, he had infected 10 guests who had been staying at the same hotel (MMWR 2003;52:241-248). These individuals were subsequently responsible for major outbreaks in hospitals in Hong Kong, in Vietnam, Canada, Singapore, and in Amoy Gardens, a housing estate in Hong Kong .

As soon as the extent of the epidemic was recognized, the Hong Kong health authorities 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. After the initial phase of exponential growth, the rate of confirmed cases fell to less than 20 per day by April 28 following the implementation of these guidelines (Figure 1).

To date, 1637 cases of SARS have been diagnosed in Hong Kong. 187 patients have died.

Vietnam, February 2003

The outbreak in Vietnam began on February 26, when a middle-aged Asian-American businessman was admitted to hospital in Hanoi with a high fever, dry cough, myalgia and mild sore throat. He had visited Hong Kong before traveling to Hanoi, where he became ill three days after his arrival. During his visit to Hong Kong, he had stayed at the same Hotel M as the index patient of the Hong Kong outbreak.

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

The government of Vietnam implemented a nationwide control system, including daily follow-up of contacts of probable SARS cases and community surveillance for suspected SARS cases.

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 change in Vietnam's status followed 20 consecutive days (the duration of two incubation periods) after the last new case was detected.

The absence of any new cases for a continuous 20-day period (as of April 28) 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. Vietnam was one of several countries, affected by the local transmission of SARS, that had implemented detection and protection measures including (WHO, WER 18/2003):

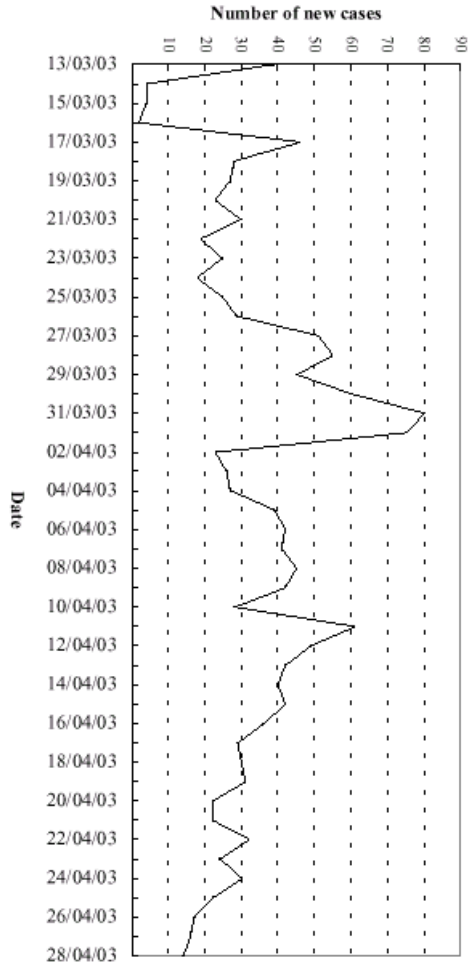

Figure 1. New SARS cases in Hong Kong

At the end of April, the daily number of new cases ranged from 2 to 80 and a peak was seen at the end of March, which was mainly attributable to the upsurge of cases in Amoy Gardens. The average daily number of new cases reported in the first 4 weeks of April was 39, 44, 30 and 22 respectively (Government of Hong Kong Special Administrative Region).

- 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 travellers;
- timely and accurate reporting and sharing of information with other authorities and/or governments.

Toronto, February 2003

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 patient 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 nonproductive 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).

To date, 148 cases of SARS have been diagnosed in Canada, most of them in the Toronto area. 22 patients have died. On April 23, the WHO (Update 37) recommended that persons planning to travel to Toronto consider postponing all but essential travel. Five days later, the travel advice was lifted again (WHO Update 42), on the grounds of three changes over the preceeding week: the decreased magnitude of probable SARS cases; a twenty day period without any new cases of community transmission; and no new confirmed exportation 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. Over a period of several days, she infected at least 20 other people.

No further transmission from this patient was observed after strict infection control measures were implemented. These involved use of N95 masks, gown, gloves, and handwashing before and after patient contact (Hsu).

To date, 204 cases of SARS have been diagnosed in Singapore. 26 patients have died.

Beijing 2003, April 20

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 announced more than 400 (WHO Update 35) new SARS cases. Additional reports (WHO Update 36) indicate that SARS has now spread to some of China's poorer 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, 4280 cases of SARS have been diagnosed in China. 206 patients have died.

Taiwan, late April 2003

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.

The number of cases began to increase steadily in the last weeks of April. Several staff at two hospitals became infected. On April 28, the Taiwanese government imposed a mandatory 14-day quarantine on all incoming travellers from China, Hong Kong, Singapore, Macau and Toronto, Canada.

To date, 116 cases of SARS have been diagnosed in Taiwan. 8 patients have died.

Other countries

The number of probable SARS cases reported from other countries over the time period November 1, 2002 to May 5, 2003, is shown in Table 1. Updated data are available at http://www.who.int/csr/sars/en/

Country	Cumulative number of case(s)	Number of deaths	Number recovered
Australia	4	0	4
Brazil	2	0	2
Bulgaria	1	0	0
Canada	148	22	93
China	4280	206	1433
China, Taiwan	116	8	25
France	5	0	4
Germany	7	0	7
Hong Kong	1637	187	930
Indonesia	2	0	1
Italy	9	0	4
Kuwait	1	0	1
Macao	1	0	0
Malaysia	7	2	4
Mongolia	8	0	4
New Zealand	1	0	1
Philippines	3	2	1
Poland	1	0	0

Republic of Ireland	1	0	1
Republic of Korea	1	0	0
Romania	1	0	1
Singapore	204	26	149
South Africa	1	1	0
Spain	1	0	1
Sweden	3	0	2
Switzerland	1	0	1
Thailand	7	2	5
United Kingdom	6	0	6
United States	61	0	26
Viet Nam	63	5	58
Total	**6583**	**461**	**2764**

Notes:
The cumulative number of cases includes the number of deaths.

Map of Cumulative Number of Reported Probable Cases

The geographical distribution of reported probable SARS cases on May 5, 2003, is available at the SARS Reference archive: http://SARSReference.com/archive/whomap2003_05_05b.gif.

Check for updates at http://www.who.int/csr/sars/en/.

SARS in children

SARS seems to have a less aggressive clinical course in younger children in comparison to that seen in adults and teenagers (Hon) (see also the chapter on Pediatric SARS). Up until April 25, children less than 15 years of age, accounted for only 3 % of all cases reported in Hong Kong. The reason for this is unclear (Health, Welfare & Food Bureau).

Age group	Male	Female
0-14	3%	3%
15-24	4%	7%
25-34	10%	16%
35-44	9%	12%
45-54	6%	9%
55-64	4%	4%
65 or above	9%	5%
Total	**44%***	**56%**

* This figure is slightly different to the sum of the relevant seven individual age groups (by 1%) due to the rounding effect.

Outlook

As of this writing (May 8, 2003), most countries that report probable SARS cases are dealing with a small number of imported cases. When these cases are promptly detected, isolated, and managed according to strict procedures of infection control, further spread to hospital staff and family members either does not occur at all or results in a very small number of secondary infections (Chan-Yeung).

Outbreaks of SARS seem to have peaked in Canada, Singapore, Hong Kong and Vietnam, but not in China. The new outbreak in Taiwan is of concern.

Many questions still remain unsolved. When epidemiologic evidence indicates that face-to-face contact still appears to be the most common mode of spread, why do a few persons seem to be especially infectious whereas the majority are less likely to serve as sources of infection? Airborne transmission appears to be the exception rather than the rule for the spread of SARS, although it accounted for the extensive spread within buildings and other confined areas in Asia. Why has SARS shut down public life in Beijing, but not in Shanghai (WHO Update 40)?

And finally, 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 Africa? 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?

Again, we don't know. It is the nature of epidemics to be unpredictable (Bloom).

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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.

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

- 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.

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

- detection of the SARS-CoV antibody by indirect fluorescent antibody (IFA) or enzyme-linked immunosorbent assay (ELISA)
- isolation of SARS-CoV in tissue culture

- detection of SARS-CoV RNA by reverse transcriptase-polymerase chain reaction (RT-PCR), which must be confirmed by a second PCR test

Negative laboratory results for PCR, viral culture, or antibody tests obtained within 21 days of illness do not rule out coronavirus infection. In these cases, an antibody test of a specimen obtained more than 21 days after the onset of illness is needed to determine infection.

The "Updated Interim Surveillance Case Definition for Severe Acute Respiratory Syndrome (SARS)", published April 29, 2003, is available on the Internet at

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5217a5.htm

Chapter 7: Diagnostic Tests

Wolfgang Preiser, Christian Drosten

Laboratory tests

Due to the efforts of the WHO-led international multi-centre 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/) for the first time includes laboratory results: 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

The 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 web site (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/) is available (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. On the other hand, contamination of samples in laboratories may 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.

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) 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.

The following test formats are being developed, but are not yet commercially available:

– 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 immunofluorescence-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 will soon be available commercially.

– Neutralisation 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 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 titre 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 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 standardisation 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 organisations 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/).

Table, Figures

Table 1: Currently (May 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
Neutralisation 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

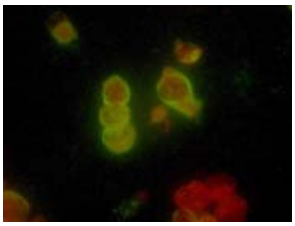
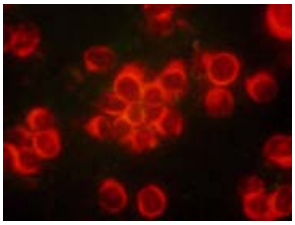


Figure 2. Immunofluorescence assay (IFA): SARS-CoV-infected Vero cells incubated with negative control serum. (Source: Source: Institute for Medical Virology, Director: W. Doerr)

http://www.sarsreference.com/archive/verocells_controlserum.jpg



Chapter 8: Diagnosis

Clinical Presentation

The clinical presentation of SARS is unspecific. The symptoms may resemble those of other forms of "atypical pneumonia" which are usually caused by legionella, mycoplasma and chlamydia species. After an incubation period of 2 to 10 days, patients develop a fever (> 38.0° C) associated with other symptoms including chills, rigors, headache, dizziness, malaise, and myalgia (see Table 1) (CDC, Lee, Tsang, Peiris, Chan-Yeung). Sputum production, sore throat, coryza, nausea and vomiting, and diarrhea are less common (Lee).

Table 1 – Cinical symptoms at presentation (in %)

	Lee, et al. n=138	Peiris, et al. n=50
Fever	100	100
Chills or rigors	73	74
Cough	57	62
Myalgia	61	54
Malaise	n.a.	50
Runny nose	23	24
Sore throat	23.	20
Shortness of breath	n.a.	20
Diarrhea	20	10
Headache	56	20

Physical examination reveals a high body temperature in most patients. Inspiratory crackles may be heard at the base of the lung. Wheezing is generally absent.

The most common laboratory abnormalities include lymphopenia, leukopenia, thrombocytopenia, elevated lactate dehydrogenase levels, elevated aspartate aminotransferase levels, and elevated creatine kinase levels (Lee, Tsang, Poutanen, Peiris, Chan-Yeung, see Table 2). Leukopenia is mainly caused by decreasing lymphocyte counts over the first few days following admission. In one study,

none of the patients with elevated creatine kinase levels had abnormal values of creatine kinase MB or troponin T, indicating that the source of creatine kinase was unlikely to be cardiac muscle (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
Creatinine 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.

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. Future diagnostic tests will make these investigations possible.

Chest Radiographic Abnormalities

Chest radiographs may be normal during the febrile prodrome and throughout the course of illness. However, at the onset of fever, most patients have abnormal chest radiographs with air-space consolidation (Lee). 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.

In one cohort, 59 out of 108 patients (54.6 percent) had unilateral focal involvement and 49 (45.4 percent) had either unilateral multifocal or bilateral involvement. Air-space opacities developed in all patients eventually during the course of the disease. The initial

radiographic changes were indistinguishable from those associated with other causes of bronchopneumonia. There was a predominant involvement of the peripheral-zone. Pleural effusions, cavitation, and hilar lymphadenopathy were absent (Lee). Respiratory symptoms and positive auscultatory findings were disproportionally mild compared with the chest radiographic findings (Lee).

In patients who deteriorate clinically, the air-space opacities may increase in size, extent, and severity 7 to 10 days after admission (Tsang, Lee).

The predominant abnormalities found on initial CT scans were areas of subpleural focal consolidation with air bronchograms and ground-glass opacities. These usually occur in the posterior aspects of the lower lobes (Tsang). The characteristic peripheral alveolar opacities may resemble those found in the pneumonia caused by bronchiolitis obliterans. 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).

One 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).

Clinical Course

The severity of the illness is highly variable, ranging from mild symptoms to a severe disease process with respiratory failure (> 20 %) and death. Increased 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). Mortality might be as high as 50 %, depending on the age group affected, with an overall estimate of case fatality of 14% to 15% (Donnelly, WHO Update 49).

Body temperature normally remains above baseline during the progression of the disease. In the first published follow-up study, patients developed recurrent fever (85.3%) on day 8.9 ± 3.1 (range 4 to 18), watery diarrhoea (73.3%) on day 7.5 ± 2.3 (range 3 to 15), radiological deterioration (80%) on day 7.4 ± 2.2 (range 3 to 13) and respiratory deterioration (45.3%) on day 8.6 ± 3 days (range 5 to 19) (Peiris II).

In 45.3% of patients, a marked improvement of the initial pulmonary lesions was closely associated with the appearance of new radiological lesions at other sites (Peiris II).

Interestingly, quantitative RT-PCR of nasopharyngeal aspirates consistently demonstrated a peak viral load at day 10 and a decrease to admission levels at day 15. This finding suggests that deterioration during the second week may not be related to uncontrolled viral replication but may rather be caused by immunopathological damage (Peiris II).

Risk factors that have been associated with a progressive disease are summarized in Table 3.

Table 3 – Risk factors associated with clinical deterioration

Authors	n	Risk factors
Lee et al.	138	Older age, high neutrophil count, high LDH peak
Peiris et al.	50	Older age, severe lymphopenia, impaired alanine aminotransferase, delayed starting of ribavirin and steroids
Peiris II et al.	75	Older age, chronic Hepatitis B infection

In a small percentage of patients, various degrees of pulmonary fibrosis have been reported following recovery. The pathophysiological mechanism of this finding is unclear. True relapses of SARS, although possible, seem to be rare. However, the possible development of long-term sequelae requires careful post-treatment surveillance.

Diagnosis

Unless specific laboratory tests (PCR, detection of SARS antibodies; see Chapter "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.

The initial diagnostic testing for suspected SARS patients should include chest radiography, pulse oximetry, blood cultures, sputum Gram stain and culture, and testing for viral respiratory pathogens, notably influenza A and B and respiratory syncytial virus. A specimen for Legionella and pneumococcal urinary antigen testing should also be considered (CDC, http://www.cdc.gov/ncidod/sars/diagnosis.htm).

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.

In the early stages, SARS may be hard to differentiate from other viral infections, and diagnostic delays may contribute to the spread of the epidemic (Hsu).

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).

Postmortem Findings

Post mortem 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). 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).

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).

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Chapter 9: Treatment

At present, the most efficacious treatment regimen for SARS, if any, is unknown. For patients with progressive deterioration, intensive and supportive care is of primary importance.

Ribavirin and steroids are the drugs which have been administered most frequently over the past two months. Ribavirin is a broad-spectrum purine nucleoside analog antiviral agent that is structurally related to guanosine. It shows antiviral activity against a variety of RNA viruses and is usually used in combination with interferon to treat infection with the hepatitis C virus. The rationale for the administration of steroids is the observation that changes in lung tissue suggest that part of the lung damage is due to cytokines induced by the microbial agent.

The combination of ribavirin and steroids is generally thought to be responsible for some clinical improvement in SARS patients (Lee, Poutanen, Tsang). Some clinicians, however, failed to observe a clinical benefit when using smaller doses of steroids than those used in Hong Kong (Hsu). The best treatment results obtained from using a combination of ribavirin and steroids have thus far been reported from Hong Kong. The following empirical treatment has been suggested, initially based on the experience obtained from a small number of cases, and subsequently confirmed by favourable results in a greater proportion of patients (see Table 1).

However, even in Hong Kong, the question as to whether Ribavirin should continue to be part of the therapeutic regimens, continues to be debated. Some physicians no longer use the drug, while others continue to use it (Moira Chan-Yeung, personal communication, May 5).

In Canada, Health officials decided on May 1 that the Special Access Programme (parenteral ribavirin is not approved for sale in Canada) will no longer provide routine access to ribavirin for the treatment of SARS (Health Canada). This decision was made after reviewing the existing anecdotal clinical experience with ribavirin, negative results from in vitro testing with ribavirin against SARS related coronavirus, and knowledge of reports of serious and unexpected adverse drug reactions.

Table 1: Empirical treatment of SARS*

Drug	Administration
Ribavirin	8 mg/kg every 8 hours intravenously or 1.2 g every 12 hours orally, with an oral loading dose of 4 g for those with normal renal function tests. Administer for 7-14 days depending on the response and the time of tailing off of corticosteroids.
Hydrocortisone	2 mg/kg every six hours or 4 mg/kg every 8 hours intravenously. Tail off over one week when there is clear clinical improvement. For severe and rapidly deteriorating cases give methylprednisolone 10 mg/kg every 24 hours intravenously for two days, and then continue with hydrocortisone as above.
Antibacterial drugs	Coverage for typical and atypical agents for 7-14 days using drugs such as levofloxacin and macrolides.
Patients should be given anti-ulcer prophylaxis and monitored for haemoglobin concentration, reticulocyte count,and blood glucose and potassium concentrations. The efficacy of this regimen requires careful assessment	

* as suggested by the Hospital Authority, Hong Kong (from Chan-Yeung)

Since Ribavirin is a known teratogen and a drug that can potentially cause severe adverse events, including severe hemolytic anemia (Koren), physicians currently treating patients with ribavirin are strongly advised to critically re-examine the risk/benefit for each patient before continuing treatment.

Another antiviral drug, licensed for treating influenza, the neuraminidase inhibitor oseltamivir (Tamiflu®), has so far not shown any proven efficacy (Lee, Poutanen).

Mechanical Ventilation

Patients who require mechanical ventilation generally fulfill the diagnostic criteria for ARDS with diffuse infiltrates on chest radiography and hypoxemia without evidence of left ventricular failure. Therapy is supportive (Poutanen).

The best approach for ventilatory support of patients with SARS is not known but should probably follow a lung-protective strategy that has

been shown to decrease mortality in patients with ARDS (ARDS Network, 2000).

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)
- Take samples (sputum, blood, sera, urine,) to exclude standard causes of pneumonia (including atypical causes); consider possibility of coinfection with SARS and take appropriate chest radiographs.
- Take samples to aid clinical diagnosis SARS including:
- White blood cell count, platelet count, creatine phosphokinase, liver function tests, urea and electrolytes, C reactive protein and paired sera. (Pair 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 aerolization 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 multicentred approach to establishing 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. faeces) of a suspect or probable cases of SARS.

Management of Contacts of Probable SARS Cases

- Give information on 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 health care 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 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.

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Pediatric SARS

One study has so far reported on SARS among childen. Persistent fever, cough, progressive chest radiograph changes and lymphopenia were noted in all 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.

The children were treated with high-dose ribavirin, oral prednisolone, or intravenous methylprednisolone, with no short-term adverse effects:

Table 1. 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 Hsu: 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.

Four teenagers required oxygen therapy and two needed assisted ventilation, whereas none of the younger children required oxygen supplementation. The clinical course was much milder and shorter among patients less than 12 years of age. In addition, the radiological changes were milder and generally resolved more quickly than in the teenagers. Compared with adults and teenagers, SARS seems to have a less aggressive clinical course in younger children (Hon).

Eight out of the ten children had been attending school at the time of presentation. There was no evidence that they had spread the infection to their classmates. This finding is in sharp contrast to the experience reported among adults that SARS carries a high infectivity rate (Hon).

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