Emerging Diseases:

A Novel Coronavirus and the Severe Acute Respiratory Syndrome (SARS) Epidemic

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Internal Medicine Grand Rounds
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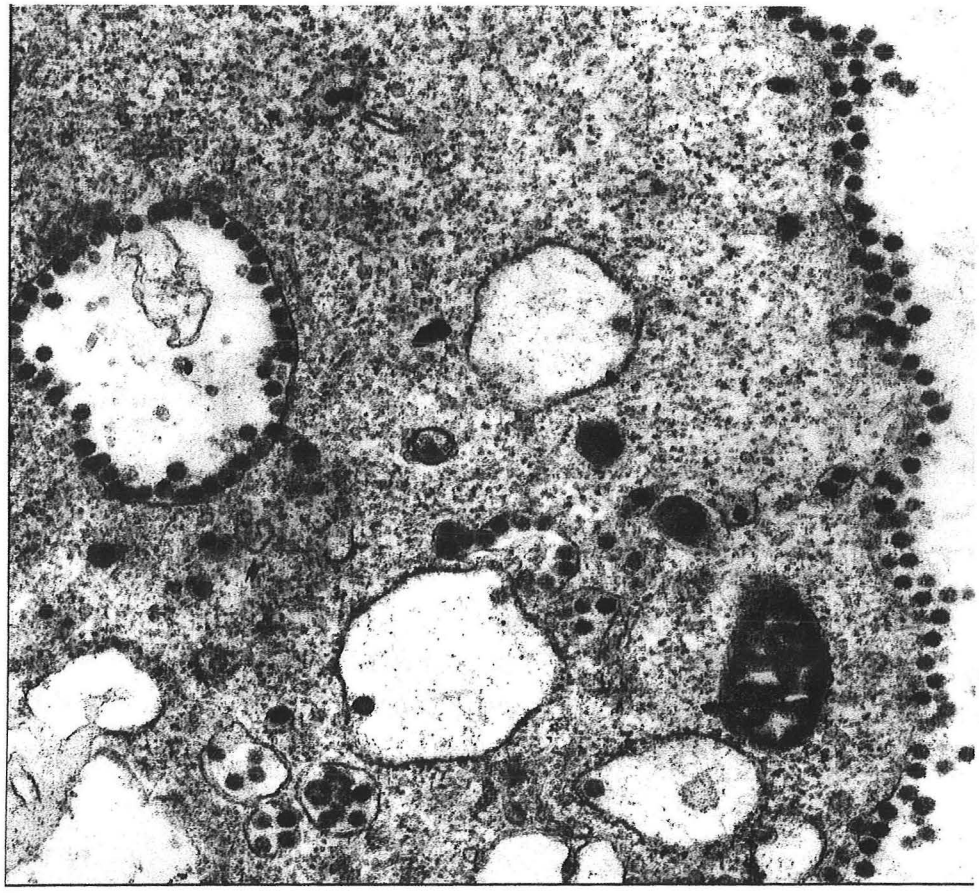


This is to acknowledge that Dr. Race has not disclosed any financial interests with commercial concerns related directly to this program. Dr. Race will be discussing off-label uses in her presentation.

Genesis of the Severe Respiratory Syndrome (SARS) Outbreak

SARS first emerged in farmers / locals of Guangdong Province, China in November of 2002. On February 9, 2003 WHO received a report about an outbreak of acute respiratory syndrome from China. The outbreak affected Guandong province with 305 cases and 5 deaths. Tests came back negative for influenza. On February 14: WHO published a report in its Weekly Epidemiological Record. By February 20, 2003: Chinese Ministry of Health had reported to WHO that the infectious agent was probably *Chlamydia pneumoniae* (found in two fatal cases).

Retired nephrologist (Dr. Liu Jianlun; Pt A) traveled from Guangdong Province to Hong Kong to visit family in February 2003. He began to note symptoms of a respiratory illness on February 15,2002. On 2/21/03, he checked into a 9th floor room of Hotel M. Shortly thereafter, on 2/22/03, Dr. Jianlun sought medical attention at Sun Yat-Sen Hospital (Hospital 2) & requested that he be isolated; he then expired on 3/4/03. Two members of his family also contracted SARS, and one expired. Four HCW's were exposed during his hospital stay and contracted the new infection.

The index case for Hong Kong (Patient J) visited Pt A at Hotel M in late February and developed a respiratory illness within a few days. He was admitted to another hospital (Hospital 1) on 3/4/03. Unfortunately, the hospital staff failed to recognize and isolate the patient, leading to a major nosocomial outbreak of SARS.[1,17]

Twelve additional guests at Hotel M became infected; ten of whom had stayed at Hotel M the same day as Dr. Jianlun. Their subsequent international travel, combined with the nosocomial cases, ultimately resulted in the global dissemination of this previously localized emerging disease.

By 3/11/03, the Hong Kong Department of Health (HKDOH) had received a report of an outbreak of pneumonia in health care workers (HCW's). at a public hospital. 25 out of 56 hospital staff were ill with high fever, muscle aches, headache and sore throat. Ten HCW's presented with radiographic signs of pneumonia, and some were in acute respiratory distress. On March 14, WHO reported detection of the outbreak in Hong Kong and Vietnam. (See diagram below from Sampathkumar P, et al., Ref. 17).

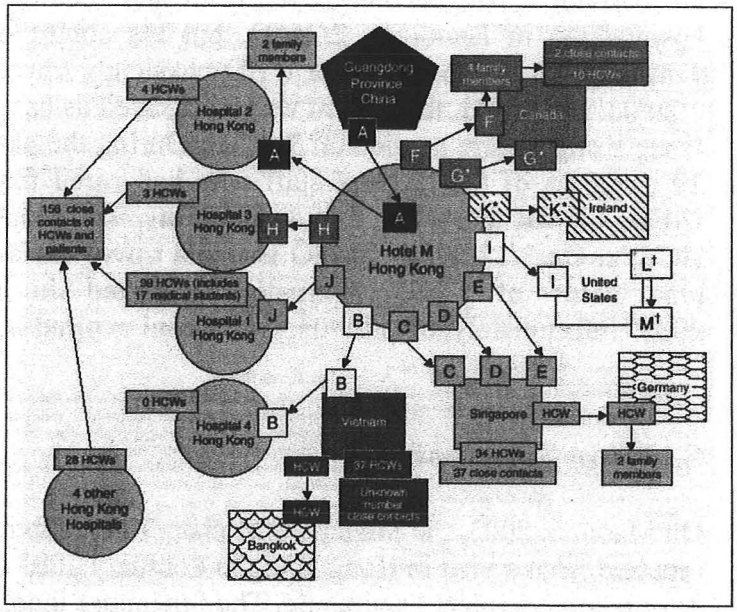


Figure 1. Chain of transmission of severe acute respiratory syndrome from the initial patient to other guests at Hotel M in Hong Kong in 2003. *All guests except G and K stayed on the ninth floor of the hotel. Guest G stayed on the 14th floor, and guest K stayed on the 11th floor. †Guests L and M (spouses) were not at Hotel M during the same time as index guest A but were at the hotel during the same times as guests G and H and were ill during this period. HCWs = health care workers. From the Centers for Disease Control and Prevention.[2]

Clinical Correlates of SARS Patients in Hong Kong[2]

138 suspect cases of SARS associated with a hospital outbreak
Incubation period 2-16 days (median 6 days)
Fever in all cases
Rigor & chills in >70% of cases
Cough in >50% of cases
Dizziness in >40% of cases
Predictors of intensive medical care or death:
Advanced age
High neutrophil count
High peak lactate dehydrogenase

On 3/25/03, the HKDOH recognized the existence of almost 300 cases of an acute, severe respiratory illness, and reports emerged that 13 of these patients had in fact stayed at Hotel M.

SARS in Viet Nam

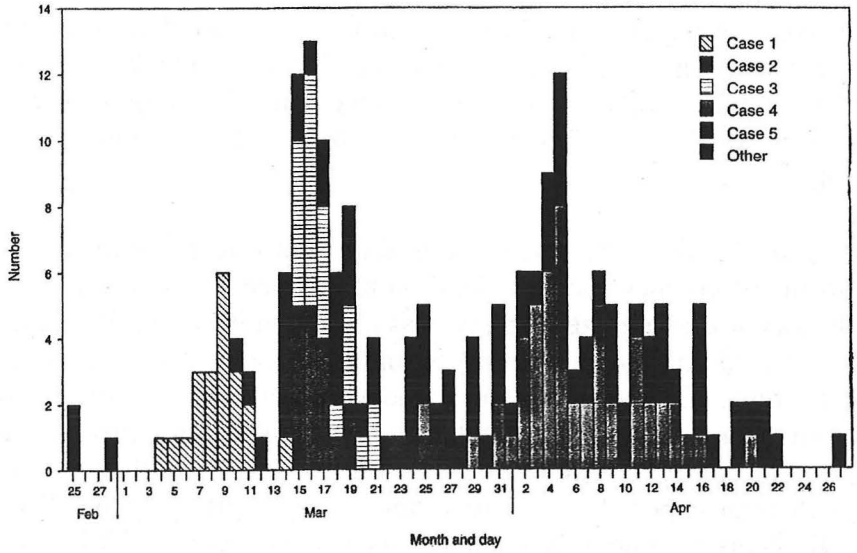
The index patient for Viet Nam (Patient B) was an Asian-American businessman who had traveled to Shanghai & Hong Kong. While in Hong Kong, he stayed on the 9th floor of Hotel M. Upon his return to Viet Nam in late February 2003, the businessman developed an acute febrile illness and reported to his colleagues that he was too ill to go on a planned inspection tour of a garment factory. When the coworkers returned from the outing, they discovered that the individual had become severely ill and required immediate care. The businessman was hospitalized in Hanoi on 2/26/03, but his condition deteriorated and he was placed on a ventilator. Dr. Carlo Urbani, a WHO physician, traveled to Hanoi and examined the patient on 2/29/03. By 3/5/03, the patient was recognized as having SARS, and he was transferred back to Hong Kong, where he died on 3/12/03. During the patient's hospital stay and shortly thereafter, 29 members of the hospital staff who had cared for the patient became ill. On 3/10/03, Dr. Urbani alerted the WHO that an acute atypical pneumonia was spreading quickly throughout HCW's. On 3/12/03, the WHO issued a travel advisory for Hong Kong and Viet Nam. Fifty-nine cases of SARS ultimately occurred in Hanoi during the month of March 2003.Unfortunately, on 3/29/03, Dr. Urbani expired from SARS.

SARS in Singapore

On March 6, 2003, the Singapore Ministry of Health received a report of three patients who had returned from a visit in Hong Kong in February 2003 and had been admitted to Singapore hospitals for atypical pneumonia. The Singapore index patient and a traveling companion had stayed at Hotel M on Kowloon, Hong Kong, on February 20 and 21, 2003. By March 14, 6 additional patients (including two HCW's) were admitted to Tan Tock Seng Hospital for pneumonia – all had been in close contact with the index case. By April 30, 2003, 201 probable and 722 suspected SARS cases had been reported. Among these individuals, CDC and WHO

recognized five of the first "super spreaders" of SARS. These five patients each appeared to have infected > ten additional persons, including HCW's, family members, friends and visitors. The epidemic curve of SARS in Singapore is shown below.[26]

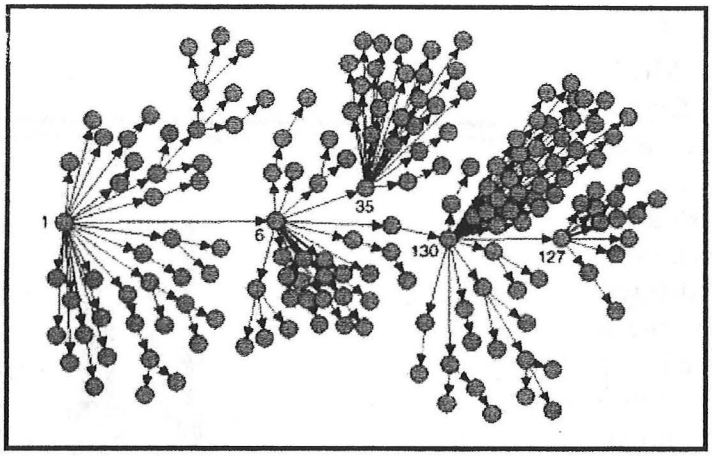
FIGURE 1. Number of probable cases of severe acute respiratory syndrome,* by date of fever onset and reported source of infection — Singapore, February 25–April 30, 2003



*n = 201.

The diagram below represents the magnitude of the "super spreader" phenomenon, in which five patients demonstrated a unique ability to transmit the disease to large numbers of contacts.[26]

Probable cases of severe acute respiratory syndrome, by reported source of infection* — Singapore, February 25–April 30, 2003



* Patient 1 represents Case 1; Patient 6, Case 2; Patient 35, Case 3; Patient 130, Case 4; and Patient 127, Case 5. Excludes 22 cases with either no or poorly defined direct contacts or who were cases translocated to Singapore and the seven contacts of one of these cases.

Reference: Bogatti SP. Netdraw 1.0 Network Visualization Software. Harvard, Massachusetts: Analytic Technologies, 2002.

New World Spread

Ms. Suichu Kwan, a 78-year-old grandmother from Toronto, was attending a wedding in Hong Kong; and stayed at the Metropole Hotel (9th floor). She returned from Hong Kong to Toronto on 2/23/03; became ill, and expired at home on 3/5/03. Two days after her death, her 43-year-old son, Chi Kwai Tse was admitted to Scarborough Grace Hospital in Toronto on 3/7/03; where he soon expired and where HCW's began to fall ill. Joe Pollack, a 76-year-old atrial fibrillation patient, and Mr. D, another 77-year-old cardiac patient were on gurneys next to Chi in the ER observation ward for a 24-hour period; both patients contracted SARS and subsequently expired.

Before Mr. Pollack's death, his wife, who by this time was infected with the SARS virus, brought him back to the emergency room at Scarborough Grace Hospital on 3/29/03. On this visit, his exposure history was recognized, and he was placed on isolation. While in the waiting area of the ER, she infected an elderly Filipino community leader & his two sons, who were also in the ER at the time. The elderly male , who was a member of the Filipino Roman Catholic group known as the Bukas-Loob Sa Diyos Covenant Community (numbering 500) contracted SARS from his brief exposure to Mrs. Pollack and subsequently expired. Prior to his death, he and his two sons exposed an entire Filipino prayer group to the SARS virus on 4/12/03. Over 30 individuals became infected, and three deaths occurred. Unfortunately, before the prayer group was successfully quarantined, two members traveled to Montreal & to Pennsylvania.

Meanwhile, Mr. D. was discharged to home; became ill and returned to Scarborough Grace Hospital a few days later, where he was briefly placed in the CCU. He was subsequently transferred to York Central Hospital in N. Toronto, where he infected dozens of HCW's (with 3 deaths). The entire hospital was quarantined – up to 3000 individuals – to halt the spread of he disease. The connection to SARS was made one day prior to Mr. D's death on 3/29/03 – another example of the failure to perform timely contact tracing in the setting of a fast-moving outbreak.

The unfortunate transfer of Mr. D to a previously uninvolved facility was felt to be one of the most significant preventable events in the chain of transmission. Had his association with Mr. Pollack been recognized and addressed appropriately by cohorting within the affected hospital, then the subsequent quarantining of 3,000 individuals and the deaths might have been avoided.

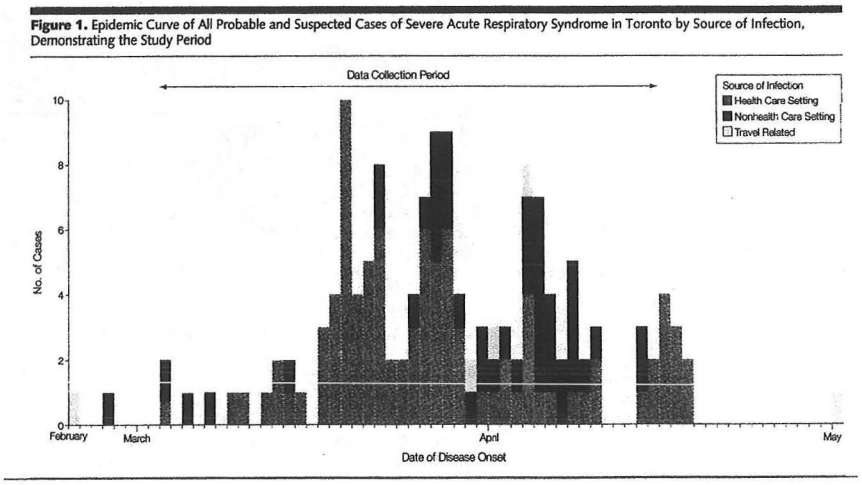


Figure 1. Epidemic Curve of All Probable and Suspected Cases of Severe Acute Respiratory Syndrome in Toronto by Source of Infection, Demonstrating the Study Period

The Canadian outbreak quickly resulted in 330 probable and suspected cases, with 136 in Toronto and 14 deaths initially.

Canadian Etiologic Study [11,12]

- Negative for bacterial pathogens
- Coincidence or a viral cause?
- Five of nine bronchoalveolar-lavage fluid and nasopharyngeal swabs tested positive for human metapneumovirus
- Five of nine similar specimens also tested positive for a novel coronavirus
- Smoking as a risk factor (four of five who needed mechanical ventilation were smokers)

Canadian Study: MMWR 5/16/03

A Canadian family physician cared for three patients on April 1-2, 2003:

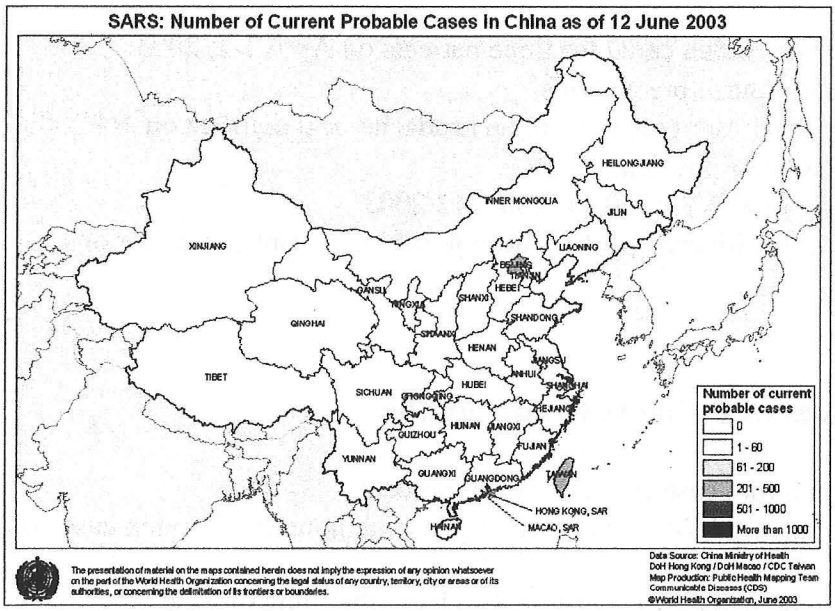
- No infection-control precautions
- Developed fever, dry cough, myalgia headache, and diarrhea on 4/4/2003
- Home isolation of physician
- Temperature of 104.7 F (40.4 C) on 4/12/2003
- Eleven other health care workers despite infection control precautions

Clinical Features of Patients from Canada [11,12]

- Eight of ten initial cases were of Asian descent
- All were adults (24-78 years), five in the same household, index cases traveled to Hong Kong
- Three had type 2 diabetes mellitus, two had other lung disease
- Incubation period 3-10 days
- Fever in all ten cases, dry cough in all ten cases, others (dyspnea, malaise, diarrhea, chest pain, headache, sore throat, myalgia, vomiting)
- Infiltrate on chest X-ray, low white cell, lymphocyte & platelet count, high LDH, high AST, & high CK
- Five of ten required mechanical ventilation, two died

SARS in China

Mainland China experienced the largest outbreak of SARS recorded to date. 5,124 cases and 267 deaths as of 5/14/03; Hong Kong alone had 1,458 cases with 105 deaths. The largest point-source epidemic (291 affected individuals) within Hong Kong occurred in an apartment complex and was traced to sewage / water overflow. The postulated mechanism involved residents walking through standing water and contaminating their shoes. It was then suggested that the inhabitants of the complex returned to their apartments, removed their shoes and then contaminated their faces or household objects via unwashed hands. The source individual was a SARS patient with the diarrheal form of coronavirus infection, well-described in the veterinary literature. This individual reportedly excreted coronavirus in fecal material for up to a thirty day period. It was subsequently recognized that 10% of SARS patients have diarrhea and a subset may have prolonged GI carriage of the virus.



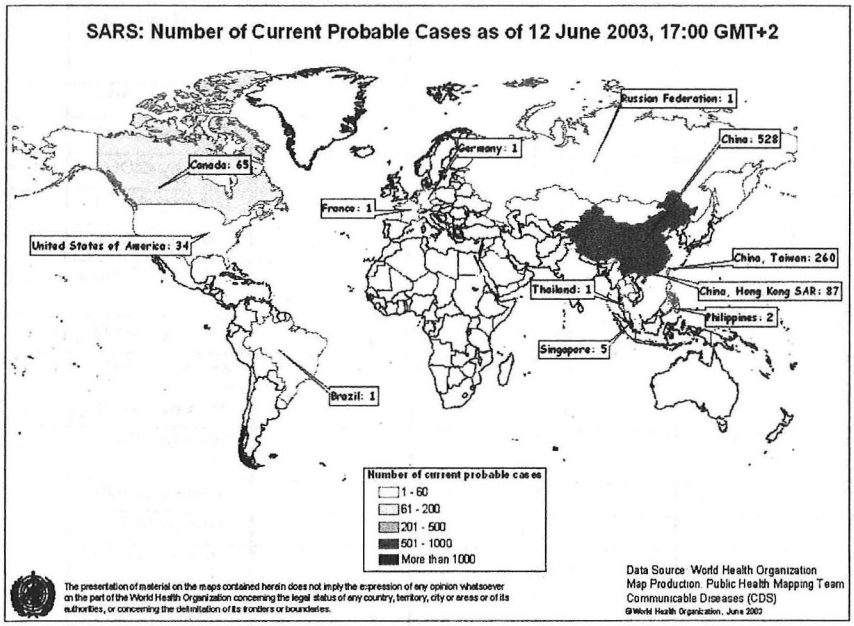
In mainland China, Guangdong Province had at least 1,330 cases and 48 deaths; but the epidemic slowly drew to a close with isolation and quarantine procedures. As the epidemic spread from Guangdong Province outward and ultimately to the major cities (especially Beijing), WHO investigators began to suspect that Chinese health authorities were not being fully open about the actual number of suspected and probable SARS patients. On 4/8/03, Chinese physicians confirmed WHO suspicions, reporting that the government was "hiding" patients. As the investigation progressed in early April 2003, the WHO team first encountered evidence that a minority of SARS-infected individuals were "super spreaders" of the virus – that certain individuals could infect dozens of HCW's or close contacts. By comparison, the majority of individuals infected with the SARS virus (perhaps 80%) either do not pass the virus on at all; or pass it on to very few contacts.

By 4/23/03, thousands of frightened Beijing residents were attempting to flee the city, which alarmed health officials who feared the spread of the virus to medically underserved and resource-poor rural villages. At the same time, symptomatic patients were being turned away from overcrowded hospitals, and plans were made (and subsequently carried out) for the

construction of an enormous SARS hospital facility in record time. On 4/26/03, the Chinese government fired the Chinese Health Minister and the Beijing mayor for failure to disclose the actual number of SARS cases. Over the Easter weekend in 2003, the number of reported cases jumped from 44 to 339, ushering in a new era of cooperation between Chinese health authorities and the WHO.

A subsequent epidemic became evident on Taiwan by 4/22/03. The Taiwan Health Department received notification of seven HCW's presenting with SARS at a large municipal hospital in Taipei [27] By 5/22/03, 483 cases were recognized, with a 12% case fatality rate. The majority of cases were documented in Taipei City and Taipei County, and the outbreak was successfully contained by the implementation of aggressive isolation and quarantine methods.

Magnitude of the SARS Outbreak:



Cases of SARS reported : 7,699 cases and 598 deaths

CFR=7.8% by 05/15/2003 - up to 8,402 cases with 772 deaths;
CFR = 9.2% by 6/4/03

China	– 5,163 cases and 271 deaths; CFR=5.2%
Hong Kong	– 1,703 cases and 234 deaths; CFR=13.7%
Singapore	– 205 cases and 28 deaths; CFR=13.7%
Canada	– 142 cases and 23 deaths; CFR=16.2%
Vietnam	– 63 cases and 5 deaths; CFR=7.9%

Subsequently, Taiwan reported 677 cases and 81 deaths

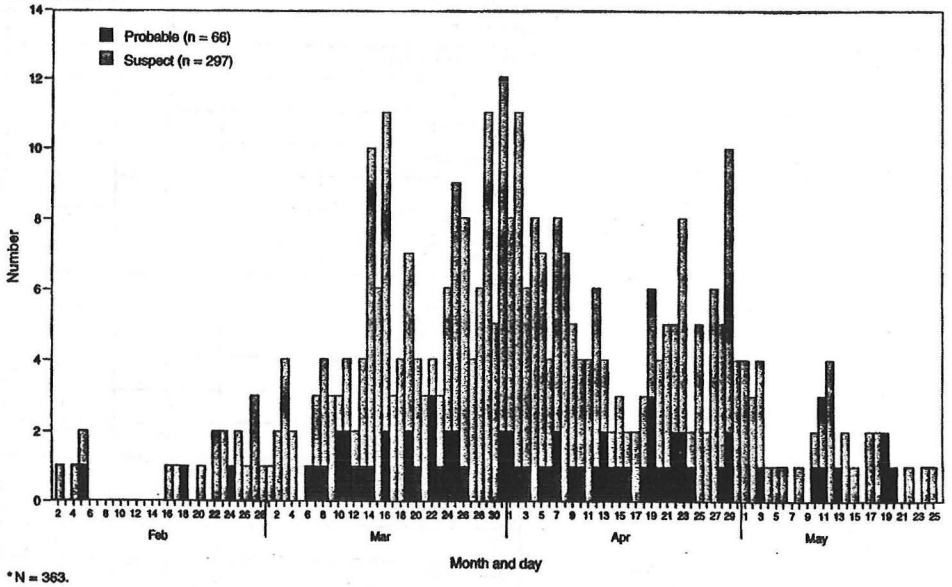
Cumulative SARS Cases As Reported By The World Health Organization, July 15, 2003.

Country	Cumulative number of case(s)[2]	Number of new cases since last WHO update[2]	Number of deaths	Number recovered[3]	Date last probable case reported	Date for which cumulative number of cases is current
Australia	5	0	0	5	12/May/2003	27/Jun/2003
Brazil	1	0	0	1	9/Jun/2003	1/Jul/2003
Canada[4]	250	0	38	194	9/Jul/2003	10/Jul/2003
China[5]	5327	0	348	4941	25/Jun/2003	11/Jul/2003
China, Hong Kong Special Administrative Region[6]	1755	0	298	1433	11/Jun/2003	11/Jul/2003
China, Macao Special Administrative Region	1	0	0	1	21/May/2003	10/Jul/2003
China, Taiwan	671	0	84	507	19/Jun/2003	11/Jul/2003
Colombia	1	0	0	1	5/May/2003	5/May/2003
Finland	1	0	0	1	7/May/2003	20/May/2003
France	7	0	1	6	9/May/2003	11/Jul/2003
Germany	10	0	0	9	4/Jun/2003	23/Jun/2003
India	3	0	0	3	13/May/2003	14/May/2003
Indonesia	2	0	0	2	23/Apr/2003	19/Jun/2003
Italy	4	0	0	4	29/Apr/2003	8/Jul/2003
Kuwait	1	0	0	1	9/Apr/2003	20/Apr/2003
Malaysia	5	0	2	3	20/May/2003	4/Jul/2003
Mongolia	9	0	0	9	6/May/2003	2/Jun/2003
New Zealand	1	0	0	1	30/Apr/2003	25/Jun/2003
Philippines	14	0	2	12	15/May/2003	11/Jul/2003
Republic of Ireland	1	0	0	1	21/Mar/2003	12/Jun/2003
Republic of Korea	3	0	0	3	14/May/2003	2/Jul/2003
Romania	1	0	0	1	27/Mar/2003	22/Apr/2003
Russian Federation	1	0	0	0	31/May/2003	31/May/2003
Singapore	206	0	32	172	18/May/2003	7/Jul/2003
South Africa	1	0	1	0	9/Apr/2003	3/May/2003
Spain	1	0	0	1	2/Apr/2003	5/Jun/2003
Sweden	3	0	0	3	18/Apr/2003	13/May/2003
Switzerland	1	0	0	1	17/Mar/2003	16/May/2003
Thailand	9	0	2	7	7/Jun/2003	1/Jul/2003
United Kingdom	4	0	0	4	29/Apr/2003	30/Jun/2003
United States[7]	75	0	0	67	23/Jun/2003	9/Jul/2003
Viet Nam	63	0	5	58	14/Apr/2003	7/Jun/2003
Total	**8437**	**0**	**813**	**7452**		

SARS in the US: Probable Cases Concentrated in California and New York

By 6/4/03, a total of 373 SARS cases had been reported in the US: 306 (82%) defined as suspect SARS; and 67 (18%) defined a probable SARS. Of the 67 probable cases, 97% were attributable to international travel, suggesting a low incidence of secondary cases and "super spreaders";-perhaps due to early recognition and isolation of suspected cases. The remaining 3% of cases (representing two patients) occurred in a HCW and a family contact of a SARS patient. In the US case series, 65% of patients were hospitalized, and 3% required mechanical ventilation. Fortunately, no deaths attributable to SARS CoV have been reported to date in the United States.[28,29]

FIGURE. Number* of reported cases of severe acute respiratory syndrome, by classification and date of illness onset — United States, 2003



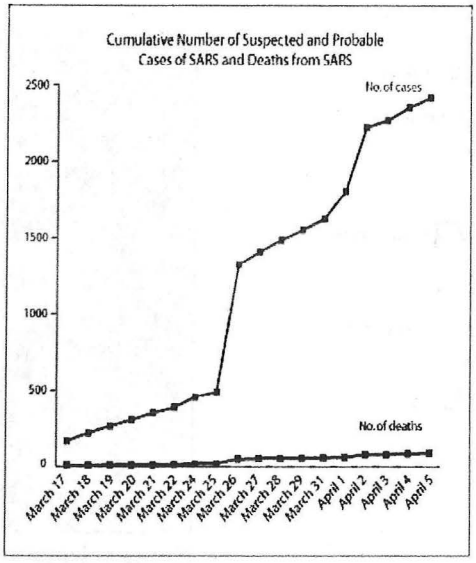
*N = 363.

State-by-state cumulative SARS case reports for the United States, reported as of July 15, 2003 by WHO.

State	Total Cases	Case Classification†	
		Suspect	Probable
Alabama	0	0	0
Alaska	1	1	0
Arizona	0	0	0
Arkansas	1	1	0
California	39	29	10**
Colorado	4	3	1
Connecticut	3	3	0
Delaware	1	0	1
Florida	7	5	2
Georgia	3	3	0
Hawaii	1	1	0
Illinois	8	7	1
Indiana	1	1	0
Iowa	0	0	0
Kansas	1	1	0
Kentucky	6	4	2
Maine	1	1	0
Maryland	4	3	1
Massachusetts	11	10	1
Michigan	0	0	0
Minnesota	3	2	1
Mississippi	1	0	1
Missouri	4	4	0
Montana	0	0	0
Nebraska	0	0	0
Nevada	3	3	0
New Hampshire	1	1	0
New Jersey	4	3	1*
New Mexico	1	0	1*
New York	34	28	6
North Carolina	4	3	1*
North Dakota	0	0	0
Ohio	2	2	0
Oklahoma	0	0	0
Oregon	1	1	0
Pennsylvania	10	9	1*
Puerto Rico	1	1	0
Rhode Island	1	1	0
South Carolina	3	3	0
South Dakota	0	0	0
Tennessee	2	2	0
Texas	12	10	2
Utah	7	6	1*
Vermont	2	2	0
Virginia	6	5	1*
Washington	14	13	1
West Virginia	1	1	0
Wisconsin	2	2	0
Wyoming	0	0	0
Total	211	175	36

Global Prevalence of SARS versus Cumulative Deaths:

Global prevalence of SARS



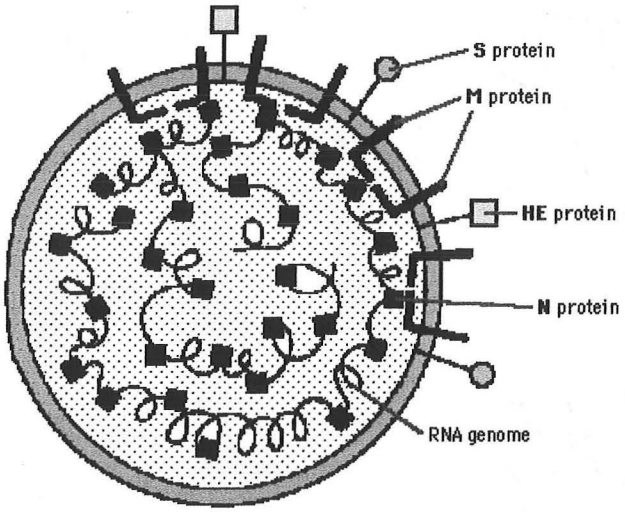
Data are from the World Health Organization (WHO). Cases identified in China between November 16, 2002, and February 28, 2003, were added to the WHO total on March 26, 2003.

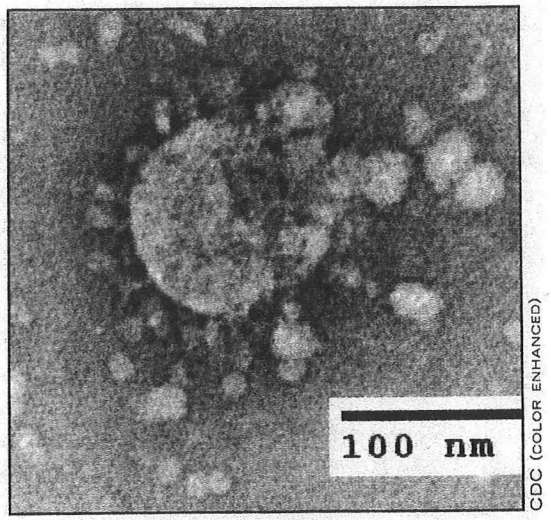
Etiologic Agent of SARS

After the recognition of the worldwide spread of SARS, 13 laboratories devoted their resources round-the-clock for four and a half weeks to the problem of identifying the etiologic agent of SARS. Among these were the following: Ksiazek and colleagues at CDC; Peiris and colleagues in Hong Kong, the National Microbiology Laboratory, UCSF; Erasmus University Laboratory in Rotterdam; the Bernard Nocht Institute in Hamburg, and the Canadian National Microbiology Laboratory in Winnipeg. After a remarkably brief period of time, the CDC and the Hong Kong investigators announced on March 24, 2003 the identification of a novel coronavirus as the probable pathogen of SARS; followed shortly by a similar report from the European group. [5,15,18-19] Clinical specimens from individuals in seven countries meeting the WHO case definition were analyzed, utilizing viral culture, electron microscopy (EM), histology, serology and molecular techniques. The Hong Kong group isolated the virus from nasopharyngeal aspirate and lung specimens from a local patient; while the CDC utilized clinical specimens from a Vietnamese patient; and the European investigators isolated the virus

from blood and respiratory specimens from a Singapore physician and his wife, both SARS patients.

Cytopathic effects of a newly described coronavirus on Vero E6 cells were confirmed by immunohistochemistry and immunofluorescence staining – the preparations reacted with group 1 coronavirus polyclonal antibodies. EM studies of the endoplasmic reticulum confirmed the presence of characteristic 80-100 nm coronavirus particles with spiky, crown – like appendages. Remarkably, the virus was sequenced by the Canadian National Microbiology Laboratory in Winnipeg by mid-April, 2003; within a month of its isolation. Additional groups subsequently reported successful sequencing efforts as well, and by April 20, 2003, four SARS-CoV strains had been fully sequenced and analyzed. Interestingly, comparisons among the four strains revealed minor amino acid sequence variations, suggesting strain diversity and /or expression of alternate proteins.

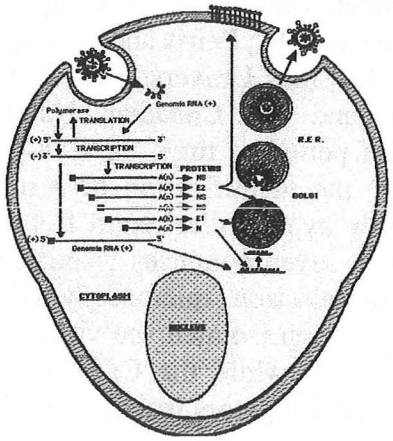


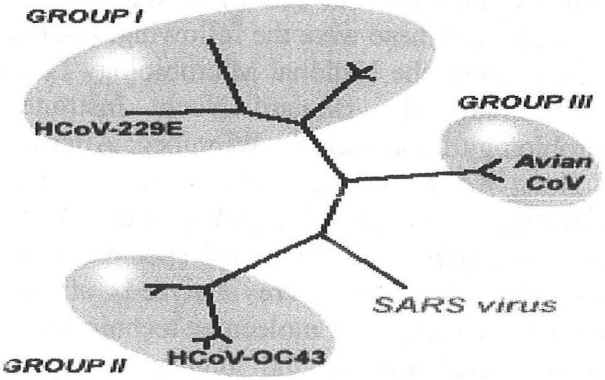


Coronaviruses have a halo or crown-like appearance under a microscope.

The potential for the newly isolated coronavirus to cause disease in an experimental setting was established by mid-April, 2003, as well. Albert Osterhaus and colleagues at Erasmus University in Rotterdam demonstrated transmission of SARS-CoV to primates, and confirmed that the resultant disease was remarkably similar to that seen in human infection. [19,20]

Rource: CDC





SARS-CoV: Characteristics

The SARS-CoV strain is a single-stranded RNA virus consisting of 29,727 nucleotides with 11 open reading frames. The organization of the SARS CoV is similar to the organization of other coronaviruses, and is comprised of the following:

Polymerase 1a, 1b
Spike protein (S)
Small membrane protein (E)
Membrane protein (M)
Nucleocapsid protein (N)

Phylogenetic analysis indicated that the new strain of coronavirus is distinct from the three previously described members of the coronavirus family. [5]

Identification of a novel coronavirus was achieved by reverse transcriptase polymerase chain reaction (RT-PCR).[5] Infection of 19 individuals by the new SARS-CoV was demonstrated by viral isolation, RT-PCR or serological methods. Twelve patients showed evidence of having been involved in a point-source outbreak, as RT-PCR studies from a limited portion of the polymerase gene revealed identical sequences.

Work on a diagnostic SARS-CoV diagnostic test began immediately, and on 4/15/03, antibody tests were shipped free to Asian hospitals.

Microarray Technology

In order to stimulate SARS-related investigation, NIAID has established a free-access program for a novel SARS-CoV microarray. This technology should allow researchers to quickly analyze subtle variations in genetic expression among and between coronavirus strains. A "wild-type" reference strain of SARS-CoV embedded in a quartz chip is available along with the microarrays for distribution to qualified investigators worldwide. NIAID's Pathogen Functional Genomics Resource Center (PFGRC) will coordinate the distribution of the Affymetrix GeneChip SARS Array.[36,37]

The new array is comprised of 29,700 DNA base pairs of SARS-CoV. Sequencing information was garnered from the US, Canadian and Asian laboratories who successfully completed the SARS genome project. Objectives of the new NAID program include genome comparison of SARS-CoV sub-species for the purpose of constructing a coronavirus family tree. In addition, attempts will be made to correlate SARS-CoV strains with differing degrees of pathogenicity, if any. Information obtained may be useful in the rational design of SARS-CoV antiviral compounds, as well as for vaccine development. Finally, microarray technology will undoubtedly contribute to epidemiological studies of SARS and related coronaviruses.[36,37]

Alternative Etiologies for SARS

Separate labs in Germany initially identified a paramyxovirus (a measles – like agent); as the probable etiologic agent of SARS. In fact, a paramyxovirus was initially felt to be a more likely pathogen, based on the previously well-described syndromes of paramyxovirus-related pneumonias. The other agent initially postulated to be responsible for the outbreak in China was *Chlamydia pneumoniae* (the TWAR agent), since this pathogen was detected in two of the Chinese patients with atypical pneumonia.

Recent Evidence for Coronavirus Outbreaks Associated with Lower Respiratory Tract Disease

In addition to "common cold" viral URI syndromes, human coronaviruses (HCoVs) have been associated with serious respiratory disease (even prior to the advent of SARS-CoV). The two main antigenic group of HCoVs are represented by their prototypic viruses: HCoV229e and HCoV OC43. [23]

Investigators in France analyzed 501 respiratory specimens from patients presenting with respiratory symptoms between 2/8/01 and 3/27/01. Researchers tested for the presence of HCoVs, influenza A and B, parainfluenza 3, and respiratory syncytial virus by RT-PCR. 30 patients (6% of 501 patients) representing all age groups tested positive for HCoV OC43. Some of the most common signs and symptoms included fever (59.8%), GI symptoms (56.8%), rhinitis (36.6%), pharyngitis (30%), bronchitis (16.6%), bronchiolitis (10%) and frank pneumonia (6.6%). In fact, of the patients with viral lower respiratory tract disease, HCoV OC43 accounted for one third of the cases.[23] Typically, the greatest number of known coronavirus infections in the US are seen from December to May; within a cyclical pattern noted every 2 to 4 years.

The Immune Response to Coronavirus Infection

The immune response to the two prototypic human coronaviruses, HCoV 229e and HCoV OC43, have been characterized in healthy volunteers.[34] By the age of 6, the humoral response to coronavirus is detectable in the majority of individuals, and consists of neutralizing antibodies. Although it was known from murine models that the cellular immune response to coronaviruses is directed at the spike (S) protein and the nucleocapsid (N) proteins, the cellular immune response had not been well characterized in humans. Spencer and colleagues at Colorado described eleven CD4+ T cell clones directed at coronavirus-specific antigens on HCoV 229e. Six T cell clones were evaluated against a panel of HCoV 229e – derived purified proteins. Three out of six CD4+ clones recognized the 180kD spike glycoprotein, and the other three clones were specific for the 55kD nucleocapsid phosphoprotein. Preliminary evidence suggests that the spike (S) protein and the nucleocapsid (N) protein may be immunodominant epitopes; and thus critical for the human cellular immune response to human coronavirus infection.

In a second study by Callow, et al, from the MRC in the United Kingdom, fifteen healthy volunteers were challenged with HCoV229e infection and monitored for the development and time course of the humoral immune response.[35] Interestingly, the volunteers with the highest levels of pre-existing HCoV antibodies did not become infected. Those individuals with lower levels of antibodies did become infected, and eight out of these ten individuals became symptomatic with URI's. Antibody levels began to rise one week post-inoculation, and peaked at approximately two weeks of infection. One year after the initial coronavirus challenge, antibody levels had waned to the point at which volunteers could be re-infected. Of note, at the time of re-infection, symptomatology was milder in these partially immune individuals. [35]

Clinical Presentation of a non-SARS Coronavirus (CoV OC43)[23]

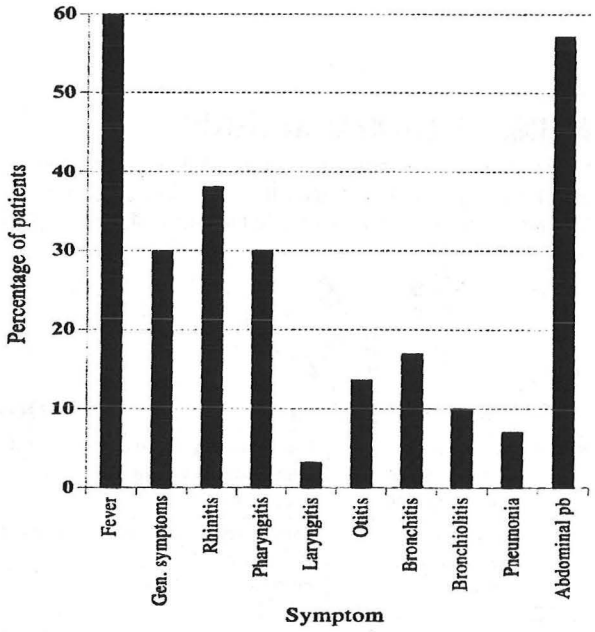


Figure 2. Clinical data for 30 patients who tested positive for human coronavirus OC43 by RT-PCR hybridization, February and March 2001, Lower Normandy, France. Gen., general; pb, problems.

Source of the SARS Coronavirus

Despite initial suspicion that SARS-CoV represented a recombination event between avian and /or swine coronaviruses into a form infectious to humans, phylogenetic studies (noted above) revealed a distinct lineage of coronavirus. On 5/23/03, the WHO announced in Hong Kong the discovery of a strain of coronavirus virtually identical to SARS-CoV in a tree-dwelling mammal eaten as a delicacy in China, as well as in two other mammalian species. In the investigation of the origins of SARS-CoV, WHO investigators analyzed 25 specimens from eight exotic animal species purchased in the Shenzen (Guangdong Province) marketplace. The marketplace was selected as a likely starting point, due to the finding that the initial cases of SARS appeared to originate in food handlers involved in the sale of exotic species for human consumption in Guangdong Province - the earliest cases were reported in food handlers in Foshan, which is approximately ninety miles up the Pearl River from Hong Kong. The practice of consuming wild and exotic animals is known in Chinese as "ye wei", which translates to "wild taste". The popularity of these dishes may be traced to claims that consumption of "ye wei" enhances immunity to disease as well as virility.[24]

SARS-CoV was isolated from six masked palm civets – a small forest-dwelling mammal prized as a delicacy in Chinese markets. In addition, the virus was isolated from the only raccoon undergoing analysis, as well as from the bloodstream of a badger.[24]

Of note, the masked palm civet or Himalayan civet is an endangered species related to the mongoose family; with physical characteristics similar to those of a weasel. After the association between exotics and SARS-CoV was established, the Chinese government issued a ban on the sale of civets and other exotics for human consumption. Snakes, bats, badgers and pangolins (anteater-like creatures) have also been removed from public sale, with a renewed emphasis being placed on the sale of traditional fare such as ducks and rabbits.

ANIMALS LINKED TO VIRUS

Researchers are investigating a possible link between three species of animals in China and the SARS outbreak. It's impossible at this point to tell if the infected animals spread the virus to humans or if they caught the virus from people.

	BADGER	CIVET	RACCOON DOG
Habitat	Open plains of western U.S., Canada, Asia and Europe.	Forest dwelling in southeast China, Southeast Asia and East Indies.	East Asia, China, Japan, Eastern Europe
Uses	Fur is used for shaving and paint brushes.	Considered a culinary delicacy in China; also secretes a musk used in perfume.	Used for fur and meat.

Raccoon Dog

Ferret Badger

The Chatou Wild Animal Food Market in the business district of Guangzhou, and other markets like it, have been ordered to discontinue trade, and breeders of exotic animals have been instructed to quarantine their animals. Violations of the ban are punishable with fines of

up to $12,000 USD. The collapse of the Chinese wildlife food markets is believed to be contributing to the overall profound economic losses associated with the SARS outbreak on mainland China.

Transmission of SARS-CoV

Current data suggests that SARS-CoV is primarily transmitted via infected respiratory droplets from coughs, sneezes and respiratory secretions; rather than via true "airborne" transmission which characterizes such highly infectious entities as varicella zoster virus (VZV) and measles virus. In addition, the virus can survive on contaminated surfaces such as doorknobs, tableware and light switches for at least 24 hours, so surface decontamination with traditional household cleaners is critical (for example bleach, 70% ethanol, ammonia, etc.)[10] A gastrointestinal route of spread was suggested by an outbreak of SARS at the Amoy Gardens apartment building in Hong Kong (see SARS in China above). In this outbreak, a patient with the diarrheal form of the illness is believed to have caused widespread infection of residents of the building via a malfunctioning sewer system and overflow of sewage onto the walkways of the building. Of note, the patient was found to have excreted live coronavirus in his stool for a period of 30 days, indicating a prolonged period of GI carriage of the virus.

SARS: Case Definition / Clinical Syndrome

Suspect Case:

The CDC has continued to update and refine the case definition for SARS. In the summer of 2003, SARS was suspected in patients with the onset of a respiratory illness (of unknown etiology) and an onset after February 1, 2003 with the following features:

- Fever (100.5 º Fahrenheit or 38 º Celsius) AND
- Respiratory symptoms & signs (Dry cough, difficulty breathing, hypoxemia, CXR consistent
- with pneumonia or ARDS) AND
- History of travel to countries or areas with known SARS transmission in the last 10 days prior to onset of symptoms (China, Hong Kong, Taiwan, Canada) OR
- Close contact to a documented SARS case within 10 days prior to onset of illness
- Detection of antibody to SARS-CoV in acute specimens or >21 days after onset of illness

The case definition entails investigation and exclusion of known causes of respiratory symptoms:

- Community acquired bacterial pneumonia
- Respiratory syncytial virus
- Influenza virus

Probable Case

A suspect case with one of the following:

- Radiographic evidence of pneumonia or respiratory distress syndrome
- Autopsy findings consistent with respiratory distress syndrome without an identifiable cause

Estimates of the Case Fatality Rate (CFR) of SARS range from 3.5 to 6%.
(By comparison: untreated HIV = 100% CFR; Smallpox = 30-50%; Ebola = 40%; Spanish Flu = 3%)

Clinical Syndrome

After an incubation period of 3-10 days (also estimated at 6 to 16 days) 11 SARS patients often present with a prodrome: fever to 100.4 or greater, with chills, headache, myalgias, sore throat and diarrhea in 10% of patients. Within one week, infected individuals generally experience the onset of a nonproductive cough, which may progress to dyspnea and frank respiratory distress. Approximately 10-20% require mechanical ventilation.

Clinical Presentations of Patients with SARS-CoV Infection [1,2,18,20,33]

	Hong Kong			Toronto
	Tsang et al[1]	Lee et al[2]	Peiris et al[3]	Poutanen et al[4]*
No. of patients	10	138	50	10
No. of health care workers/ medical students affected	5	85	14	1
No. of patients with coexisting disease	3	19	6	6
No. of patients with history of smoking	2	NR	NR	4
Age (mean)	53	39	42	53
Male:female ratio	5:5	66:72	22:28	6:4
Incubation period (range in days)	1 – 11	2 – 16	NR	3 – 10
Symptoms (% of patients):				
Fever (above 38°C)	100	100	100	100
Chills, rigor	90	73	74	NR
Cough	80	57	62	100
Headache	70	56	20	30
Malaise	70	NR	50	70
Myalgia	50	61	54	20
Dyspnea	60	NR	20	80
Diarrhea	30	20	10	50
Dizziness	NR	43	12	NR
Sore throat	0	23	20	30
Coryza, rhinorrhea	10	23	24	NR
Nausea, vomiting	NR	20	NR	10
Signs (% of patients):				
Auscultatory findings	90	NR	38†	63
Chest film abnormalities	90	78	100	100
Oxygen saturation < 95%	60	NR	NR	78
Leukopenia	20	34	26	22
Lymphopenia	90	70	68	89
Thrombocytopenia	20	45	40	33
LDH elevations	NR	71	NR	80
ALT elevations	50	23	34	56
AST elevations	86‡	NR	NR	78
CK elevations	NR	32	26	56
Percentage of patients requiring mechanical ventilation	20	14	38	44
Mortality (% of patients)	20	4	2	30

SARS, severe acute respiratory syndrome; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; NR, not reported.

* One patient in this series died before she could be hospitalized; as a result, no laboratory or radiographic studies were peformed. All results listed under "signs" are therefore based on nine patients, except for auscultatory findings (which were reported for only eight patients) and LDH (which was measured in only five patients).

† Only auscultatory findings at initial presentation were reported.

‡ AST was measured in only seven patients; six of the seven had elevated levels.

SARS, severe acute respiratory syndrome; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; NR, not reported.

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‡ AST was measured in only seven patients; six of the seven had elevated levels.

Characteristic Laboratory Abnormalities

Hematologic abnormalities, especially leukopenia and thrombocytopenia, are commonly seen in SARS-CoV – infected patients. Abnormal liver function tests are a nonspecific finding, and may be mild and / or transient. Elevated creatine phosphokinase (CK) levels may also be seen. With pulmonary involvement, pulse oximetry and arterial blood gas measurement may demonstrate the degree of impaired gas exchange.

Radiographic findings are nonspecific, and may be unremarkable early in disease; progressing to bilateral perihilar infiltrates and to findings consistent with adult respiratory distress syndrome (ARDS) in a subset of patients.

Routine sputum gram stain and cultures should be obtained to exclude alternative bacterial etiologies. Nasopharyngeal and oropharyngeal swabs should be submitted on ice for viral culture and direct fluorescence assays for both SARS and for typical viral pathogens: influenza A and B; respiratory syncytial virus (RSV), parainfluenza 3, adenovirus. Serum specimens should be collected and submitted to the CDC and to the performed to exclude other agents of atypical pneumonia: serologic testing (and cultures where appropriate) for *Mycoplasma pneumonie*; *Chlamydia pneumonie / Chlamydia psittaci, Legionella pneumophila; Coxiella burnetii* (Q fever), and *Francisella tularensis.*[3]

Spectrum of Disease

The spectrum of SARS CoV – associated clinical syndromes ranges from asymptomatic infection to fulminant disease. In a Canadian study, 40% of probable cases tested positive, 35% of suspect cases tested positive, and 20% of random patients from endemic regions tested positive; implying a high rate of asymptomatic infection!

Life-Threatening Infection with SARS-CoV: The ICU Experience

Investigators in Canada performed a retrospective case series of 38 adult SARS patients admitted to 13 Toronto area ICU's, with the objective of characterizing mortality 28 days after ICU admission. They also examined the number of HCW's who were placed under quarantine and / or contracted SARS. Of 198 patients with SARS, 19% (38 patients) developed critical illness, with a median age of 57.4 years. 76% (29 patients) required mechanical ventilation, and 34% of these (10 patients) experienced barotraumas. 28-day mortality was 34% (13/38).16% (6 patients) remained intubated and ventilated on day 28. Risk factors for death included age, pre-existing diabetes and bilateral infiltrates at presentation to the hospital. [31] (see Kaplan-Meier curve below)

A second group of investigators in Singapore performed a similar retrospective study of the Singapore experience with critically ill ICU patients with SARS. [32] Of 199 patients requiring hospitalization for SARS, 23% (46 patients) required ICU care. 28-day mortality for all patients was 10.1% (20 patients), while ICU mortality was 37% (17/46). Complications relating to advanced ARDS included bronchospasm, decreased airway secretions, and hyperinflation. Higher baseline PaO2 to FiO2 ratios were shown to predict earlier recovery. Proximate causes of death are shown below: [32]

Lew, et al. Singapore, Ref. 32

Box. Proximate Cause of Death in 24 Patients*

Early (<7 Days in ICU; n=5)

Dilated cardiomyopathy (1)
Cardiac failure with septicemic shock (1)
Ventricular fibrillation and end-stage renal failure (1)
Biliary peritonitis and acute-on-chronic renal failure (1)
ARDS with bacterial pneumonia and pulmonary embolism (1)

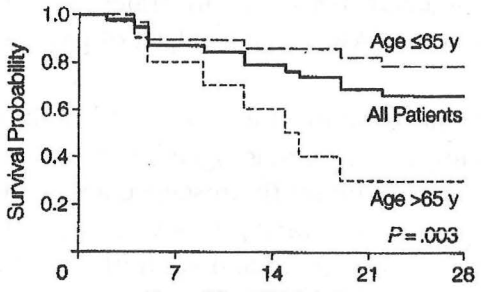
Late (≥7 Days in ICU; n=19)

End-stage renal failure (1)
Late ARDS with multiorgan failure (7)
Late ARDS with intractable hypoxia (single-organ failure) (2)
Acute myocardial infarction (1)
Postanoxic brain ischemia (1)
Massive cerebrovascular accident (2)
ARDS with acute pulmonary embolism (3)
Septicemic shock (2)

*ICU indicates intensive care unit; ARDS, acute respiratory distress syndrome. Autopsies were performed in 5 of these patients.

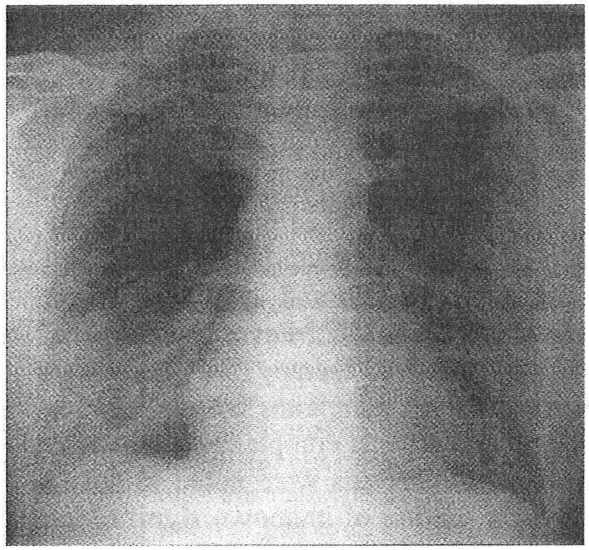
Fowler, et al. Ref. 31

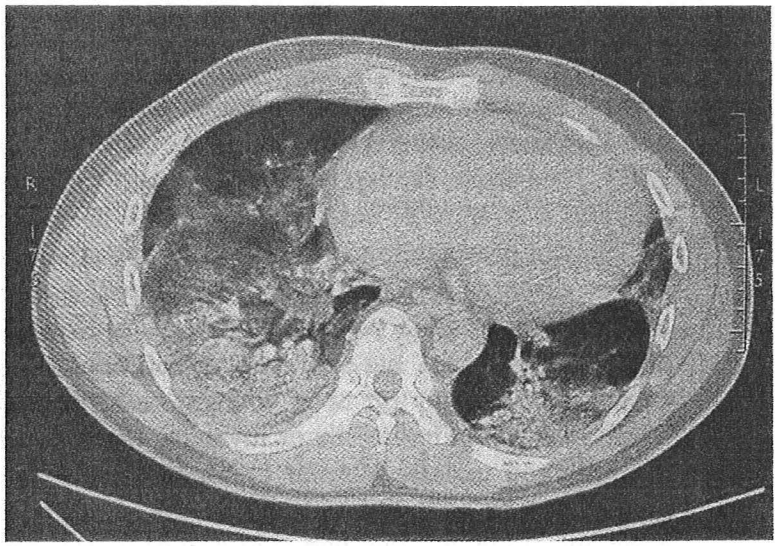
Figure 2. Kaplan-Meier Curve of the Probability of Survival Over Time for Patients With Severe Acute Respiratory Syndrome–Related Critical Illness*



No. at Risk					
All Patients	38	33	30	26	25
Age ≤65 y	28	25	24	23	22
Age >65 y	10	8	6	3	3

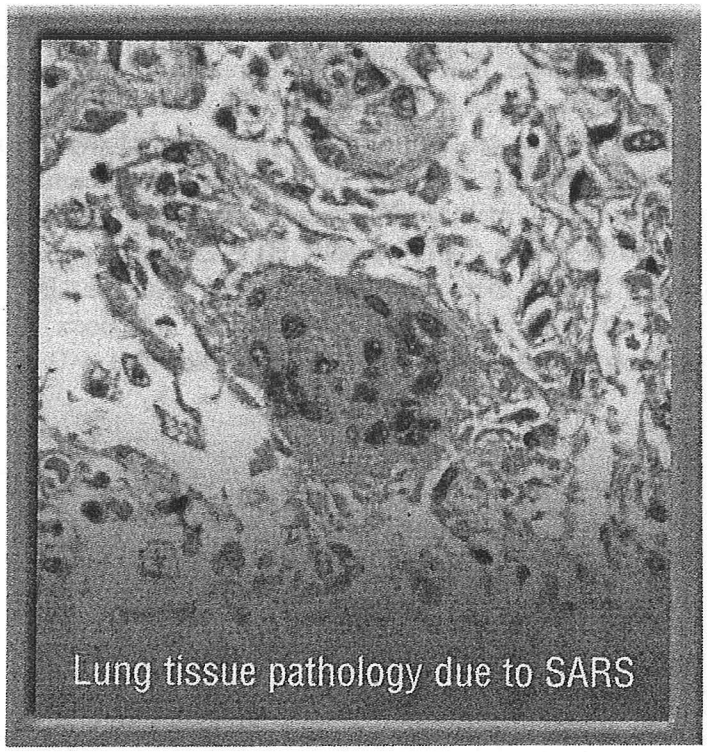
*No nonventilated patients died in the study group.





Chest radiograph and chest CT of a 40 year old male on day 9 of illness (day 2 ICU) who survived a SARS-related critical illness.

CDC slide of representative SARS-CoV lung pathology:



SARS in Children

Despite the epidemic spread of SARS in Southeast Asia, pediatric cases have remained relatively rare. Through June 9, 2003, only 3% of hospitalized SARS patients in Hong Kong were < 14 years old. The distribution between males and females was roughly equal. In China and Singapore, patients less than 18 years of age made up only 2.4% of total cases by April 11, 2003. Data from Taiwan revealed that 1.9% of cases had occurred in children less than 4 years old, and that 3.3% of cases were reported in children aged 5 to 17 years of age.[6,7] Fortunately, the clinical presentation of SARS-CoV in the pediatric population appears to be associated with milder disease. A recent report in *Lancet* detailed the clinical signs and symptoms in ten children (aged 1to 16 years) hospitalized in Hong Kong with SARS-CoV.[8] Fever was universal among the children, but they defervesced after 2 days of corticosteroid therapy (see Therapy for SARS-CoV below). Of note, younger children experienced coryza symptoms more often than adults, but rarely had chills or myalgia. Older children and adolescents complained more often of chills and malaise, similar to adult patients. In addition, adolescents were noted to have a greater degree of lymphopenia than the younger children, a finding of unknown significance. Nine out of ten children had evidence of consolidation on chest radiographs, and there were no deaths attributable to SARS in the Hong Kong pediatric cohort.[8] Interestingly, there were no secondary SARS cases in the classmates of the Hong Kong patients, suggesting perhaps that "super spreaders" may be less common in the pediatric age group.

SARS and HIV

The risk of severe acute respiratory syndrome in the setting of chronic HIV infection is currently unknown. It is conceivable that HIV/ AIDS patients may experience increased morbidity / mortality coincident with SARS-CoV acquisition, if the HIV-activated immune system is anergic and the virus acts as an opportunistic pathogen. However, it is also possible that the partially functioning immune system will provide sufficient cytokine-mediated enhancement of respiratory tract lymphocytes and macrophages in order to limit the spread and cytopathic effects associated with SARS-CoV. Of note, HIV-infected individuals experience no more (and possibly fewer) URI's then non-HIV-infected individuals.[21] However, their propensity for development of severe bacterial pneumonias has been well-described, and recurrent bacterial pneumonia constitutes an AIDS-defining syndrome.

Laboratory Diagnosis of SARS-CoV

Serological diagnosis relies on demonstration of IgM, IgG, or IgA antibodies by enzyme immunoassay (EIA) and by indirect fluorescent antibody assay (IFA). Antibodies may not be present until three weeks into the illness, however. RT-PCR for the presence of SARS-CoV RNA may be undertaken in specimens of serum, stool or respiratory secretions. Of note, the rapid mutation rate associated with RNA viruses may complicate nucleic acid amplification techniques, and false negative results may be encountered. Viral isolation techniques are more difficult and time-consuming, but may be undertaken on a research basis.

Table 2. **Diagnostic Approach to Patients With Possible SARS***

Chest radiograph
Sputum Gram stain and culture, blood culture
Pulse oximetry
Consider testing for other pathogens such as influenza, respiratory syncytial virus, *Legionella*
Save clinical specimens (respiratory, blood, serum, stool) for possible additional testing until a definitive diagnosis is made
Acute and convalescent serum (>21 days after symptom onset)
Contact local and state health departments for SARS-CoV testing

*SARS = severe acute respiratory syndrome; SARS-CoV = SARS coronavirus.

Source: Ref. 17

Approach to Possible SARS Patients

Upon recognition of a possible or probable SARS-CoV patient, strict airborne isolation (in a negative pressure room) and universal precautions should be instituted immediately. Most SARS experts describe the "absolute minimum" of personal protective equipment to consist of gowns, latex gloves, eye protection, and an N-95 mask (defined as a mask which can filter particles of 1 micron with 95% efficiency or greater)[9] Patients requiring respiratory monitoring or support should be hospitalized, while patients with less severe respiratory disease should be quarantined at home to prevent secondary cases. The recommended length of quarantine is ten days after the resolution of fever and respiratory symptoms.[16,17]

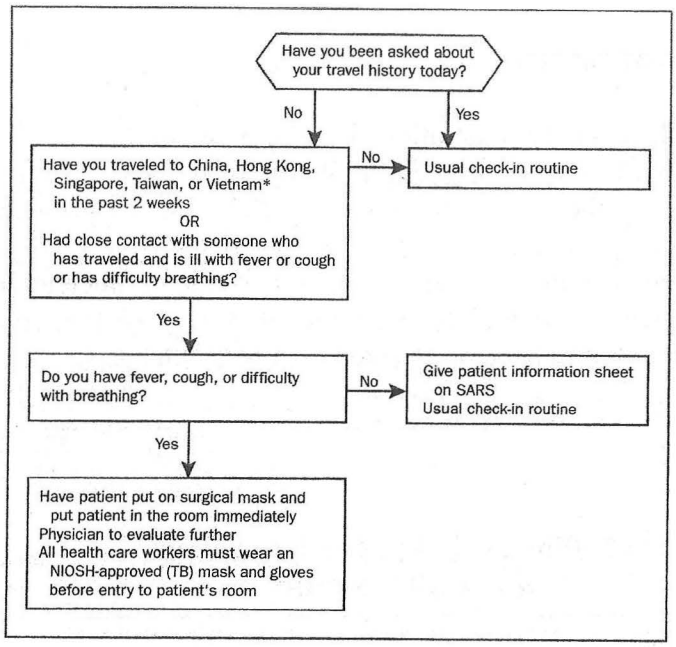


Figure 2. Screening algorithm used to triage patients at first point of contact.
*List of affected countries may change; the evaluating physician should check the Centers for Disease Control and Prevention Web site on severe acute respiratory syndrome (SARS) for the most current epidemiological case definition. NIOSH = National Institute of Occupational Safcty and Health; TB = tuberculosis.

From Sampathkumar P, et al. Ref. 17

Infection Control and SARS

In addition to the above mentioned strategies to limit the spread of SARS within the health care setting, the importance of handwashing cannot be over-emphasized. The Ontario Ministry of Health and Long Term Care recommend frequent hand washing utilizing a soap and water approach first; followed by a alcohol hand rinse; especially if the HCW's hands have touched any surface in the interim.[13]

Table 3. **Infection Control Precautions for Patients Hospitalized With Suspected/Probable SARS***

Ref. 1, 17

Place patient in a negative pressure, specially vented room
Maintain a log of all persons entering the patient's room
Restrict visitors as much as possible
Limit the number of hospital personnel caring for the patient
All health care workers entering the room should use a combination of contact (gowns, gloves, hand hygiene) and airborne (N-95 respirator) precautions and eye protection
Do not bring pens, hospital charts, etc, in and out of the patient's room
Minimize air turbulence when changing linens
Clean surfaces in the room carefully and frequently with EPA-registered hospital-grade disinfectant
Limit cough-inducing procedures (sputum induction, administration of nebulized medications, suctioning, bronchoscopy)
Avoid use of noninvasive positive pressure ventilation (eg, CPAP, BiPAP)
For patients receiving mechanical ventilation, use closed-suctioning devices, HEPA filtration on exhalation valve port
Educate personnel involved in the care of these patients to be vigilant for symptoms of SARS for 10 days after contact with the patient
Quarantine personnel with unprotected contact with a SARS patient during an aerosol-generating procedure

*BiPAP = biphasic positive airway pressure; CPAP = continuous positive airway pressure; EPA = Environmental Protection Agency; HEPA = high-efficiency particulate air; SARS = severe acute respiratory syndrome.

Infection Control Issues in the ICU Setting

ICU patients represent a unique hazard for nosocomial transmission of SARS-CoV to HCW's. Normally stringent ICU infection control practices need to be enhanced even further, especially when high-risk procedures are planned – i.e. sputum induction, intubation, airway suction and bronchoscopy. At least one of the nosocomial outbreaks of SARS-CoV was traced to nebulized bronchodilator therapy of an index patient, which appeared to augment the number of infected respiratory droplets to which the ICU staff was exposed. [14] Therefore, it is recommended that nebulizer treatments, bronchoscopy and high-frequency oscillation techniques be performed with the minimum number of required staff in a negative pressure room; and in accordance with strict adherence to SARS infection control practices and handwashing. [14]

Therapy for SARS-CoV Infection

Thus far, no antivirals have been shown to be clearly effective. Ribavirin / IFN + corticosteroids and mechanical ventilation constitute the recommended strategy, based on the available data (see below). Preliminary research from the CDC suggests that ribavirin has little *in vitro* inhibitory effect on growth or on cell-to-cell spread of at least one strain of SARS-CoV. [22]

Additional agents under investigation for anti-SARS-CoV activity include oseltamavir and alfa and beta interferons. Pentoxifylline has been proposed as a therapeutic agent based on its anti-inflammatory, antiviral, immunomodulatory and bronchodilatory effects. At least one pharmaceutical company, Viropharma, had been working on FDA approval for anti-coronavirus drugs; screening is underway to identify compounds with anti-SARS-CoV activity.

Development of a Treatment Protocol for SARS

Investigators in Hong Kong devised a therapeutic strategy for coping with SARS-CoV-infected patients, publishing their findings in *Lancet*.[4] During the period from 3/9/03 and 3/29/03, 31 patients with probable SARS were evaluated and treated per protocol at a Hong Kong hospital. All patients received antibacterial therapy until typical pathogens were ruled out. On 3/12/03, an initial protocol was implemented utilizing ribavirin + methylprednisolone. Steroid dosing and weaning schedules were refined based on knowledge gained in treating the first eleven patients and an index patient, who was admitted on 3/2/03 and expired on 3/16/03. The final protocol was initiated on 3/18/03; after which patients were followed for an average of 18.9 days. 30/31 patients required aggressive therapy and received the combination of ribavirin + methylprednisolone; beginning approximately 5 days after symptom onset. 17 patients were observed to have a rapid and sustained response to combination therapy. Two patients required dose adjusting of their methylprednisolone upwards due to failure to respond after 1-2 days. 16 patients needed supplemental oxygen therapy, and 4 patients received brief ventilatory support with 8-10 cm H2O expiratory pressure. None of the patients required endotracheal intubation and there were no additional fatalities (since the death of the index case) after the implementation of the treatment protocol. While uncontrolled, the information gleaned from this series of patients may indicate that empiric steroid therapy, with or without broad-spectrum antiviral agents, may be warranted in seriously ill patients with SARS-CoV infection.

SARS: Emerging Trends

- Increased mortality among the elderly: 50% of pts > 60 yo requiring admission in the Hong Kong outbreak expired
- Mortality among younger hospitalized pts less: approximately 6%
- Fomite transmission – Coronavirus survival on surfaces for up to 24 hours
- Easily disinfected by common household cleaners: bleach, 70% ethanol, ammonia
- Overall mortality fluctuating around 3.5-6%
- Many patients have asymptomatic infections
- Current update suggests global clinically apparent infections of 8,402; with 772 deaths; with a CFR of 9.2% (as of June 6, 2003)
- Epidemic spread has crested in Viet Nam, Singapore, Toronto, Hong Kong

Surveillance and Control of SARS in Returning Travelers

- Surveillance is the key to early recognition and containment of SARS in travelers
- Screening departing passengers to international destinations in countries with established chains of transmission
- Quarantine of passengers with symptoms in the past 48 hours
- Quarantine of patients with a history of contact with a suspect or probable SARS case
- Quarantine of passengers with fever
- Isolation of passenger with symptom & use of a separate toilet (in the case of in-flight syndrome recognition)
- Provide protective mask for ill passengers

Blood Safety Issues – WHO Guidelines

- Avoid donations in areas with local transmission
- Defer donation for three weeks if there was close contact with a case even if patient was without symptoms
- Defer donation for 3 months after cessation of treatment if probable SARS
- Defer donation for 1 month if suspect SARS

For Travelers from areas with local transmission

- Defer donation for 3 weeks after return
- Defer donation for 3 months of cessation of treatment if probable SARS
- Defer donation for 1 month if suspect SARS

Comparisons Between the 1918 Influenza Pandemic and the SARS Epidemic
30

Table 1. **Parallels Between 1918 Influenza and SARS***

Like more recent strains of the influenza A virus,[34] the 1918 (H1N1) strain was almost certainly a human-animal recombinant that originated in southern China [35,36]	In all likelihood, so is the SARS coronavirus (SARS-CoV)[4-7]
H1N1 influenza was extraordinarily contagious presumably because there was so little natural immunity in the general population worldwide[36]	Serologic surveys by the CDC using specimens from US serum banks show no persons with preexisting antibodies to the new SARS virus[5]
H1N1 influenza A had high mortality among young and healthy individuals[2,3]	SARS has also had a prohibitive mortality[8] and has killed previously well health care workers, including the discoverer of SARS, Dr Carlo Urbani[37]
Influenza A classically spreads in the late fall and winter months and is rarely seen during the late spring and summer months[34]; in 1918, influenza continued to occur, inexplicably, all summer[3]	SARS has caused epidemic disease all spring and will likely continue to spread slowly throughout the summer months
In 1918, pandemic influenza surged worldwide in late August and the fall[2,3]	With SARS, we do not know what will occur, but we must be prepared for the worst; countries, regional and municipal health departments, hospitals, and individual practitioners must be informed and prepared

*CDC = Centers for Disease Control and Prevention; SARS = severe acute respiratory syndrome.

Summary / Conclusions

- SARS is an emerging infectious disease of global public health importance, with profound social, cultural and economic impact;
- The probable etiologic agent is the novel SARS-CoV; representing the most pathogenic strain of coronavirus discovered to date;
- Early detection & prompt control measures can halt spread and reduce morbidity/mortality;
- Effective interventions, while costly, are not technologically demanding and can be undertaken in a resource-poor setting
- Successful containment of the spread of SARS requires close cooperation between local, national and international health organizations, with an emphasis on the timely, thorough and accurate reporting of cases
- Despite rapid advances, there is still an acute need for better diagnostic methods, as well as treatment and prevention tools.

For the latest information on SARS, go to the web

Centers for Disease Control and Prevention (CDC)
www.cdc.gov/ncidod/sars

World Health Organization (WHO)
www.who.int/csr/sars

Recent articles on SARS have been published on the following medical journal web sites:

New England Journal of Medicine
www.nejm.org

The Lancet
www.thelancet.com

Physicians with questions or concerns can contact:
CDC Emergency Operations Center
(770) 488-7100

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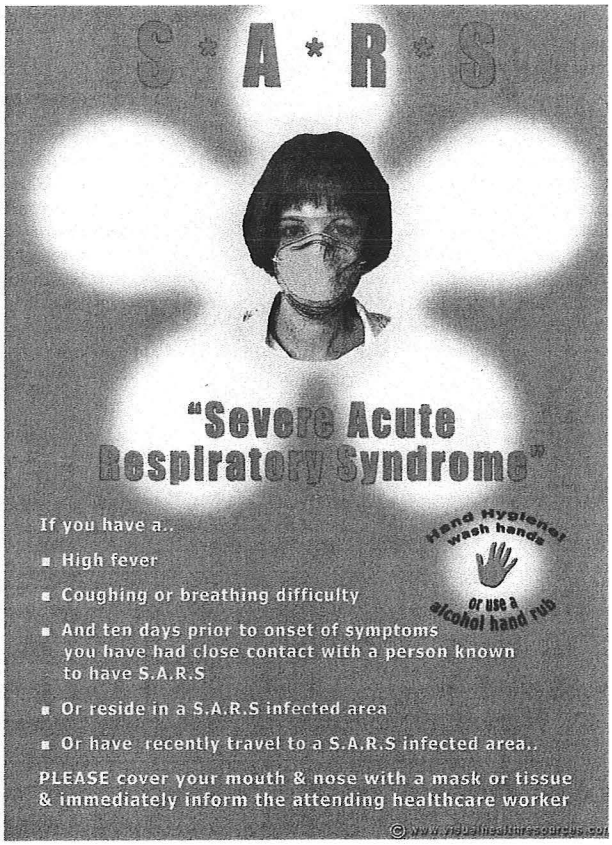

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