

SARS — Looking Back over the First 100 Days

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Each winter, a number of surveillance networks are put in place to detect unusual outbreaks of severe respiratory disease. Last winter, although there had been some minor activity, nothing serious came up until late February 2003, when Dr. Carlo Urbani alerted the World Health Organization (WHO) that there was a novel form of severe pneumonia at a hospital in Hanoi, Vietnam. The pneumonia had a peculiar hallmark: health care workers were being stricken at an alarming rate. With this key observation and many negative diagnostic tests for known pathogens, it became clear that we had a new disease, severe acute respiratory syndrome (SARS), on our hands.

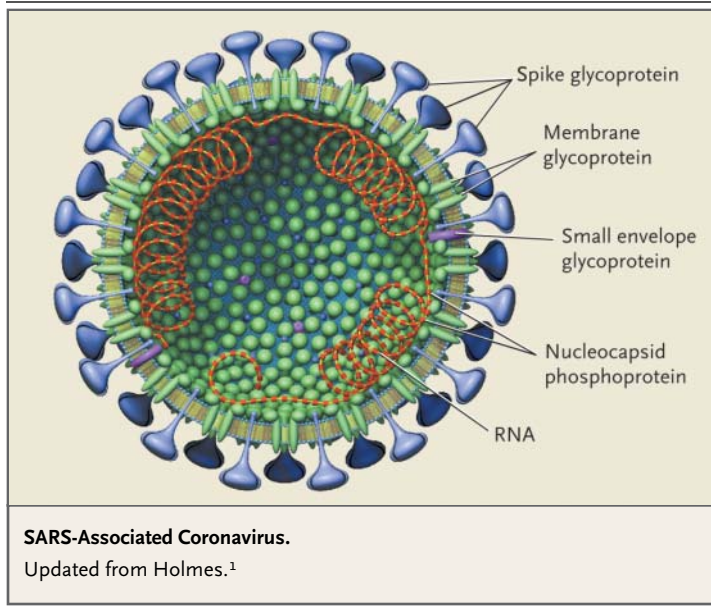
In late June of 2003, just about 100 days after it issued its first alert about SARS, the WHO sponsored an international conference about the disease hosted by the Malaysian Ministry of Health. The conference brought to life the maxim of the 19th-century Danish philosopher Søren Kierkegaard: life must be lived forwards, but it can only be understood backwards. The more than 1400 attendees, who included both scientists studying SARS and ministers of health, reviewed what we understand so far. There were no major revelations, but having the current knowledge encapsulated helps to provide some perspective.

Koch's postulates, as modified for viral diseases, have been fulfilled for the SARS-associated coronavirus (SARS-CoV) and the clinical illness now known as SARS. Investigators used a combination of old-fashioned electron microscopy and state-of-the-art molecular biology to identify the previously unknown pathogen (see Figure). As multiple laboratories confirmed each other's work in real time, it became clear that the SARS-CoV is only distantly related to previously known coronaviruses. The genomes of a number of strains of the virus have been sequenced, and as one might predict, there are regions of stability and regions of variability. Molecular diagnostic tools, such as specific protocols for amplifying parts of the viral genome by polymerase chain reaction, have been developed. Although the

resulting reactions are specific, these tools are not yet sensitive enough to be used as diagnostic tests to confirm the presence or absence of the virus in a given patient. Serologic tests have been developed to identify persons who have been infected with the virus, but such tests are of value only after the immune system has had enough time to produce antibodies. Thus, the definition of a case remains clinical. There is no effective treatment for the disease, which has a case fatality rate on the order of 5 to 10 percent. Not surprisingly, the elderly and persons with coexisting medical conditions are more likely to die from the illness.

The epidemiology of SARS is now better understood. The SARS-CoV has been recovered from wild civets and raccoon dogs that are considered culinary delicacies in southeastern China; domestic pigs and poultry do not appear to be hosts. Serologic data suggest that there has been previous infection of humans and animals in this region of China. In humans who are infected with the virus, there is a wide range of incubation periods, from 5 to 15 days, before patients become symptomatic. This lag time allows apparently healthy people to travel by air almost anywhere in the world after they have been exposed. Once it becomes symptomatic, the disease is most likely spread through person-to-person transmission. Most, but not all, cases arise from close contact with an infected person, but details regarding transmission have yet to be elucidated.

Because health care workers are often in close contact with patients, they are at high risk, especially if there has been no reason to raise the clinical suspicion of SARS. Most of the outbreaks of SARS have occurred in this fashion, because there is not much that distinguishes the clinical picture of SARS from that of any common community-acquired pneumonia. Fever, myalgias, diarrhea, and lymphopenia are frequent but not universal findings. Known exposure to a person from a SARS-infected area remains a critical epidemiologic clue, but patients have contracted SARS during air travel — circumstances in which such a clue is easily lost.



According to data from the WHO, the SARS epidemic appears to have peaked and to be on the wane. This evolution has occurred without our having gained clear knowledge of the mode of transmission, without a firm laboratory-based diagnostic test that may be used in real-time case definition, without a vaccine, and without an effective treatment. The success has been attributed to traditional, pavement-pounding epidemiologic work. Source cases and contacts have been identified and isolated. Large-scale quarantine has been used when health officials thought it was appropriate, although the effectiveness of this approach is not known. Whatever we have been doing seems to be working. Although the decrease in worldwide incidence is gratifying, it may simply reflect the seasonal variation in the transmission of the virus. If so, SARS will emerge again in the Northern Hemisphere next winter. The only way to know whether we have made a dent in this infection is to wait and see — at least

this time, we think we know what we will be looking for.

SARS has left its mark. There have been more than 800 deaths and many secondary consequences. Busy airports became temporary ghost towns, stock markets lost substantial value, and schools have been closed. In some areas, health care workers have been subject to discrimination. Life is now returning to normal.

The SARS epidemic, in which the disease spread to more than 30 countries within a few weeks, proves how small our planet has become. It has also illustrated how united we can be. A worldwide network of laboratories, assembled by the WHO, was responsible for the identification of the SARS-CoV, for elucidating its molecular genetics, and for demonstrating that the SARS virus could induce respiratory illness in monkeys. There is now a coordinated effort to identify and test effective vaccines for the prevention of SARS.

Moreover, the coordination has gone beyond the scientific realm. Heads of state around the world realized that without cooperation among nations, SARS could not be contained or controlled. The SARS-CoV refused to be hidden behind national boundaries. At the meeting in June, the minister of health of Vietnam, the first country outside of China to have SARS cases and the first to become SARS-free, attributed that nation's success to its close working relationship with the WHO. The vice-minister of health of China admitted that the initial Chinese response had been slow and inadequate. China has now received help from the WHO, and as of the beginning of July, the disease appears to be under control. The SARS virus shows that when confronted by a common enemy, we can forget our differences and work together fruitfully. This was the most important lesson from the conference and from SARS. Let us hope that we can all benefit from it.

1. Holmes KV. SARS-associated coronavirus. *N Engl J Med* 2003; 348:1948-51.

Periosteal Bone Formation — A Neglected Determinant of Bone Strength

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Life forms that have low body mass can hunt for food on the undersurface of branches or along shear cliff faces quite unperturbed by gravity. For larger

animals, the hunt for dinner and the struggle to avoid becoming someone else's meal require rapid movement against gravity. This need is met by the