CHAPTER 6

COPING WITH BIOLOGICAL THREATS AFTER SARS

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The outbreak of an often fatal lung disease, initially called "Severe Acute Respiratory Syndrome" (SARS)[1] took the international public health community by surprise. Denoted with the typical medical nomenclature of a syndrome—a combination of symptoms and signs—SARS occurred at a time of extraordinary tension among public health practitioners. The not-too-distant memories of the anthrax bioterror event in the United States in the fall of 2001 and the rapid downhill course of dozens of SARS victims captured headlines and invited endless speculation as to the source of the SARS illness (natural vs. sinister), its cause (infectious agent vs. toxic chemical), and the real rate of growth of the epidemic. Because of sketchy reporting from China, the probable initial focus of the outbreak only added to confusion and fear. Travel to China, Southeast Asia, and Singapore plummeted, and passengers disembarking from ships and airplanes from those same areas were screened carefully for respiratory symptoms when they arrived at destinations in the West and Europe. Passengers waiting to board airplanes also were screened carefully, while millions of Chinese and Singaporeans took their own initiatives against the presumed infection by wearing surgical masks and staying out of circulation on crowded streets and public transport. Even into the fall of 2003, some parts of China still were visited infrequently by domestic and international travelers for fear of continuing contagion.

At the time of the writing of this chapter, it is far too soon to enumerate the lessons of the SARS outbreak for national security (and indeed, international security) in a comprehensive way. However, several observations may be instructive to both policy decisionmakers and public health planners.

First, it is abundantly clear that rapid, uncensored information from physicians and hospitals is essential in managing this—or any—infectious disease outbreak, whether it is naturally occurring (as SARS turned out to be) or resulting from bio-terrorism (as

initially was feared in the SARS outbreak). There is little question that the "quality" of the information, coming as it does from expert clinicians and infectious disease specialists, is good enough in its raw form to provide "actionable" data. Indeed, once the World Health Organization (WHO) heard from a few isolated clinicians that an apparently severe form of respiratory illness had appeared in just a small handful of patients, it was sufficient to organize teams of epidemiologists and virologists to travel to widely separated parts of the globe to begin to nail down the source of the disease, isolate the causal agent and even divine its mechanism of spread. Transmission of the data in near-real time via the Internet (and with only minimal review and proofing) probably saved tens of thousands of lives in this epidemic.

Second, it is equally clear that a forced *absence* of information in the midst of an outbreak is devastating for individuals and for the local economy. The Chinese government, in particular, actively suppressed the exchange of data internally and shared nothing with foreign or WHO public health officers until embarrassed into doing so by international outcry. No one can doubt any longer the magnification of fear and panic—and thus loss of reason and reasonable behavior of masses of people—when physicians and local public health officials are operating in a scientific vacuum. I return to this point about information in the text of this chapter several times as I think it may be the most important lesson of all from the SARS outbreak of 2003.

Third, even when a severe and novel disease entity emerges, with open flow of information it is possible to effectively "rule out" a biological weapons attack. This lesson is, of course, tenuous, but when the SARS experience is combined with previous outbreaks of mysterious, fatal respiratory disease—such as the Hantavirus pulmonary syndrome in New Mexico in 1991—decisionmakers can take great comfort in the ability of epidemiologic sleuthing to distinguish between nefarious activities and acts of nature. Needless to say, a misstep in the face of *possible* bioterrorism could result in a catastrophe.

Fourth, the tools of modern molecular biology are now so widely spread that it is possible, even easy, for investigators working simultaneously in multiple laboratories to, in effect, independently

validate each others' work. In the earliest days of the SARS outbreak, there was some confusion over what organism might be causing the disease. But for the use of gene sequencing in two separate laboratories, this confusion could have undermined an understanding of the source and nature of the pathogen for many weeks. Molecular biology is, unfortunately, a two-edged sword and can certainly be used for illicit purposes, but, in this case, the needed knowledge was discovered swiftly and verified collaboratively. It is hard to overstate the profound power of biological science to do good.

These lessons certainly will affect the response of the public health community to future outbreaks. New outbreaks have always been inevitable, but one could not be nearly so certain about the effectiveness of public health actions. Past successes have been realized much more slowly (for example, with the eradication of smallpox in the wild) or depended on a considerable amount of luck (Hantavirus did not, thank Providence, spread from person-to-person by any route, nor did anthrax in Washington, DC). We will have to do as well in the next outbreak as we did during the SARS epidemic—even better, if our luck runs out, and we face a highly communicable, fatal disease such as a new strain of influenza. I will expand on this requirement more in the text.

While the pathogen responsible for the illness—a novel Coxsackie Virus—seems clear, the economic costs, lives interrupted, and the effectiveness of the public health response still are being tallied. This much appears certain: The virus does not seem to transmit easily as an aerosol as does influenza, but rather as a heavier-than-air droplet that falls onto surfaces or the host's face and hands. These surfaces are then contaminated, and an unwitting individual who touches those surfaces and then touches his nose or mouth provides the transmission mechanism for infection. Had SARS spread by an airborne route, one person coughing or sneezing might well have been able to infect dozens of other people who had no immunity to the virus (and most probably do not). An infectious disease catastrophe might have resulted, reminiscent of the world "pandemic" of influenza in 1918-19 that killed about 10 percent of the world's population, including most prominently young, otherwise healthy adults.

It is not possible to extract the instructive lessons of SARS without some understanding of the fundamental scientific facts. Thus, I will

summarize briefly the medical aspects of SARS (including short-term and long-term prognosis in patients) and review the history of the SARS epidemic to date, while highlighting the early dynamics and often frightening spread of the disease. Virologists around the world quickly responded to the need for identification of the pathogen and developed a diagnostic test within a few weeks of the earliest indications of the outbreak—a phenomenal set of accomplishments. Rapid communication of results between several centers in Europe, Asia, and the United States permitted confirmation of laboratory findings; this not only dramatically facilitated an understanding of the fundamental biology of the organism and its interaction with nonimmune human hosts, but also enabled public health officials to define a likely epidemiologic model for the spread of the disease.

I will also speculate as to how the international community might do better when the next new epidemic makes its appearance, as it most assuredly will. Speculation is a dangerous exercise in medicine and biology where rarely, if ever, do the complexities of disease spread fit into compact mathematical expression like the equations of motion in physics, but there is little doubt that the SARS epidemic underscored, yet again, the unfortunate triumph of politics over reason in many aspects of the collaborative management of communicable disease. It seems that high-ranking officials in the Chinese health establishment, and even Chinese government leaders, sought to hide the extent of the epidemic, as they hoped that microorganisms would respect borders, political decisions, and national sovereignty. Even in the short-run, this was a bankrupt policy. The Chinese economy suffered severe losses—even more than the rest of eastern and southern Asia, struggling to recover from an economic recession made all the worse by the September 11, 2001, terrorist attacks and subsequent war in Afghanistan and the Middle East. After the passage of nearly a year, the full extent of the epidemic on the Chinese mainland was still uncertain, with incomplete accounting of even the total number of victims and their location. The reservoir of origin for the disease remains a mystery.

In addition, I believe that the SARS epidemic is instructive for the arms control community currently debating the utility of monitoring and verification proposals for treaties such as the Biological and

Toxin Weapons Convention (BTWC), and trying to uncover the trail of physical and documentary evidence of the Hussein regime's biological weapons program in Iraq. Here the lessons are not so pleasant. It perhaps is obvious that the illicit, intentional use of a biological weapon, or an accident that might occur in their development, would engender even tighter control of information and greater volume of denials than what we witnessed in China in the early days of the SARS outbreak. That the Chinese government could cover up a serious outbreak for months is sobering; it is much easier to cover up illicit work on biological agents for weapons purposes as the latter occur almost exclusively in laboratories or in other highly controlled facilities.

Tracking disease—especially when the disease causes severe symptoms and spreads in ways not previously seen—is problematic even under the best of circumstances. When there is a deeper political agenda designed to obfuscate the data and deny access to time-sensitive information, the outcome can be disastrous, as might well occur if a state or terrorist organization employed biological weapons. We were fortunate that the SARS agent's mechanism of spread was inefficient, for had transmission been like that of other viral diseases such as measles or influenza, many more people would have died for lack of easily obtained pieces of data, let alone the enormous strain on limited medical resources such as intensive-care unit beds that were needed to save the lives of the most ill patients. We will not necessarily be so lucky the next time.

Medical Aspects of SARS: Diagnosis, Treatment and Outcome.

As of early August 2003, WHO reported[2] that there had been approximately 8,500 cases of SARS in 32 countries and territories. The median age of SARS patients was about 40 years (although patients as young as 1 and as old as 90 have been confirmed as SARS victims). About 20 percent of patients were health-care workers, indicating that, despite reasonable precautions from the outset of the epidemic, close contact with patients confers a high risk for transmission. SARS has a high mortality: about 11 percent of patients die. More than half of the currently known SARS cases are from China where reporting

remains incomplete; there will probably be more patients among survivors of SARS in China, and certainly among those who have died in recent months. We now know that older patients fare badly, as about 45 percent of all patients over age 60 die. The combination of advanced age, intensive care unit (ICU) admission, and the need for mechanical ventilation is associated with an 80 percent mortality rate.

WHO believes that the first case of SARS occurred in November 2002 in southeastern China, some 2 months before the first case occurred outside of the country—as it happens, in the United States on January 9, 2003. The vast majority of nonmainland Chinese cases have occurred in just four countries or territories: Hong Kong (now a Special Administrative Region of China), Taiwan, Singapore, and Canada accounting for approximately 3,000 cases. In the United States, there have been 33 cases of SARS, though it should be noted that, because of the similarities between SARS and other causes of acute respiratory illness, the diagnosis of some of the initial "suspected SARS" cases, will doubtless turn out to have been due to other causes, both infectious and noninfectious.

Medical school professors are fond of saying that "the human body has only so many ways of responding to assault from toxic or infectious agents." What they mean is that the symptoms that patients experience—including severe symptoms such as shortness of breath and high fever—can be caused by a large number of agents. Indeed, SARS initially begins like most respiratory viruses with fever, dry cough, muscle aches, and headache. The changes in the levels of white blood cells mirrors those of influenza and even the common cold virus. SARS is one more in a long list of "flu-like" illnesses, but the emerging picture is one of much higher than "flu-like" mortality. Fortunately, as already noted, SARS is much harder to transmit and catch than influenza.

A large series of SARS patients from Canada—the country with the most SARS cases outside of Asia—points to the severity of the clinical disease.[3] About one out of five SARS victims are admitted to an ICU, and almost all of these patients require mechanical ventilation due to respiratory failure, with low blood oxygen saturation, severe fatigue from increased work of respiration, and accumulation of large

amounts fluid in the air sacs (alveoli) of the lungs. Significantly, half of the mechanically ventilated patients die despite the most advanced care. Thus, when respiratory failure occurs in SARS, it is an ominous prognostic indicator. A similar experience has been reported from Singapore.[4]

SARS, then, is best thought of as one form of Adult Respiratory Distress Syndrome (ARDS), defined as a clinical condition in which there is shortness of breath, abnormal findings in chest x-ray, and low oxygen levels in the blood. ARDS usually is associated with injury to the lung and may be preceded by a variety of contributory actors including trauma, infection, and shock, among many others. The mechanisms leading to ARDS in patients with otherwise uncomplicated infection from the SARS virus or other micro-organisms remain obscure. Whatever the underlying cause of disturbance of normal lung function, all cases of ARDS necessitate ICU management. Treatment is supportive, meaning that patients are provided with oxygen, fluids, nutrition via gastric tubes or intravenously, and aggressive respiratory toilet, while one hopes for the lung physiology to return to normal.

At autopsy, microscopic examination of the lung shows fluid accumulation in the alveolar sacs, loss of the normal cilia of the bronchial tubes that clear secretions from the lungs, and occasionally secondary bacterial pneumonia.[5] Interestingly, at the time of death, little or no virus is identified in the lung, even in the most severely affected portions of the organ. However, antibodies against Coronavirus almost always are found in the bloodstream, indicating a recent infection with this organism. The absence of organisms is not unusual. When influenza leads to ARDS (as it does on very rare occasion), it is the rule that the virus can not be recovered or grown from lung tissue.

The organism believed to be causal in most cases of SARS is a variety of Coronavirus (officially, "SARS-associated Coronavirus" [SARS-CoV]). It was identified by a remarkable collaboration among scientists from Vietnam, Hong Kong, Taiwan, Thailand, and the United States[6] and simultaneously by investigators in Germany, France, and the Netherlands.[7] It is probably fair to say that never before has a previously unrecognized disease been characterized so

quickly, and against the current of mainstream virologic thought. Coronavirses have been well-described as the cause of illness in humans, but never had there been fatalities from this viral family. About one-third of all cases of the common cold are caused by the Coronavirus, and it also occasionally may cause diarrhea in young children. Death from Coronavirus sub-types was unknown.

The isolation of the organism led almost immediately to a diagnostic test based on the presence of antibodies in patients who were recovering from the illness, which was invaluable for broad population studies to establish the means of transmission, as well as the overall susceptibility to and incidence of the disease. In some cases, the antibody test also could be used to make the diagnosis of SARS when it was unclear if the patient was suffering from the Coronavirus or not.

Currently, there is little information on the value of anti-viral drugs, even though it appears that the SARS-CoV is sensitive to ribavarin (a well known anti-microbial agent) in tissue culture. Based on all of the clinical studies published to date, there is almost no evidence that treatment with ribavirin alters the outcome of patients with SARS. This, too, is not unusual for virus-caused diseases, although it may be that in the known cases of SARS, the diagnosis was made after a narrow therapeutic window—between the time of initial infection and onset of the most severe symptoms—had passed. In addition, it is possible that the respiratory failure relates to an individual host's immune system response to the virus rather than to the damage caused by the infection itself.

Because there has been limited time to follow SARS survivors, it is not known if chronic lung problems will plague these patients. However, in ARDS from other causes, patients who have been ventilated mechanically have been shown to have residual functional abnormalities[8] and a generally poor quality of life[9] for many months after hospital discharge. It is unlikely that the experience of survivors of SARS will be much different.

Compared to influenza A and each of its subtypes, SARS-CoV is a highly mortal disease. However, because of the much higher prevalence of influenza worldwide and in the United States, the number of deaths attributed to influenza is many times that of SARS. Between 1976 and 1997, the Center for Disease Control in the

United States estimates that, on average, more than 50,000 people died each year, and influenza is estimated to be involved (either as a direct cause of death or contributing to death in patients with other ailments) in a bit more than 2 percent of all deaths. In 1996, about 14,000 people in the United States died as a direct result of influenza, and another 54,000 with chronic circulatory or respiratory disease died from complications of influenza. It is difficult to know the overall mortality rate from influenza as statistics on the incidence of the disease are not available, but it is probably less than 1 percent. As with SARS, patients over age 65 have the highest mortality among age groups.

Finally, it is likely that SARS has been under diagnosed, with many mildly symptomatic individuals unrecognized. WHO criteria for SARS have been shown to be very specific (that is, resulting in few false positives) but not very sensitive (that is, a large number of false negatives).[10] Future population-based serologic surveys may define the actual incidence of the disease. For now, our description of SARS illness is largely limited to the population that is sick enough to seek medical care.

Thus, SARS-CoV is a significant cause of morbidity but, in total, has involved a tiny fraction of the number of people who contract influenza in any given year. The mortality from SARS in those infected is much higher than influenza, but because of the millions of infections with influenza every year in the United States alone, the number of deaths from influenza exceed those from SARS by at least three or four orders of magnitude.

SARS: History, Epidemiology, and Isolation of Causal Organism.

It is now reasonably certain that the first cases of SARS occurred in early November 2002 in Guangdong Province in southeastern China (see Map 1). The patient was a businessman, but the significance of his disease was recognized only in retrospect, and his illness, along with those of hundreds of other individuals with the same severe respiratory symptoms in the same province, was unknown outside China for some months. By early 2003, there were four major foci of life-threatening respiratory disease beyond mainland China: Hong Kong, Vietnam, Singapore, and Canada (Toronto).

Map 1.

It is not yet clear how many people in Guangdong the businessman infected in November 2002. The first patient outside of China to become ill with SARS was a 64-year-old physician from Guangdong Province who became symptomatic while visiting relatives in Hong Kong (now commonly referred to as the Hong Kong Special Administrative Region of China).[11] When he arrived in Hong Kong on February 21, 2003, he had been mildly ill for about 5 days, but felt well enough to go sightseeing and shopping with relatives.[12] He was admitted to the hospital the following day. About 3 days later, a 53-year-old male who accompanied the physician on his excursion around Hong Kong then became ill, and he was hospitalized 2 days later on February 26. Over the next 17 days, eight other people became ill with identical symptoms, all of them either staying at the same hotel as the physician index case, or who had contact with him in

the hospital or with other patients with respiratory disease recently hospitalized.

At about the same time, on February 28, a patient presented to the Vietnamese French Hospital of Hanoi with an influenza-like illness. Because of recent small outbreaks over the past 2 years in Southeast Asia of influenza transmitted directly from humans to birds, physicians in Hanoi became concerned that they were seeing another similar outbreak. Mortality in previous human avian influenza ("bird flu") cases was extremely high, and because of the fear that avian influenza had once again jumped into humans, WHO was contacted. Dr. Carlo Urbani, an infectious disease expert, was dispatched, and, within a few days, he and a small team of virologists and epidemiologists arrived in Hanoi. With in a few weeks, Dr. Urbani and at least five other health care workers would also be dead, all from the mysterious new disease contracted from patients they cared for.

Urbani and his colleagues set to work immediately collecting specimens, reviewing patient histories, and assisting hospital workers with infection control and patient isolation procedures. By March 9—just 10 days after the first patient in Vietnam appeared at the French Hospital—WHO was worried enough by Dr. Urbani's data to request an emergency meeting with high ranking health ministers in Hanoi, and recommended strict enforcement of patient isolation and barrier protection for all healthcare workers in Hanoi hospitals caring for patients with respiratory symptoms. *Medecins sans Frontiers* (Doctors without Borders), an international medical aid agency, provided additional physicians and personal protective equipment. More infection control specialists were dispatched to Hanoi.

Also on March 9, a 32-year-old Singaporean physician became ill with a high fever while in New York City on a visit. The previous week while in Singapore, he had cared for a patient from Hong Kong who presented "atypical pneumonia" on March 3. Four days later the doctor developed a dry cough and a rash. On March 16, while in Frankfurt on his way back to Singapore, he became so short of breath that he was sent to Frankfurt University Hospital and was admitted to the ICU. Subsequently, two people in close contact with

this physician—his wife and his mother—became ill about the time the doctor was admitted to the hospital.

Unknown to physicians in Hong Kong, Singapore, and Frankfurt, on February 25, 2003, in Toronto, Canada, a 78-year-old woman developed fever, sore throat, and a dry cough 2 days after returning from a 10-day visit to Hong Kong. She was given an oral anti-bacterial antibiotic but became progressively more ill. She died on March 5 while at home. Her 43-year-old son became ill with symptoms essentially identical to those of his mother on February 27, and on March 2 was admitted to the hospital. Progressive respiratory difficulties supervened, and he was placed on a mechanical ventilator on March 3. Despite careful intensive treatment, he died on March 13, roughly 2 weeks after becoming ill. An autopsy was performed, which revealed changes typical of the Adult Respiratory Distress Syndrome, but no evidence of viral infection was identified.[13]

By the end of March, there would be more than 100 cases of SARS in Canada, 156 in Hong Kong, and at least 40 in Vietnam. Many other countries would go on to identify cases of what became known as SARS within weeks. But, there was little, if any, information forthcoming from China. The Chinese government reported 305 cases of "atypical pneumonia" with at least five deaths to WHO on February 11, 2003 (even though an unusual disease outbreak had first been recognized in November 2002), but initially the disease was attributed to a rare cause of pneumonia, Chlamydia pneumonae.

WHO first alerted public health officials to the presence of a "severe form of pneumonia" on March 12, 2003,[14] after connecting the illnesses described above. A case definition was established and promulgated via the Internet and WHO bulletins. This case definition consisted of a set of symptoms (patient complaints) and signs (physicians' findings at the time of physical examination and also laboratory tests and X-ray results). The combination of signs and symptoms—a "syndrome"—is not to be confused with a diagnosis based on a specific, known cause (such as an infectious organism) and was called "Severe Acute Respiratory Syndrome" (SARS).

The first summary of the epidemiology of SARS—the patterns of disease by age, sex, and travel history of victims—appeared on March 31, published on the Web page of the *New England Journal of*

Medicine (NEJM). Never before had information about a completely new syndrome been categorized, collated, analyzed, checked, and distributed so quickly, nor had multicountry peer review ever before been marshaled so expeditiously. NEJM has an international reputation for high standards, and its requirements for publication, even in electronic form, are as stringent as any scientific journal anywhere in the world.

Then, remarkably on March 24, scientists at the CDC working closing with researchers in Hong Kong isolated and identified a virus of the family of viruses called Coronavirus (CoV) from the first patients with SARS (see Figure 1). They had taken respiratory secretions, blood samples, and other body fluids from SARS victims and plated the material out on a wide variety of animal cells growing in tissue culture vats. Within a few days of starting these experiments, investigators noted that in one particular cell culture—monkey kidney cells—were dying. Inspection of the cells under the electron microscope showed that they were filled with viral particles.

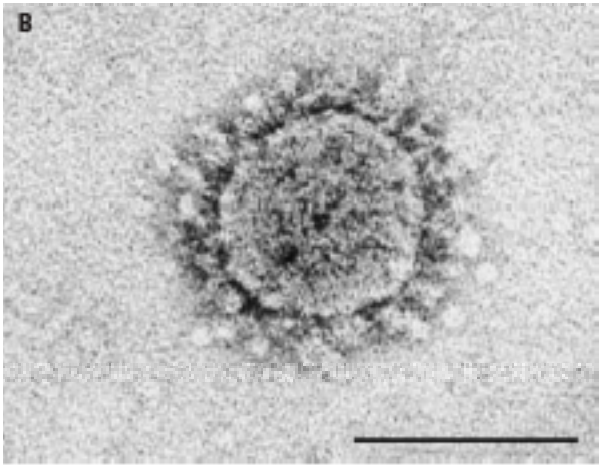

Figure 1: Coronavirus Urbani as Seen in the Electron Microscope (NEJM 348: 1954-66, 2003).

Within a week, a key portion of the genome of CoV had been completely sequenced and compared with all other known Coronavirus strains. It was found to be different not only from all other strains of Coronavirus that cause disease in humans, but from those strains that cause disease in a multitude of animal species: birds, cattle, pigs, and cats (both wild and domesticated). A group of investigators in Germany did the same, and proved that their gene sequencing was completely consistent with the CDC-Hong Kong group. Their results, along with a detailed description of clinical and autopsy findings, laboratory studies, and even a highly-specific prototype antibody test were described and published on the New England Journal web site on April 10, less than 7 weeks after the first cases of SARS appeared in Canada and Hong Kong. In honor of Dr. Urbani, the proposed name of the novel Coronavirus is the "Urbani strain of SARS-associated coronavirus).

How Do We Know That *C. Urbani* Causes SARS?

In response to any infection, mammalian immune systems produce a panoply of responses. At least a dozen different cells capture and degrade the invading organism, and some of these cells engulf and kill the virus directly. Other cells dismember the outer membrane constituents of the virus and deliver selected pieces to other cells that, after the passage of a few days, begin to generate antibodies that bind more-or-less specifically to the infectious agent. The quantity (called "titer") of antibodies (of several subtypes) slowly rises, usually over the course of 3 to 8 weeks. The presence and quantity of these antibodies can be identified by using antibodies from other animals (goats are a typical source) that bind to *human* antibodies—caprine anti-human antibodies—that are tagged further with fluorescent markers. If human anti-Coronavirus antibodies are obtained from an individual patient's blood and exposed to cells on a microscope slide containing the offending viral particles growing in them, the antibodies will bind to the cells. When the tagged caprine anti-human antibodies then are applied to the microscope slide, the cells become dotted with brightly fluorescing material (easily seen when illuminated with ultraviolet light source) and quantified. This

process is called "indirect-immunoflourescence," so named because the binding of the patient's own antibodies against the infectious agent is seen "indirectly" via the fluorescence of the tagged antibodies that, in turn, are bound tightly to target sites on the virus on a microscope slide, rather than by visualizing the antibodies themselves (which are too small to be seen with ordinary microscopes).

The case for Coronavirus *Urbani* as the cause of SARS was capped with the demonstration of increasing titer of antibodies in patients who recovered from SARS during 3 or 4 weeks of convalescence *and* a survey of hundreds of old (pre-SARS) blood-bank samples that failed to reveal any antibodies against C. *Urbani*. Thus, not only were patients who recovered from SARS generating specific antibodies to the virus, the virus had to be novel for, if it were ever in circulation previously in the human population, at least some blood donors would be expected to show evidence of past infection.

To date, Coronavirus *Urbani* has been found in respiratory secretions and fecal matter, but rarely in the bloodstream of patients suffering with disease. In animals, various strains of Coronavirus are isolated from the same sources. Most virologists believe that all of these materials are infectious.

Origin of Coronavirus Strain Urbani.

The family of Coronavirus is known to mutate frequently, that is, the genome of the virus may change suddenly, resulting in a new species of Coronavirus that may have a different host range or result in more severe disease. One way this mutation can occur is via the process of *recombination*, wherein two (or perhaps more) Coronavirus species that happen to infect a given animal at the same time shuffle and exchange their DNA within animal host cells. The daughter virus types that emerge from the animal cell then may contain an entirely new DNA construct (or, multiple types may result each with a unique and novel genome). A similar process occurs from time to time with the influenza virus, and when it does, a never-before seen strain of the virus may begin to circulate in the population. In addition, close and repeated contact between animals that carry these reassorted strains of influenza and humans—as occurs often in

crowded live-animal markets in Asia and on farms—seems to create a perfect niche for the passage of novel influenza strain to humans. It is not surprising that new varieties of influenza in recent decades have first appeared in Asia, particularly in China and Hong Kong.

Since Coronavirus species are the cause of a multitude of animal diseases (usually presenting as fatal respiratory disease or dehydration from diarrhea), and since agricultural animals tend to live in close quarters, spread from animal to animal is the rule, thereby permitting enormous numbers of reassortment variants.[15] Human farmers or customers in crowded animal markets are potential targets for novel strains that may have surprising changes in their host range. All of the known human Coronavirus species characterized to date cause mild illnesses: about 30 percent of "colds" (technically upper respiratory infections, not involving the lungs or interfering with respiration) are caused by a Coronavirus. On rare occasion, mild diarrhea in humans also results from Coronavirus.

Thus, it appears that an unwitting human in southern China acquired a novel strain of Coronavirus sometime in the fall of 2002. The source has not been identified yet. Some virologists believe that the organism was transmitted to humans from the civet cat, a gastronomic delicacy in China. However, human consumption of this animal, a 5,000 year tradition in China, casts doubt on the civet as the primary source of the disease;[16] nonetheless, Chinese officials banned the sale of wild animals in Guangdong. Dr. David Heyman, WHO's executive director for communicable disease, cautioned that the source of the virus remains speculative, and that it is possible that a seasonal pattern may emerge over time, suggesting environmental niches that might provide alternative paths of transmission beyond consumption of wild animals[17] or direct contact with Coronavirus-infected humans.

Transmission and Response:
Should SARS Have Caused such a Fuss?

In the early stages of a disease outbreak involving a manifestly novel agent, many uncertainties arise in predicting the speed of transmission of disease. As with SARS, the mode of transmission

is not immediately apparent early in many epidemics. Among the questions that epidemiologists try to answer are:

- Are there animal and/or insect vectors?
- Do infected individuals spread the micro-organism via aerosolization during coughing or sneezing? If individuals are infectious to others, how long do they remain so?
- What is the rate of new cases (sometimes called the "incidence") of disease?
- Are quarantine and travel restrictions necessary?

After establishing a "case definition," the primary data that public health officials need to answer these questions comes from the simple reporting of the time of onset of each case, location of the individual, and demographic information such as sex, approximate age, recent travel, and perhaps the individual's employment. With statistical tests to determine the degree of confidence in the data, epidemiologists can plot the data in a variety of ways to determine trends and thus infer the "behavior" of the epidemic. Needless to say, in the absence of routine information flow—as occurred in mainland China—even this simple analysis is impossible.

In March and April 2003, during the first few weeks of the SARS epidemic outside of mainland China, reporting was timely and generally complete. Although the media tended to focus on the fear (even panic) attendant to the unknown cause of the syndrome, it was possible to discern that the epidemic was growing slowly, and not at all what one might expect from an influenza-like virus that spread via aerosol from person-to-person. Simply by plotting the total number of reported cases by country over time, a benign picture emerged:[18]

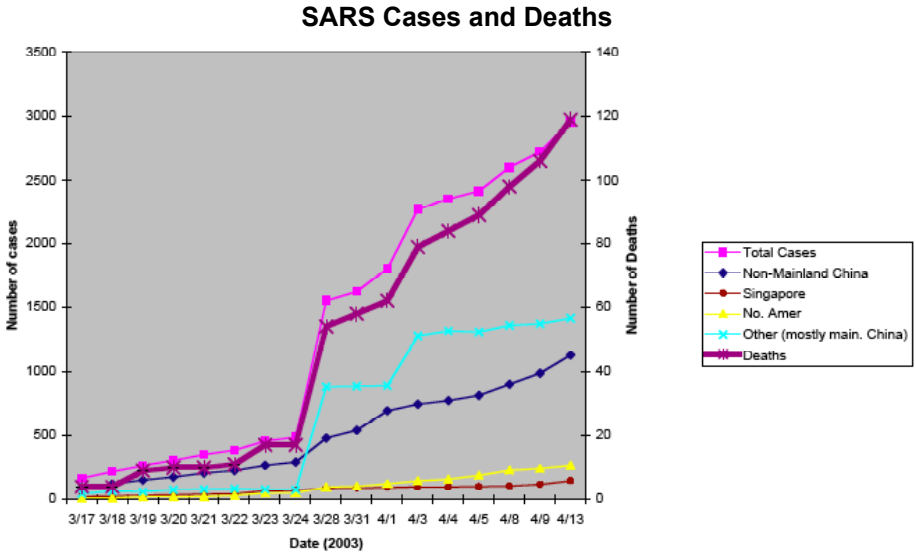

Figure 2.

Note that, the China mainland aside, the growth in the number of cases is approximately linear. Indeed, using basic statistical tools, it was possible to postulate a linear growth model, and test this hypothesis against actual number of cases:

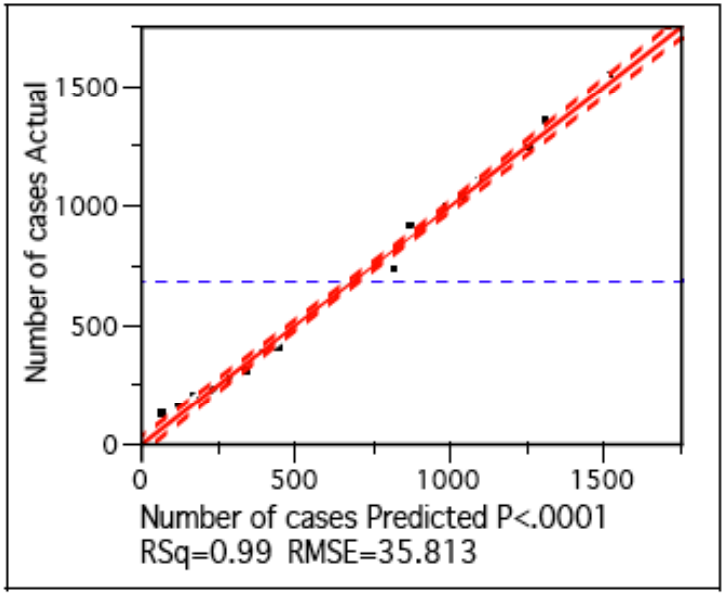

Figure 3.

Influenza (or closely related virus strains) almost certainly would have caused an exponential increase in the number of cases. As the epidemic proceeded and more cases were reported, public health personnel increasingly were confident that spread of the virus depended on close contact with infected individuals or contaminated surfaces.

With the exception of mainland China, exchange of data in the SARS epidemic was unprecedented.

Early Lessons from the SARS Epidemic for Public Health and Counterterrorism.

The tools of molecular biology, epidemiology with contact tracing, and modern communications via the Internet resulted in an unprecedented public health triumph: Within a few days of the first cases, WHO was able to organize collaborating teams of virologists, epidemiologists, and infectious disease experts, each critical to the isolation, identification, and containment of the disease. That the organism responsible for SARS was never before described underscores the profound importance of the global response and the value of independent groups working simultaneously. Indeed, the contemporaneous sequencing of the viral genome in the United States and Germany provided at once the identification of the organism and verification thereof. Further, the results along with expert interpretation in the context of the epidemic were communicated worldwide within days. As has been noted by others, if "business as usual" had applied in SARS, we might still be trying to identify the causal organism, and the disease might have been much more widely spread.

At the same time, the response to SARS might have been quicker—with fewer attendant deaths and fewer cases—had international public health workers been aware of the "atypical pneumonia" cases in China that began in November 2002. More than ever before, the management of novel infectious disease outbreaks is highly dependent on timely information. Transportation and commerce virtually assure that microbial pathogens in one part of the globe will be in major transport hubs within days or even hours, increasing the

likelihood of multipoint outbreaks and adding to the bewilderment of infectious disease experts trying to unravel the origin and modes of spread of the agent. The key, of course, is open dissemination of information; it appears that the Chinese public health infrastructure failed to do its part in what we now know to be the first days of SARS-CoV. Indeed, it was not until July 2005 that Chinese investigators published substantive information on their experience with SARS,[19] when an entire issue of the most widely read Chinese medical journal was devoted to SARS. An editorial accompanying the scientific papers mentioned nothing about reporting delays nor interrupted information flow as contributors to both domestic and international spread of SARS.

The ingress of human activity into previously unexplored regions and the close contact between humans and hundreds of animal species guarantees the exchange of countless organisms. Mercifully, most of them will not result in disease (in either humans or animals).

SARS is but the latest in a series of "emerging" diseases—illnesses due to infectious agents that were not described previously—that have begun to affect humans. In just the past few decades, medical journals and newspaper headlines have been filled with articles about these new disease entities: Ebola hemorrhagic fever (from squirrels and perhaps monkeys), Hantavirus Pulmonary Syndrome (from mice), Spongioform encephalopathy (from cows), and monkeypox (transmitted by prairie dogs), all occurring in people. Although this list is incomplete and doubtless other novel diseases await us, similarities can be identified readily. All of the organisms originate in nonhuman species and have occurred when humans and the natural animal hosts come in close contact (indeed, in the case of both Ebola and Spongioform encephalopathy, consumption of infected animal tissue seems to be required). Each of the organisms causes diseases with high mortality (in the case of Ebola and Spongioform encephalopathy, nearly 100 percent), and none can be treated successfully yet. Finally, while treatment is elusive, prevention generally is simple, with either avoidance of contact or, in the case of SARS-CoV, careful isolation of infectious patients until their disease resolves.

Given the characteristics of emerging disease pathogens, rapid identification of disease foci is essential. Remarkably enough,

having a pathogen in hand (or surrogate diagnostic test results) is not necessary in order to recognize that a problem may be brewing. Syndrome-based surveillance (SBS), depending only on the signs and symptoms in seriously ill people or animals, may be sufficient to mobilize international action—first with quarantine, followed by the application of new techniques in genomics, molecular biology, immunology and cell culture to identify causal organisms *combined with* the sharing of results so that they may be independently verified. The power of SBS to give early warning to public health officials and government decisionmakers has been described recently,[20] and at least two systems, ESSENCE II and the Syndrome Reporting Information System (SYRIS),[21] have been in operation in several U.S. states for the past 2 years,[22] and SYRIS has been used in Singapore to help manage the SARS epidemic there. Each system draws on the basic tenants of epidemiology: establishing what *kind* of illness a patient (or animal) has; *when* the illness began; and *where* the patient is located or has traveled.

Approaches to SBS fall into two broad categories: "passive" systems that utilize data commonly gathered in the care of patients such as emergency room records, ambulance flowsheets, and even billing from physician offices; and "active" systems that depend on health care providers to identify the case and describe the signs and symptoms observed. There are advantages and disadvantages to each. Passive systems are nonspecific, depend on availability of sensitive patient data via electronic means, and assume that the kind of information cataloged in western medical systems is similar to that gathered elsewhere. Analysis therefore may be difficult, and false alarms may occur. However, passive systems do not require specific input from busy healthcare providers; clerks or administrators (and automated billing systems) can provide much of the needed data.

Active systems exploit physician judgment, depending on doctors to enter required information (preferably via a computer interface with immediate dissemination of reports). In any surveillance system, there is a trade-off between the *quantity* of data and its *quality*, often referred to as the "signal to noise" ratio in scientific disciplines. Active systems operate on the hypothesis that physician are able to determine quickly the severity of illness, even though the underlying etiology is unknown. It may be the case that nonspecific indicators—

such as the raw number of patients ill with mild symptoms (generally not captured in billing statements or "chief complaints" recorded by nursing or ambulance personnel)—will lead to false alarms, triggering costly investigations or preventive measures that are unwarranted. On the other hand, the sudden appearance of even a small number of patients with severe constitutional symptoms (high fever and prostration, for example), along with certain clinical signs such as rash or pneumonia, may be indicative of the earliest stages of an epidemic, including one caused by terrorist use of biological weapons.[23]

Active and passive surveillance systems have not demonstrated their cost-effectiveness yet. However, in at least one important case, syndrome surveillance enabled public health officials to determine rapidly that a report of stolen samples of virulent plague organisms from a medical school in Texas was a hoax.[24] By noting the *absence* of respiratory disease at a time when a high incidence of seasonally-related respiratory symptoms was expected, local officials could assure physicians and the public that there was no reason for worry. In addition, public health officials used the syndrome surveillance system to communicate new information and all-important diagnostic criteria for plague to physicians in the community who, by and large, had never seen a case of this disease.

Conclusions.

The management of the SARS-CoV epidemic of 2003 was, for the most part, a victory for scientists working in epidemiology and molecular biology. Within weeks, the organism was isolated and identified, and a diagnostic test was perfected. Perhaps more important, by careful reporting and contact tracing, it was possible to determine that the disease spread slowly, implying that there was little likelihood of aerosol transmission from person-to-person, a key discovery that changed travel recommendations and even trade dramatically.[25] While there is no question that there were serious economic consequences from the epidemic and nearly 1000 people have died to date, the impact would have been much more severe in the presence of greater uncertainty about the behavior of the virus and the disease it caused.

SARS provides decisionmakers and public health officials with a model that generates valuable lessons for the response to future disease outbreaks, including those that are introduced intentionally into the human or animal population by terrorists. The key to the successful management of SARS was the rapid sharing of information. Countries that openly reported information benefited both themselves and other nations. Mortality, though substantial, was modest when compared to the yearly toll from influenza, and economic catastrophe via draconian travel and trade restrictions was avoided.

The international community may be poised to adopt a formal system of routine data sharing via the Internet, overcoming the time delays inherent in traditional reporting hierarchies. Several promising Internet-based applications operating in the United States, Europe, and Asia can provide invaluable information to public health officials trying to limit the spread of infection and to the physicians who care for those who become ill during epidemics. A modest amount of political will is all that is required. Since infectious disease respects no border, people living in countries whose leaders choose to suppress information or subvert open reporting may suffer immeasurably in future outbreaks that are certain to occur.

ENDNOTES - CHAPTER 6

1. I will use the abbreviation "SARS" when referring to the syndrome and SARS-CoV when discussing the disease caused by the newly discovered Coronavirus. More detail is provided in the text.

2. See *www.who.int/csr/sars/country/2003_08_15/en/*.

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12. K. W. Tsang, P. L. Ho, G. C. Ooi, *et al*., "Cluster of Cases of Severe Acute Respiratory Syndrome in Hong Kong," *New England Journal of Medicine*, Vol. 348, 2003, pp. 1977-1985.

13. S. M. Poutanen, D. E. Low, Henry B., S. Finkelstein, *et al*., "Identification of Severe Acute Respiratory Syndrome in Canada," *New England Journal of Medicine*, Vol. 348, 2003, pp. 1995-2005.

14. See *www.who.int/csr/sars/archive/2003_03_12/en/*. The WHO on-line archives serve as the single most comprehensive source of information about SARS.

15. It is believed that the vast majority of recombinant strains of virus are nonviable because their DNA does not contain the necessary codes to produce functioning daughter virus particles.

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17. *Ibid*., June 21, 2003, p. 1350.

18. The graphs are taken from an informal paper that I circulated among public health officials in Switzerland, the United States, and Singapore, updated twice weekly in the early weeks of the SARS outbreak. This work was not peer-reviewed, but was reported in *Science*, Vol. 300, April 25, 2003, pp. 558-559.

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