SARS: A Global Response to an International Threat

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AN ESTIMATED 6.4 MILLION PEOPLE die each year from AIDS, tuberculosis, and malaria, while vaccine-preventable diseases afflicting children kill some 1.3 million more.[1] Yet severe acute respiratory syndrome (SARS), which infected some 8,000 people and killed almost 800 during a seven-month period in early 2003, has transformed the way we think about infectious diseases. No matter how remote the area in which a newly emerged infectious disease occurs, we now have a clear demonstration of its potential to cause human suffering and death, spread internationally, and profoundly affect economies and societies.

The emergence of SARS is the second major event of the 21st century to change the perception of the infectious disease threat in the eyes of politicians and the general public. The deliberate use of anthrax to incite terror, which quickly followed the events of 11 September 2001 in the U.S., was the first event. Prior to this, the emergence of new diseases, especially AIDS, had sharpened concern about the threat of infectious disease as a disruptive and destabilizing force and given it a place in national security debates.[2] Altogether, more than forty new diseases have emerged over the past three decades—an unprecedented trend that is certain to continue.[3] Of these, AIDS has most vividly demonstrated the capacity of a new disease to spread around the world, affect the poor disproportionately, and cause damage on a scale that reaches far beyond its immediate effects on health.[4]

The reality of bioterrorism immediately raised the infectious disease threat to the level of a high-priority security imperative worthy of attention in defence and intelligence circles. In so doing, it focused attention on several features of the infectious

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disease situation that make outbreaks, whatever their cause, an especially ominous threat. These include silent incubation periods that allow microbes to cross borders undetected and undeterred, the rapid speed of international spread made possible by the volume of air travel, and the potential for public concern that was amplified by instantaneous electronic communications. In particular, debates about the possible deliberate use of the smallpox virus revealed the public concern that can ensue when a severe and contagious disease, whether old or new, has no effective cure.

SARS has now demonstrated these theoretical concerns in a concrete way. It was the first severe and readily transmissible new infectious disease of the 21st century to spread rapidly along the routes of international air travel, placing any country with an international airport at risk of an imported case. As noted in a recent National Intelligence Council report, the SARS threat has convinced even sceptical government leaders that health problems can have profound social, economic, and political consequences.[5] It has shown how, in a closely interconnected and interdependent world, a new and poorly understood disease with no vaccine and no effective cure can adversely affect economic growth, trade, tourism, business and industrial performance, political careers, and social stability. SARS made people feel so vulnerable that people started to wear surgical masks as they went about their daily lives—often in low-risk situations—and provided dramatic images of empty airports and cancelled flights. The perceived risk of SARS was many times greater than the actual risk, an aspect that compounded its negative social and economic impact.

SARS has also demonstrated some positive features of a globalized society: the advantages of rapid electronic communications and new information technologies for emergency response, and the willingness of the international community to form a united front against a common threat. These features contributed significantly to the world's prompt response to SARS.

New infectious diseases are poorly understood as they emerge and are often associated with high mortality rates.[6] Appropriate control measures are often elusive in the absence of knowledge about the causative agent, modes of transmission, or groups at special risk. Initial efforts to treat them rely on selecting among therapies that are known to work in other diseases. SARS was no exception, and it proved to be an especially difficult disease to diagnose and treat.

Many new diseases have features that limit their potential for international spread. Some never establish efficient person-to-person transmission, while others depend on the presence of a mosquito or other vector as part of the transmission cycle. Still others remain closely tied to a specific geographical region. In some cases, patients are visibly too ill to travel during the most contagious period. In contrast, SARS spread readily from person to person. It required no vector, displayed no particular geographical af-

finity, mimicked the symptoms of many other diseases, took its heaviest toll on hospital staff, killed around 10 percent of those infected, and spread internationally with alarming ease. The rapid containment of SARS holds many lessons for an international community already concerned about the resurgence of the infectious disease threat.

Preparedness for the SARS Response: Under Development for Six Years

The international response to SARS was the roll-out of a series of mechanisms for outbreak detection and containment that had been under development since 1997. These years of planning took their impetus from a sequence of events that dramatically demonstrated both the resurgence of the infectious disease threat and the magnitude of its impact. In 1991, epidemic cholera returned to Latin America for the first time in almost a century, causing 400,000 cases and 4,000 deaths within a year.[7] In Peru alone, the arrival of cholera is estimated to have cost the country's economy US$770 million in lost trade and tourism.[8] In 1992, the Institute of Medicine published its landmark report on emerging infections, mapping out trends in the resurgence of the microbial threat while examining the causes and consequences for the United States and international health.[9] In 1994, sensational media coverage of pneumonic plague in Surat, India led to severe economic losses estimated in the range of US$2 billion. Most significant, however, was the 1995 outbreak of Ebola hemorrhagic fever in Kikwit, Democratic Republic of the Congo.[10] The highly publicized outbreak, which caught the international community by surprise, signalled the need for stronger infectious disease surveillance and control worldwide, improved international preparedness to provide support when similar outbreaks occur, and redoubled efforts to assist the press in providing accurate information. A need for more broad-based international health regulations and electronic information systems within the World Health Organization (WHO) also became evident, as did the idea that timely and adequate outbreak detection and response would need support from a broad coalition of partners.[11]

In 1997, WHO began developing several new mechanisms to meet these needs. Systems of electronic communications were set up to ensure that WHO, supported by its 141 country offices concentrated in the developing world, could provide around-the-clock authoritative information during outbreaks. More than 110 existing institutes, laboratories, agencies, and surveillance systems, with a diverse range of expertise in infectious diseases and a broad geographical representation, were brought together to form the electronically interlinked Global Outbreak Alert and Response Network (GOARN). WHO also began using the Global Public Health Intelligence Network (GPHIN) developed for WHO by Health Canada, a computer application designed to improve the speed of outbreak detection. It is a web-crawling system that is pro-

grammed to search for key words suggesting an outbreak in over 950 news sources and electronic discussion groups worldwide, in several languages. GPHIN thus brought tremendous advances in response time compared to traditional systems, where an alert sounds only after case reports at the local level progressively filter to the national level and are then reported to WHO.

All these mechanisms have been well-tested. GPHIN currently picks up, in real time, the first hints of close to 40 percent of the roughly 200 outbreaks investigated by WHO each year. Of these yearly outbreaks, around 50 will require an international response to prevent further spread. GOARN partners provide the staff, specialized expertise, secure laboratory facilities, and other resources needed to investigate serious outbreaks and mount rapid containment activities.

In other developments, a WHO network for the surveillance of influenza viruses, established in 1948 to keep the world alert to the emergence of new strains, became the model for similar electronically linked networks, now also within GOARN. These networks of experts and laboratories were set up to keep watch over other especially worrisome epidemic-prone diseases, including dengue and dengue hemorrhagic fever. Concepts of outbreak verification, definitions of what constitutes a disease event of international concern, and procedures for investigating the many events picked up by GPHIN each day were also worked out. All of these developments became the driving force behind a sweeping revision of the International Health Regulations, which govern international procedures for the reporting of epidemic-prone diseases and the application of measures to prevent their spread. All of these new mechanisms, networks, and procedures were severely tested during the SARS outbreak and played a decisive role in its containment.

THE EMERGENCE OF A NEW DISEASE

The first cases of SARS are now thought to have emerged in mid-November 2002 in the southern Chinese province of Guangdong. Retrospective studies of patient records, by Chinese and GOARN epidemiologists, suggest that the first case occurred in Foshan city on 16 November.[12] Altogether, early cases were identified in seven municipalities. No links among the various outbreaks have so far been traced, adding weight to theories that the SARS virus jumped to humans from some animal species or other environmental reservoir found in southern China. Most of these early outbreaks were small, with the largest chain of transmission affecting 20 persons.[13] Early reports suggested a link between cases and the handling of wild animals captured or bred and marketed for human consumption.[14] Recent studies have detected a virus genetically similar to the SARS coronavirus in two animal species, the masked palm civet and the raccoon dog.[15]

However, much more research is needed before firm conclusions about the origins of SARS can be reached.

The number of SARS cases began to grow dramatically during the last week of January 2003, when hospitalized cases became the source of the virus's rapid spread to health care workers, other patients, and visitors. One person with SARS, admitted to a hospital on 30 January and subsequently treated at several facilities, is thought to have spread the virus to 91 persons, with secondary spread to 37 of 47 (79 percent) of staff contacts at one hospital.[16] The outbreak peaked during the first ten days of February, when close to 40 new cases were being reported each day. Altogether, some 1,512 cases are thought to have occurred during the Guangdong outbreak, which took its heaviest toll on health care workers in urban hospitals. This pattern of occurence in urban areas, with most cases concentrated in hospitals and hospital infections playing a major role in transmission, was repeated as the disease began to spread internationally.

SARS is thought to have first moved out of southern China on 21 February 2003, when a medical doctor from Guangdong who had treated patients, and was himself suffering from respiratory symptoms, spent a single night in a Hong Kong hotel. Through mechanisms that may never be fully understood but probably involved personal contact with a concentrated source of the virus, he transmitted the SARS virus to at least 16 other guests and visitors, all linked to the same hotel floor. They carried the virus with them as they travelled to Toronto, Vietnam, and Singapore or entered the hospitals of Hong Kong. Thus, from contact on a single hotel floor, the international outbreak began.[17]

Prime Suspect: Influenza

Chinese authorities did not report the Guangdong outbreak to WHO until 11 February. Hints of an outbreak had surfaced, however, and influenza was the prime and most feared initial suspect. The influenza virus, which is highly unstable and genetically labile, undergoes constant small mutations ("drifts") in its antigenic properties, necessitating annual changes in the composition of influenza vaccines in anticipation of each year's epidemic season. The influenza virus can also change suddenly and markedly in a process known as antigenic "shift." These changes, which occur around three to four times each century, result in a new virus strain to which populations may have no immunity and against which no existing vaccine may confer protection. When this happens, highly lethal influenza pandemics can rapidly sweep the globe. The great influenza pandemic of 1918–1919, which caused an estimated 40 to 50 million deaths worldwide, was followed by pandemics in 1957–1958 and 1968–1969. Experts agree that another influenza pandemic is inevitable and probably imminent. Conditions for

the emergence of antigenic shift are most favourable in areas characterized by a large population of aquatic birds and by humans living in close proximity to poultry and pigs, which facilitate the scrambling of genetic material of human and animal influenza viruses. These conditions are readily present in southern China, which provided the setting for the emergence of viruses implicated in the 1957 and 1968 pandemics.[18]

On 23 November 2002, during a Chinese national influenza workshop attended by a WHO scientist, a participant from Guangdong Province reported a "serious outbreak with high mortality and involvement of health care staff." On 27 November, GPHIN picked up reports of a "flu outbreak" in mainland China. WHO requests for further information were met in mid-December with assurance that influenza activity in Beijing and Guangdong was normal, that schoolchildren were mainly affected, and that no unusual strains of the virus had been detected. On 10 February, GPHIN and other GOARN partners identified reports of a "strange contagious disease" with respiratory symptoms affecting health workers in Guangdong hospitals and causing "widespread panic." An urgent alert was sent to Network members. The next day, WHO received reports from the Chinese Ministry of Health confirming the outbreak of an acute respiratory syndrome with 300 cases and five deaths in Guangdong Province, said to be coming under control. Concern intensified on 19 February, when authorities in Hong Kong reported an outbreak of avian influenza, or "bird flu," in members of a family who had recently travelled to southern China.[19] WHO alerted its collaborating laboratories and activated its influenza pandemic plans. On the last day of February, a WHO staff member attending cases of an unusual respiratory illness in a Hanoi hospital alerted WHO officials to features of the outbreak that gave cause for great concern about further international spread. Although avian influenza was initially suspected, all tests for influenza viruses and all other known causes of severe respiratory disease were negative.

THE FIRST EMERGENCY ALERTS

The first global alert to what would later be known as SARS was issued on 12 March 2003, following reports from Hong Kong authorities of an unusual outbreak of respiratory illness in one of its public hospitals. Cases had symptoms similar to those seen in staff and patients at the Hanoi hospital. These symptoms, which included atypical pneumonia, were also similar to those described in the report on the Guangdong outbreak. Laboratory tests at the three outbreak sites ruled out all known causes of severe respiratory illness, including influenza. Faced with reports of a severe disease of unknown cause rapidly spreading in hospitals, WHO issued a global alert describing the symptoms and recommending that any persons with atypical pneumonia be isolated

and managed according to the strict procedures of infection control. Within two days, health authorities in Singapore and Toronto reported similar cases, likewise concentrated in hospitals. At the same time, a physician who had treated the earliest cases in the Singapore outbreak and travelled to a medical conference in New York became ill on a return flight to Singapore and left the flight midway for medical care during a stopover in Frankfurt. He and an accompanying family member became Europe's first imported cases of the new disease. The potential for international spread via air travel had become clear.

Following this rapid escalation of events, WHO issued a second, stronger alert on 15 March, this time in the form of an emergency travel advisory. It set out a case definition, provided advice to international travellers should they develop similar symptoms, and gave the new disease its name: severe acute respiratory syndrome. At that time the cause of SARS had not been identified. It did not respond to medicines known to be effective against a number of respiratory infections, and many patients were becoming seriously ill, some requiring artificial ventilation. The situation on 15 March was alarming to public health experts because the majority of cases appeared to be occurring in health workers, almost half were listed in serious or critical condition, none had yet recovered, and this previously unknown infectious disease was spreading to major cities along the routes of international air travel. Public health officials, confronting an emergency and compelled to act, had only one option: to attempt to contain the disease by interrupting human transmission, and hopefully prevent it from becoming as constant a threat to humans as AIDS, tuberculosis, and malaria. The emergence and spread of SARS in the developing world would be particularly worrisome, given the high fatality rates, the concentration of cases in health care settings, the need for highly specialized protective equipment and isolation facilities, and the long periods of intensive care needed for many patients.

Altogether, only 123 cases occurred outside the initial outbreak sites, with the notable exception of Taiwan, where amplification of transmission in a single hospital contributed to an outbreak of over 600 cases and 180 deaths.

In terms of the further evolution of SARS, the global alerts of mid-March provided a clear line of demarcation between the earliest outbreaks in China, Hong Kong, Hanoi, Toronto, and Singapore—all of which were severe—and the situation in the 26 additional areas where cases probable occurred. Areas with outbreaks prior to the global alert accounted for approximately 90 percent of the global total number of cases and 79 percent of total deaths. Due to high levels of vigilance and preparedness, prompt

isolation of cases, management adhering to strict procedures of infection control, and rigorous tracing and management of contacts, the additional 26 sites were able to prevent further transmission or limit it to just a handful of cases. Altogether, only 123 probable cases occurred outside the initial outbreak sites, with the notable exception of Taiwan, where the amplification of transmission in a single hospital contributed to an outbreak of over 600 cases and 180 deaths. By early May, outbreaks had begun to peak at all major sites, with the exception of mainland China and Taiwan. On 5 July, WHO declared that all known chains of human-to-human transmission had been broken—a triumph of both political commitment and time-honoured control measures.

Control Measures

Two days after issuing the emergency travel advisory, WHO used a secure web site and telephone and video conferences to set up "virtual" networks of scientists, epidemiologists at all outbreak sites, and clinicians. These experts set aside competition and collaborated around the clock to identify the SARS causative agent, sequence its genome, define its clinical features, and investigate its modes of transmission in record time. Within a month, the laboratory network identified the cause of SARS as a new coronavirus unlike any other known human or animal virus in its family.[20] The network of epidemiologists confirmed that the virus was transmitted among humans by close person-to-person contact. Real-time information sharing also confirmed that hospital workers were at particular risk, along with their family members and those with whom they and their family members had contact. The clinical network also confirmed that no known drugs could cure the infection. Nor was a vaccine available for prevention.

The control of SARS therefore depended on evidence-based measures of outbreak control that date from the mid-19th century, when John Snow, sometimes called the father of modern epidemiology, successfully controlled an outbreak of cholera in London.[21] By mapping the households where residents had died from severe debilitating diarrhea, Snow was able to link the outbreak to a water source on Broad Street in Central London. Based on this evidence, he directed health workers to remove the handle from the Broad Street water pump, forcing the use of an alternate water supply. As a result of his efforts, the outbreak failed to spread further.

The evidence-based measures used to control SARS also included mapping persons who had signs and symptoms compatible with SARS, relying upon the newly available knowledge that transmission was being caused by close human-to-human contact. Once the geographical extent of the outbreak was understood, all cases were identified, treated and isolated to remove sources of infection. Moreover, with the

occasional help of civil authorities, measures were taken to avoid infecting hospital and public health workers. This was accomplished by identifying all contacts who could have been infected by patients and putting them under observation so that they in turn could be immediately isolated and hospitalized should they develop symptoms.

Though the principles of evidence-based public health were the same in Snow's time as they are today, the complexity of outbreak management in SARS was much greater. When Snow mapped the cholera outbreak in London, the disease had possibly entered London through shipyards and passengers of docking ships, and thereafter spread slowly to other ports. In contrast, SARS spread internationally within hours by air travel. Though the international outbreak began on a single floor of a hotel, control efforts never faced an option as simple as removing a handle from a single pump. However, as evidence accumulated through real-time collaboration of public health experts, other control measures were introduced to meet specific needs. One urgent need was to seal off opportunities for further international spread. It became evident, for example, that persons with SARS continued to travel internationally after 15 March, and that some of them had infected fellow passengers seated nearby. At the same time it was evident that contacts of SARS patients likewise continued to travel, becoming ill once they arrived at their destination. On 27 March, recommendations were therefore made for countries with major outbreaks to begin screening departing passengers for fever and other signs of SARS, and for a history of possible contact with a SARS patient.

Apart from the direct costs of intensive medical care and control interventions, and absenteeism from work, SARS caused widespread social disruption and economic loss.

Nonetheless, evidence that cases were being exported by air travellers to new countries continued to mount, especially in areas where chains of transmission had moved outside confined environments, like the health care setting and into the general community. In late March, Hong Kong experienced hundreds of almost simultaneous cases among residents in a single housing estate, suggesting that SARS might be transmitted by some unidentified source in the environment, further increasing the risk of spread within the community at large. Based on these and other epidemiological criteria, including the magnitude and dynamics of the outbreak at individual sites, WHO issued on 2 April the first of several recommendations that travellers consider postponing all but essential travel to designated areas where the risk of infection with the SARS virus was considered great. Travel recommendations were then removed when precise epidemiological criteria, indicative of a low risk to travellers, were met. Meeting these

criteria became a strong motivation for governments and populations to collaborate in bringing the outbreaks under control and provided the general public with reassurance about the safety of international travel.

The economic cost of the SARS outbreak was high. Apart from the direct costs of intensive medical care and control interventions, and absenteeism from work, SARS caused widespread social disruption and economic loss. Schools, hospitals, and some borders were closed and thousands of people were placed in quarantine. International travel to affected areas plummeted by 50 percent to 70 percent. Hotel occupancy in some Asian countries dropped by more than 60 percent. Many businesses failed, particularly in tourism-related areas, while some large industrial facilities suspended operations when cases appeared among workers. Preliminary estimates have placed the cost of the outbreak at nearly US$100 billion, mainly as a result of cancelled travel and decreased investment in Asia. But economic recovery began to occur shortly after the outbreaks had been controlled and continues even today, with the long-term impact estimated to be much less severe than the initial predictions.

Although control measures eventually proved effective, it is questionable whether they could have been sustained much longer. Virtually no country where large outbreaks occurred had adequate capacity to cope with the SARS caseload, especially since health care workers themselves were frequently infected. Some hospitals were designated solely to treat SARS patients, while others were closed. Still other treatment facilities were hastily organized. In Singapore, diagnoses of other epidemic-prone diseases, including dengue, were overlooked. In China, programs for childhood immunization and tuberculosis were halted as the SARS effort usurped all available staff and resources.

Heads of state became involved in the outbreak early and visibly, partly because of its profound economic impact, and partly because of the fear it created among their citizens. Moreover, they fully participated in outbreak control through frequent press briefings and declarations. Special meetings were held among ministers of health and heads of state of the APEC and ASEAN countries in order to enhance collaboration. Additionally, regional surveillance and response systems were designed and established as safeguards for future infectious disease outbreaks.

WHY THE WORRY?

SARS will not be the last new disease to emerge in our globalized world. Although the rapid containment of SARS marks a success in public health and caused few casualties when compared to many other infectious diseases, it is nonetheless a warning. SARS proves the willingness of the world's best scientists, clinicians, and public health epidemiologists to set aside academic competition and work together for the public good. At

the same time, there was an element of good fortune involved, as the most severely affected areas had well-developed health systems. Had SARS spread to countries with less developed health systems, cases could still be occurring and blending into the everyday panoply of infectious diseases that threaten human populations.

The jury is still out regarding the future of SARS—time, continued alert, and research are needed before firm predictions can be made. The prompt reporting of a suspected SARS outbreak in Canada in July and of a laboratory confirmed SARS case in Singapore in mid-September , associated with a laboratory accident are encouraging signs that vigilance for a return of SARS remains high, and that countries are ready to report the first suspicious signs. Nonetheless, the world may not be so fortunate if and when SARS re-emerges, and when the next infectious threat to follow SARS inevitably surfaces. But the lesson is clear: any new infectious disease with the potential for international spread must be reported promptly and openly. In a globalized, electronically interconnected world, attempts to conceal cases of an infectious disease for fear of social and economic consequences must be recognized as an action that carries a very high price: loss of credibility in the eyes of the international community, escalating negative domestic economic impact, damage to the health and economies of neighbouring countries, and a very real risk that outbreaks within the country's own territory can spiral out of control.

The importance of open and transparent reporting was formally acknowledged in May 2003, when delegates to the World Health Assembly adopted a resolution on SARS.[22] A second resolution, on the ongoing revision of the International Health Regulations, gave WHO the authority to take on a stronger role in coordinating the response to any infectious disease that is a threat to international public health.[23] Rather than waiting for official government notifications of an outbreak, WHO can now act to verify outbreaks based on information from any available official or nonofficial sources, including GPHIN. In addition, the resolution reaffirms WHO's leadership in determining the severity of outbreaks through on-the-spot investigations to ensure that adequate control measures are in place.

In the final analysis, the question "Why worry about SARS?" joins many other questions concerning the origins of this new disease, the prospects for the development of a vaccine, cure, and reliable point-of-care diagnostic test, and how the world will respond should the disease recur. SARS has vividly illustrated the importance of international collaboration when confronted by a shared threat. Forms of collaboration, developed either previously or because of the specific challenge of SARS, will hold the world in good stead when the next infectious disease threat emerges.

NOTES

* The evolution of the global SARS outbreak has been chronicled in daily situation updates, archived on the SARS pages at the WHO web site: http://www.who.int/csr/sars/en/index.html

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