Chapter 12

Dealing with Global Infectious Disease Emergencies

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BACKGROUND: GLOBAL INFECTIOUS DISEASE EMERGENCIES

The microbes that cause human infectious diseases are complex, dynamic, and constantly evolving. They reproduce rapidly, mutate frequently, adapt with relative ease to new environments and hosts, and frequently breach the species barrier between animals and humans. Social, economic, and environmental factors linked to a host of human populations and activities can accelerate and amplify these natural phenomena. The ability of infectious diseases to spread internationally—carried by humans, insect vectors, food and food products, and livestock—has been greatly augmented by the pressures of a crowded, closely interconnected, and highly mobile world. When they spread internationally, infectious diseases often lead to global emergencies.

The emergence of Acquired Immunodeficiency Syndrome (AIDS) and its rapid progression to endemicity demonstrates how a previously unknown pathogen can cause a worldwide emergency on a scale that threatens to destabilize social structures and economies of whole regions, leading to a potential disaster situation (Price-Smith, 2002) (see also chapter 11 by W. Gunn). Over a period of 25 years AIDS has become the most important cause of infectious disease mortality in adults, and its prevalence is predicted to continue to increase in many parts of the world (WHO/UNAIDS).

Although AIDS provides the most vivid and direct expression of the a global emergency caused by an infectious disease, the threat posed by other emerging and re-emerging infectious diseases has become increasingly difficult to ignore. These diseases affect all countries either internally, in the form of newly established or re-emerging endemic diseases, or as an external threat, in the form of internationally spreading epidemics (Heymann, 2001).

In addition to causing national or global emergencies, emerging and re-emerging infectious diseases are often highly publicized. Many are poorly understood, difficult to treat, and highly lethal as microbes from animals enter immuno-naïve human populations. New infectious diseases have emerged at the rate of one per year since the mid-1970s (Woolhouse & Dye, 2001). Ebola haemorrhagic fever in Africa, hantavirus pulmonary syndrome in the USA, Nipah virus encephalitis in Southeast Asia, and severe acute respiratory syndrome (SARS) in China are just a few examples.

Over the time frame, older infectious diseases have re-emerged as well. Cholera, now in its seventh pandemic, returned to Latin American in 1991 after an absence of almost a century. Within a year, 400,000 cases and 4,000 deaths were reported from 11 countries of the Americas (Tauxe, Mintz, & Quick, 1995). Yellow Fever has threatened to cause massive urban epidemics in Africa. An urban outbreak in Côte d'Ivoire in 2001 necessitated the emergency immunization of 2.9 million persons in less than two weeks, depleting the international reserves of vaccine stocks (WHO, 2002). Yellow fever caused urban outbreaks in 2002 in Senegal that, again, required great international efforts to secure sufficient emergency vaccine supplies (Wkly Epidemiol Rec, 2002).

The 1998 epidemics of dengue and dengue haemorrhagic fever were unprecedented in geographical occurrence and numbers of cases, and the epidemics of 2002, 2003, and 2004 continued to spread internationally, causing, to mention one country, Indonesia, the Health Minister to declare a health emergency in early 2004 (WHO, 2002; WH Assembly document A55/19). A new strain of meningococcal meningitis (W135) emerged in 2002 in sub-Saharan Africa, defying emergency preparedness in the form of stockpiled vaccines against conventional strains (WHO, 2002; Wkly Epidemiol Rec, 2002). New and more severe strains of common foodborne pathogens, including *E. coli* O157:H7, *Campylobacter*, and *Listeria monocytogens*, have made the profile of foodborne diseases distinctly more important (Tauxe, 1997; WHO Fact sheet 124(2002); Document no. WHO/CDS/CSR/APH/2002.6). The invariably fatal variant Creutzfeldt-Jakob disease, first recognized in 1996 and probably transmitted to humans through beef or cattle products, has added considerably to this concern (Document no. WHO/CDS/CSR/EPH/2002.6). Year by year, the highly unstable influenza virus is a reminder of the ever-present threat of another lethal influenza pandemic. The avian influenza outbreaks in 2003–2004, which successfully breached the species barrier between animals and humans, are particularly worrisome because of the prospect of re-assortment and recombination (Bonn, 1997).

Disease vectors are equally resilient and adaptable. Some mosquito species that transmit malaria have developed resistance to virtually all major classes of insecticide. Others, such as the tsetse fly that transmits African sleeping sickness, have returned to areas where they had previously been well controlled. The *Aedes aegypti* mosquito that transmits both yellow fever and dengue, originally confined to tropical jungles, has adapted to breed in urban litter (Gubler, 2001; Molyneux, 2001).

The infectious diseases carried by such vectors have likewise spread to new continents or returned to former homes. Rift Valley fever is now firmly established on the Arabian Peninsula. West Nile virus, first introduced on the East coast of the USA in 1999, has now been detected in all states across the US and in provinces of Canada as well (www.cdc.gov/od/oc/media/wncount.htm).

Following the deliberate and malicious use of anthrax to incite terror in the USA in 2001, the perception of the infectious disease emergencies took on a new perspective (Knobler, Mahmoud & Pray, 2002). Preparedness for a possible bioterrorist attack has now become one of the highest profile emergencies pertaining to infectious diseases in the U.S. This risk, which has moved from a remote possibility to a distinct reality, has added to existing concerns about the threat to national and global security posed by naturally occurring infectious diseases. It has also given greater urgency to questions about the capacity of public health infrastructures to detect and contain an infectious disease threat, the best strategies for protecting populations, and the extent to which resources should be devoted to preparation for an event with low probability, yet potentially catastrophic consequences (www.who.int/emc/book_2nd_edition.htm).

Naturally occurring and deliberately caused infectious disease outbreaks have thus come to be perceived as emergencies and threats to international public health security. They have also led to the understanding of the importance of universal strengthening of public health systems as the best way to prevent or mitigate their impact. Today it is generally accepted that strengthening of public health systems for naturally occurring infectious disease outbreak detection and containment ensures better preparedness for all infectious disease outbreaks no matter how they are caused (see also chapter 1 by J. Last).

Naturally occurring outbreaks of both newly identified diseases and well-known epidemic-prone diseases occur most frequently in countries that lack the public health capacity to quickly detect them and prevent their international spread (Document no. WHO/CDS/CSR/EPH/2002.16). Just as inadequate surveillance and laboratory capacity work to the advantage of infectious diseases, strong public health systems can be viewed as a national security asset (Fidler, 2002). It is therefore in the interest of both industrialized and developing countries to strengthen public health systems in developing countries. Strengthened laboratories, well-trained health personnel, and reinvigorated public health institutions benefit developing countries by ensuring early identification and containment of outbreaks, thereby decreasing the suffering, death, and economic impact they cause. At the same time, industrialized countries benefit from the decreasing risk that these diseases will spread internationally (Document no. WHO/CDS/CSR/EPH/2002.16;

Kelley, 2000; Chyba, 2002; Kassalow, 2001). These arguments have acquired much more compelling force in light of developments including the international spread of infectious diseases such as AIDS in the early 1980s and SARS in 2003: Early detection and containment of infectious disease outbreaks can prevent their international spread and their potential to cause major emergencies (www.who.int/whr/2003/chapter5/en/).

PREVENTING THE INTERNATIONAL SPREAD OF INFECTIOUS DISEASES

Efforts to prevent or contain the international spread of infectious diseases have a long history (see chapter 1). In the 14th century, ships that were potential carriers of plague-infected rats were forcibly quarantined in the harbour of the city-state of Venice to prevent importation of plague (Howard-Jones, 1975). A series of international health agreements between the newly industrialized countries, elaborated during the 19th century, culminated in the adoption of the International Health Regulations in 1969 (International health organizations, 1969). These regulations are designed to maximize security against the international spread of infectious diseases while ensuring minimum impact on trade and travel. Administered by WHO, these are the only international regulations that require reporting of infectious diseases. Three diseases—cholera, plague and yellow fever—are targeted by the Regulations for reporting by countries. They also provide norms and standards for air and sea ports designed to prevent the spread from public conveyances of rodents or insects that may be carrying infectious diseases, and describe best practices to be used to control the spread of these diseases once they have occurred.

Concern about international capacity to detect and contain emerging and epidemic-prone diseases arose following outbreaks in the early 1990s of cholera in Latin America (1991), pneumonic plague in India (1994), and Ebola haemorrhagic fever in the Democratic Republic of the Congo (1995) (Khan, Tshioko, Heymann, et al. 1995; Tauxe, Mintz, & Quick, 1995; Wkly Epidemial Rec, 1994). While all these outbreaks caused concern throughout the world, with serious economic consequences and disruptions in travel and trade, it was the highly publicized Ebola outbreak that pointed most urgently to the need for changes in the International Health Regulations. That outbreak, which caught the international community by surprise, signaled the need for stronger infectious disease surveillance and control worldwide, for improved international preparedness to provide support when similar outbreaks occur, and for accommodating the needs of the media in providing valid information. A need for more broad-based international health regulations and electronic information systems connecting WHO with its regional and country offices also became evident, as did the realization that timely and adequate outbreak detection and response would need support from a broad coalition of partners (Heymann, Barakamfitiye, Szezeniowski, et al. 1999).

The International Health Regulations are therefore currently being revised to broaden the scope of diseases under surveillance and to serve as an up-to-date framework for global surveillance and response to internationally spreading infectious diseases in the 21st century. To support the revision process, the World Health Assembly has endorsed a series of resolutions aimed at ensuring a global surveillance and response system, operating in real time and under the framework of the International Health Regulations, that facilitates rapid disease detection and rational responses while authorizing WHO to utilize information sources about infectious diseases other than official notifications submitted by governments (World Health Assembly resolution 54.14; WHA 48.7; WHA 48.13; WH Assembly document A51/8).

THE USE OF ADVANCED INFORMATION TECHNOLOGY

Potential partners in global surveillance and outbreak response were first brought together informally by WHO in 1997, and then formally launched as the Global Outbreak Alert and Response Network (GOARN) partnership in 2000 (unpublished). Electronic communication networks and new computer applications were developed to enhance the network's power in global surveillance and response (Heymann & Rodier, 2001; unpublished). Several new mechanisms and a customized artificial intelligence engine for real-time gathering of disease information support the GOARN partnership. This tool, the Global Public Health Intelligence Network (GPHIN) maintained by Health Canada, heightens vigilance by continuously and systematically crawling web sites, news wires, local online newspapers, public health email services, and electronic discussion groups for key words that could signify outbreaks in the seven official languages of WHO (www.hcsc.gc.ca/hpb/transitn/gphin_3.pdf). In this way, the network is able to scan the world for informal news that gives cause for suspecting an unusual event.

GPHIN has brought major improvements in the speed of outbreak detection 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.

Other sources of information linked together in the network include government and university centres, ministries of health, academic institutions, other UN agencies, networks of overseas military laboratories, and nongovernmental organizations having a strong presence in epidemic-prone countries, such as Médecins sans Frontières and the International Federation of Red Cross and Red Crescent Societies. Information from all these sources is assessed and verified on a daily basis. Validated information is made public via the WHO web site.

If international assistance is needed, as agreed upon in confidential proactive consultation with the affected country and with experts in the network, electronic communications are used to coordinate prompt assistance. To this end, global databases of professionals with expertise in specific diseases or epidemiological techniques are maintained, together with nongovernmental organizations present in countries and in a position to reach remote areas. Such mechanisms, which are further supported by the WHO network of Collaborating Centres (national laboratories and institutes throughout the world serving as international reference centres), help the world make the maximum use of expertise and resources—assets that are traditionally scarce for public health.

From July 1998 to August 2001, the network verified 578 outbreaks in 132 countries, indicating the system's broad geographical coverage. The most frequently reported outbreaks were of cholera, meningitis, haemorrhagic fever, anthrax, and viral encephalitis. During this same period, the network has launched effective international cooperative containment activities in many developing countries—Afghanistan, Bangladesh, Burkina Faso, Côte d'Ivoire, Egypt, Ethiopia, Kosovo, Sierra Leone, Sudan, Uganda, and Yemen, to name a few (Heymann & Rodier, 2001).

The work of coordinating large-scale international assistance, which involves many agencies from many nations, is facilitated by operational protocols which set out standardized procedures for the alert and verification process, communications, coordination of the response, emergency evacuation, research, monitoring, ownership of data and samples, and relations with the media. By setting out a chain of command, and bringing order to the containment response, such protocols help protect against the very real risk that samples of a lethal pathogen might be collected for later provision to or use by a terrorist group. Moreover, in building a global system for surveillance and response, the Global Outbreak Alert and Response Network has defined practical operational problems in ways that are guiding the revision and strengthening of the International Health Regulations. In early 2003, GOARN was put to the test during the SARS outbreak, and helped support a coordinated and effective global response.

GLOBAL OUTBREAK ALERT AND RESPONSE: THE SARS EXPERIENCE

Based on information collected by GOARN partners prior to 12 March 2003, the WHO had the information it needed to alert the world of the appearance of a severe respiratory illness of undetermined cause that had rapidly infected more than 40 staff at hospitals in Viet Nam and Hong Kong (www.who.int/csr/sars/archive/2003_03_12/en/). The alert also referred to two other events that raised the level of alarm: an outbreak of 305 cases, with 5 deaths, of atypical pneumonia reported in mid-February from the southern Chinese province of Guangdong, and an almost simultaneous report from Hong Kong of two confirmed cases of avian influenza A(H5N1) in family members with a recent travel history to southern China. The alert described the signs and symptoms of the unidentified illness and recommended that suspected cases be isolated, managed with barrier nursing techniques, and reported—simple measures that would provide the cornerstone for containing the outbreak as it spread within, and then outside of, Asia.

Prior to that alert, several international mechanisms for routine outbreak detection, investigation, and response had already begun to operate with a heightened sense of urgency. A new and potentially pandemic strain of the influenza virus was the first and most greatly feared suspected cause. Laboratories in the WHO Global Influenza Surveillance Network had been on alert since late November 2002, when the Global Public Health Intelligence Network (GPHIN) picked up rumours of severe "flu-like" outbreaks in Guangdong and Beijing (SARS-chronology of events, 2003). Studies conducted by Chinese scientists and confirmed by a network of influenza laboratories identified strains of influenza B virus as the cause, and concern eased. It mounted to new heights with the mid-February 2003 confirmation of avian influenza in Hong Kong, prompting WHO to activate its influenza pandemic preparedness plans (Influenza A(H5N1), 2003). To learn more about the outbreak in Guangdong, a team of experts, drawn from the WHO Global Outbreak Alert and Response Network, arrived in Beijing on 23 February, but was not granted permission to travel further. A second GOARN team began an emergency investigation in Hanoi on 28 February, two days after the first case of atypical pneumonia was admitted to hospital, and established infection control procedures and an isolation ward. Laboratories in the influenza network analysed specimens from this patient and other early cases, and conclusively ruled out influenza viruses as the cause. They also ruled out all other known causes of respiratory illness. With a new disease increasingly suspected, WHO began daily teleconferences linking its country and regional offices and response teams with headquarters operational staff. These mechanisms, too, proved to be decisive in tracking the outbreak, gathering the knowledge for recommending effective control measures, and getting support teams to countries requesting assistance.

By 15 March 2003, WHO had received reports of more than 150 new cases of atypical pneumonia of unidentified cause concentrated in the hospitals of six Asian countries and Canada (www.who.int/csr/sars/archive/2003_03_15/en/). The disease did not respond to antibiotics and antivirals known to be effective against primary atypical pneumonia and other respiratory infections. No patients, including young and previously healthy health workers, had recovered, many were in critical condition, several required mechanical ventilatory support, and four had died. Equally alarming, the disease was rapidly spreading along the routes of international air travel. The potential for further international spread was vividly demonstrated that same day when a medical doctor, who had treated the first cases of atypical pneumonia in Singapore, reported similar symptoms shortly before boarding a flight from New York to Singapore. The airline was alerted and the doctor and his wife disembarked in Frankfurt for immediate hospitalization, becoming the first cases in Europe (SARS: lessons from a new disease, 2003). Faced with these events, WHO issued a second and stronger global alert on 15 March, this time in the form of an emergency travel advisory (www.who.int/csr/sars/archive/2003_03_15/en/). The alert provided guidance for travellers, airlines and crew, set out a case definition, and gave the new disease its name: severe acute respiratory syndrome (SARS). It also launched a coordinated global outbreak response that tested a critical assumption: rapid and intense public health action could stop a new transmissible disease, of unidentified cause and unknown epidemic potential, from becoming endemic.

On 5 July 2003, the last known probable case of SARS completed a 20-day period of isolation, and WHO declared that the international outbreak had been contained (www.who.int/csr/don/2003_07_05/en/). While this achievement demonstrates the strength of classical public health measures—case detection, isolation, contact tracing and infection control—it also shows the importance of GOARN, set up at the international level, to improving global capacity to detect and respond to outbreaks of emerging and epidemic-prone diseases.

The international response to SARS—the roll-out of the mechanisms for outbreak detection and containment that had been under development through GOARN since 1997 (36)–became the first response to an internationally spreading outbreak during which regularly updated evidence-based recommendations for patient management and outbreak control could be collectively made in real-time as events unfolded around the world (unpublished). As the outbreak evolved, some of the world's most experienced laboratory experts, clinicians, and epidemiologists worked together in virtual networks, taking advantage of up-to-date communication technologies, including the internet, secure websites, and video and telephone conferencing. Laboratories in the existing influenza surveillance network formed the basis for a new virtual network to identify the causative agent, which was achieved within a month, and to develop diagnostic tests (WHO Multicentre Collaborative Network for SARS, 2003). Clinicians and field epidemiologists constituted other virtual networks, and by the end of the outbreak more than 150 experts from institutions in 17 countries had demonstrated how close collaboration and sharing of information, despite strong academic pressure to publish information in scientific journals, could serve the public health good. No estimates are available for the number of health staff who risked their lives in caring for patients, though the deaths of many have been documented.

The SARS outbreak also marked the first occasion where sufficient information became available rapidly enough to issue evidence-based international travel recommendations as a measure for preventing further international spread, particularly by air travel. As real-time evidence accumulated, further international spread was attributed to persons with SARS who continued to travel internationally by air, in some cases infecting passengers and crew during the flight (www.who.int/csr/sars/en/WHOconsensus.pdf). Daily tracking of cases also revealed that contacts of SARS patients continued to travel, becoming ill upon arrival at their destination. On 27 March, WHO therefore issued recommendations that countries with major outbreaks screen departing passengers for fever and other signs of SARS, or known contact with SARS patients (www.who.int/csr/sars/archive/2003_03_27/en/print.html). The choice of measures for putting this recommendation into effect was left to the discretion of individual countries. Some set up screening measures at international airports and border crossings with a variety of requirements, including a health declaration by each departing passenger, temperature monitoring of each passenger, and a stop list of contacts of SARS patients at immigration by which known contacts were asked not to travel.

As the outbreak progressed it became clear from information provided daily from the virtual networks, that contacts of probable SARS patients continued to travel and become ill after arrival at their destination, indicating the continuing risk of further international spread. Real time information further demonstrated that contact tracing at some sites did not fully identify chains of transmission, and that transmission was occurring outside confined settings such as the health care environment, possibly placing the general population at risk. In late March, an outbreak of 329 almost simultaneous probable cases among residents of a housing estate in Hong Kong suggested possible transmission by exposure to some factor in the environment, thus creating further opportunities for exposure in the general population (www.sars-expertcom.gov.hk/english/reports/reports.html). Additional evidence-based guidance was therefore made for the sites where contact tracing could not link all cases, understanding that if the disease were spreading in the wider community it would greatly increase the risk to travellers and the likelihood that cases would be exported to other countries. This guidance was aimed at international travellers, and recommended that they postpone all but essential travel to designated sites in order to minimize their risk of becoming infected (www.who.int/csr/don/2003_07_01/en/). Thus an important surgical congress scheduled for the summer of 2003 to be held in Bangkok, Thailand, was postponed.

The global alerts issued by WHO on 12 and 15 March provided a clear line of demarcation between areas with severe SARS outbreaks and those without. Following the SARS alerts, all areas with imported cases, with the exception of Taiwan, either prevented any further transmission or kept the number of locally transmitted cases very low (www.who.int/csr/sars/country/table2003_09_23/en/). Likewise, the travel recommendations issued by WHO appear to have been effective in helping to contain international spread of SARS. Of the 40 international flights known to have carried 37 probable SARS cases, current analysis has implicated five in transmission to passengers or crew (www.who.int/csr/sars/en/WHOconsensus.pdf). Following the 27 March recommendations for exit screening, no confirmed SARS case associated with in-flight exposure was reported to WHO. This may have been because awareness of screening procedures discouraged persons with fever from attempting to travel (Olsen, Chang, Cheung, et al. 2003).

Initial information from Hong Kong reveals that 2 probable SARS cases were identified by airport screening procedures, immediately hospitalized, and prevented from international travel (Hong Kong International Airport, personal communication). Travel recommendations also appear to have provided a benchmark for gauging the safety of international travel; when an area was declared safe from the risk of SARS transmission, traveller confidence was regained. Recommendations concerning travel were ended when epidemiological criteria indicating a low risk to travellers were met. That goal in itself became a motivation for governments and populations to collaborate in bringing the outbreaks under control. Many countries also set a second goal of removal from the list of areas with recent local transmission. The determination to attain this objective may have contributed to the speed with which the cycle of human-to-human transmission was broken globally, and confidence was restored (www.who.int/gb/EB_WHA/PDF/EB113/eeb11333.pdf). Passenger movement figures provided by the Hong Kong International Airport show a rapid rebound from the lowest number of passengers, 14,670, recorded just before 23 May when the travel recommendations for Hong Kong were removed, to 54,195 on 12 July, a month and a half later (Hong Kong International Airport, personal communication).

GLOBAL INFECTIOUS DISEASE EMERGENCIES: THE FUTURE

After the SARS outbreak had been contained, GOARN partners continued their global surveillance activities and detected and responded to isolated cases of SARS that were reported from Singapore and China (Taiwan and the mainland) (Heymann, Aylward, & Wolff, 2004). During 2004, avian influenza infections in humans were reported from Thailand and Viet Nam through GOARN partners, and responses coordinated through the GOARN partnership have been mounted (www.who.int/csr/don/2004_07_08/en/). In May 2005 the revised International Health Regulations will be reviewed by the World Health Assembly of WHO and submitted to an approval process. During this time, and for the years to come, infectious disease emergencies will continue to occur. The world will remain prepared for these emergencies through the GOARN partnership.

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