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Emerging and re-emerging infections

Chapter: Emerging and re-emerging infections

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Introduction

The microbial world is complex, dynamic and constantly evolving. Infectious agents reproduce rapidly, mutate frequently, cross the species barrier between animal hosts and humans, and adapt with relative ease to their new environments. Because of these traits, infectious agents are able to alter their epidemiology, their virulence, and their susceptibility to anti-infective drugs.

When disease is caused by a microbe that is newly identified and not known previously to infect humans, it is commonly called an emerging infectious disease, or simply an emerging infection. When disease is caused by an infectious agent previously known to infect humans that has re-entered human populations or changed in epidemiology or susceptibility to anti-infective drugs, it is called a re-emerging infection. A report published by the United States Institute of Medicine in 1992 first called attention to emerging and re-emerging infectious diseases as evidence that the fight against infectious diseases was far from won, despite great advances in the development of antimicrobials and vaccines (Lederberg *et al.* 1992).

All forms of infectious agents—bacteria, viruses, parasites, and prions—are able to emerge or re-emerge in human populations, and it is estimated that 70 per cent or more of all emerging infections have a source in animals. When a new infectious agent enters human populations there are several potential outcomes. In some instances, infected humans become ill, while in others, infections are asymptomatic. Once humans are infected, human-to-human transmission may or may not occur. If it occurs, it may be limited to one, two, or more generations, or it may be sustained indefinitely. Among those infectious agents that cause disease, some maintain their virulence, while others attenuate over time. Changes in the epidemiological characteristics of infectious agents may occur gradually, or they may occur abruptly as the result of a sudden genetic change during reproduction and/or replication.

Epidemiology of emerging and re-emerging infections

Rabies and variant Creutzfeldt-Jakob disease are clear examples of human infections that cause illness but cannot transmit from human to human unless there is an iatrogenic cause of transmission through non-sterile medical procedures, blood transfusion, or organ transplant. In several instances, corneal transplantation from a person who died undiagnosed with rabies-infection has caused rabies in transplant recipients. The recent identification of several humans with vCJD associated with blood transfusion demonstrates its potential to spread iatrogenically within the human population.

Human monkeypox provides a clear example of an infectious agent that can infect humans but not sustain transmissibility. Thought to have a rodent reservoir in the sub-Saharan rain forest, the monkeypox virus infects humans who come in contact with an infected animal. Transmission is sustained through one or two generations and then ceases. In the first generation of cases, the case fatality rate can approach 10 per cent, but with passage through human populations the virulence and case fatality of human monkeypox decreases as its transmissibility declines.

The human immunodeficiency virus (HIV) is an example of an infectious agent that has been able to infect humans, maintain virulence and sustain transmission. A long incubation period for HIV has ensured sustained transmission resulting in endemicity worldwide, causing an estimated 2 million deaths in 2007 alone. It is hypothesized that HIV entered human populations from a non-human primate sometime in the early twentieth century. It escaped detection in the late 1970s when human-to-human transmission was being amplified on the African continent, in island nations of the Caribbean, and in North America. By the time it was first identified in the early 1980s, it had spread widely throughout the world.

The short incubation period in persons infected with the Ebola virus, and the high case fatality rates are less compatible with long-term human-to-human transmission. Ebola endemicity in humans has not developed, though frequent re-emergence and localized outbreaks with human-to-human transmission continue to be documented. The potential for attenuation of the Ebola virus with passage is unknown, though in its present form it is unlikely that it will be able to become endemic in human populations because of its short incubation period and rapid progression to death in the majority of those infected.

The RNA virus that causes seasonal influenza is highly unstable genetically and mutates frequently during replication, requiring annual antigenic modifications in seasonal influenza

vaccines to ensure protection. Avian influenza viruses are likewise unstable and at times infect humans and cause sickness and death. Occasionally, avian influenza viruses cause human influenza pandemics. The trigger virus for the influenza pandemic of 1918 is thought to have been an avian influenza virus. One hypothesis of its origin is that over time it circulated among birds and possibly some mammals, and through adaptive mutation, the virus gradually assumed a form that could infect humans and easily transmit.

Two other influenza pandemics of the twentieth century, in 1957 and 1968, are thought to have been caused by more abrupt genetic reassortment during the intracellular replication process in an animal dually infected with a human and an avian influenza virus. Risk factors for emergence of influenza viruses in humans are thought to be highest in areas such as South China and Southeast Asia where there are large populations of aquatic birds (the hosts of many different types of avian influenza viruses) and where humans live in close proximity to animals that may be infected by these aquatic birds.

Currently, H5N1, an avian influenza virus that was first identified as the cause of human illness in 1997, continues to cause occasional severe infections in humans but remains a zoonotic human infection and does not transmit easily from human to human. Most scientists agree that this virus, like many other avian influenza viruses, has the potential to mutate and gain the epidemiological characteristics that would permit it to spread easily from human to human and cause a pandemic.

Susceptibility of infectious agents to anti-infective drugs

Bacteria, viruses, and parasites can develop resistance to anti-infective drugs through spontaneous mutation and natural selection, or through the exchange of genetic material between strains and species. They then transmit from human to human, replacing more susceptible organisms with resistant strains. Soon after development of the first antibiotics, warning signs of microbial resilience began to appear. By the end of the 1940s, resistance of hospital strains of *Staphylococcus aureus* to penicillin emerged in the United Kingdom with resistance levels as high as 14 per cent, and by the end of the 1990s, levels had risen to of 95 per cent or greater (Fig. 9.17.1).



Fig. 9.17.1
Evolution of penicillin resistance in *Staphylococcus aureus*.

In addition to acquiring genes encoding resistance to all penicillins—including methicillin and other narrow-spectrum β -**lactamase**-resistant antibiotics—*S. aureus* has developed resistance to methicillin. Methicillin-resistant *S. aureus* (MRSA) first identified in the United

Kingdom in 1961, is now widespread in hospitals throughout the world.

By 1976, chloroquine-resistant *Plasmodium falciparum* malaria was highly prevalent in Southeast Asia and 10 years later was found worldwide, as was high-level resistance to two second-line drugs, sulphadoxine-pyrimethamine and mefloquine. Today combination therapy with two antimalarial drugs with different targets is required to ensure effective treatment, as is surveillance to measure the continuing evolution of antimalarial drug resistance.

The bacterial and viral infections that contribute most to human disease are also those in which antimicrobial resistance is rapidly emerging: Diarrhoeal diseases such as dysentery; respiratory tract infections, including pneumococcal pneumonia and tuberculosis; sexually transmitted infections such as gonorrhoea and HIV; and infectious agents that have now accumulated resistance genes to virtually all currently available anti-infective drugs such as MRSA and extremely resistant tuberculosis (XDR-TB).

Geographic distribution of emerging and re-emerging infections

Emerging infections have the potential to occur in every country and on every continent (Fig. 9.17.2). Though the term emerging infections was newly introduced in the early 1990s, the previous 30 years had seen panoply of newly identified infections in humans on every continent. The year 1976 was especially illustrative of this phenomenon with the identification of the swine flu virus (H1N1), thought to be a direct descendant of the virus that caused the pandemic of 1918, at a military base in the Fort Dix (United States); the identification of *Legionella pneumophila* as the cause of an outbreak of severe respiratory illness among a group of veterans staying at a hotel in downtown Philadelphia (United States), initially feared to be a human outbreak of swine influenza (H1N1); and the identification of the Ebola virus as the cause of simultaneous outbreaks of haemorrhagic fever in Sudan and the Democratic Republic of Congo (then called Zaire).

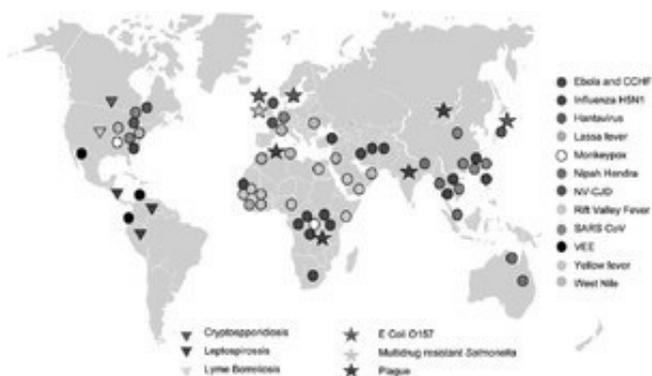


Fig. 9.17.2
Selected emerging and re-emerging infectious diseases: 1996–2004.

Nine years earlier, in 1967, the Marburg virus had been identified in an outbreak in Germany that caused 25 primary infections and seven deaths among laboratory workers who were infected by handling monkeys from Uganda, and six secondary cases in health workers who took care of primary cases, with subsequent spread to family members. A member of the same

filovirus family as Ebola, the Marburg virus has caused sporadic small outbreaks in Africa during the 1970s and 1980s, and larger outbreaks in 1998 in the Democratic Republic of Congo and 2005 in Angola. Since the Marburg virus was first identified in 1967 there have been over 40 other newly identified infectious agents in humans, an average of one per year.

Health workers and emerging/re-emerging infections

As clearly recorded during the Marburg outbreak of 1967, laboratory and health workers are at especially high risk of emerging and re-emerging infections. Outbreaks of Marburg, Ebola, and recently of severe acute respiratory syndrome (SARS), provide clear examples of the potential for health workers to become infected, and in some instances to sustain and amplify transmission in hospitals, and through their patients and family members, to the community. In the 1995 outbreak of Ebola haemorrhagic fever in Kikwit (Democratic Republic of Congo), almost one third of those infected were health workers, and in the 2003 SARS outbreak in Singapore, 10 health workers were thought to have been infected while treating an infected health worker colleague who is also thought to have infected her husband, three other patients and seven visitors to the hospital. Laboratory workers are also at risk of infection: The last human case of smallpox was caused by a laboratory accident in the United Kingdom, and the last-known human cases of SARS occurred in laboratory accidents in Singapore and China.

Economic impact of emerging and re-emerging infections

Outbreaks caused by emerging and re-emerging infections are costly (Fig. 9.17.3). They consume health-care resources and divert them from endemic disease problems, result in productivity loss, and decrease trade and tourism revenue. At times they economically devastate entire sectors. This has occurred after major outbreaks of emerging or re-emerging infections during the past 20 years, with economic losses ranging from an estimated US\$39 million after the reemergence of cholera in Tanzania in 1998, to approximately US\$39 billion after the emergence of bovine spongiform encephalopathy in the United Kingdom during the period 1990–1998.

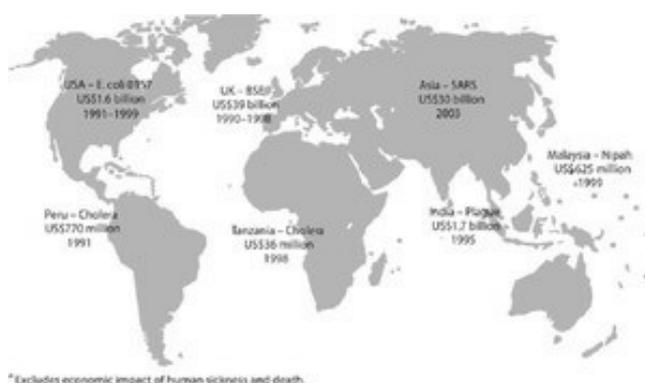


Fig. 9.17.3

Direct economic impact of selected infectious disease outbreaks, 1990–2003^a.

SARS was likewise responsible for sizeable economic losses and insecurity in financial markets

across Asia and worldwide. With fewer than 9000 cases, the outbreak was estimated by the Asian Development Bank to have cost Asian countries an estimated US\$20 billion in gross domestic product (GDP) terms for 2003, and up to US\$60 billion of gross expenditure and business losses.

The main drivers of the economic impact of outbreaks caused by emerging and re-emerging infections are travel, tourism, trade and consumer confidence. Fear of transmission causes international tourists to choose alternative holiday locations, and local population to avoid any perceived source of infection such as restaurants and other public leisure venues—sectors of the economy that are significant contributors to the GDP of many countries.

Factors influencing emergence and re-emergence

Many external factors provide opportunities for enhanced emergence or re-emergence of infectious diseases. They range from weakened public health infrastructure and failure of safety procedures/regulations to increases in population; anthropogenic activities or natural variances in climate; civil disturbance/human displacement; and human behaviour that varies from occupation and misperceptions about the use of anti-infective drugs to the safety of public health interventions and the desire to deliberately cause terror and harm.

Weakened public health infrastructure

Weakening of public health infrastructure resulted in part from decreased investment in public health during the second half of the twentieth century. *Aedes aegypti* has now become well established in many large cities worldwide following the deterioration of mosquito control campaigns during the 1970s. The resurgence of the *Aedes* species has been confounded by the adoption of modern consumer habits in urban areas where discarded household appliances, tyres, plastic food containers, and jars create abundant artificial mosquito breeding sites.

Along with the increase in *Aedes* species there has been an increased risk of outbreaks of dengue. Prior to 1970, nine countries, mainly in Latin America, reported outbreaks of dengue. Thirteen years later, during 1983, 13 countries in Latin America and Asia reported dengue outbreaks, and by 1998, 1.2 million cases were reported from 56 countries.

During 2001, 69 countries reported outbreaks of dengue, and it is now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, Southeast Asia, and the Western Pacific. During 2003 there were approximately 1.4 million cases and 6600 deaths reported to WHO. Major dengue outbreaks have occurred in Brazil, Indonesia, Thailand, Viet Nam, Bangladesh, and India.

In 2005, the Chikungunya virus, likewise transmitted by *Aedes aegypti*, emerged and spread throughout several southern Pacific islands. A total of 3100 human infections were reported by a sentinel network on La Réunion within the first 6 months of the outbreak, leading to an estimate of over 204 000 human infections by March 2006. In 2007, the Chikungunya virus spread north to Europe, where it caused an outbreak in northern Italy.

Lapses in childhood immunization coverage due to weakened childhood immunization programmes in Russia in the early 1990s resulted in the re-emergence of diphtheria, with major

epidemics in the early 1990s. Reported cases of diphtheria in the Russian Federation increased from just over 1200 in 1990 to 3897 in 1992 to over 5000 in 1993. Likewise, lapses in yellow fever vaccination programmes in sub-Saharan Africa since the 1950s have left large susceptible populations in both rural and urban areas of sub-Saharan Africa, with sporadic urban outbreaks in cities in Côte d'Ivoire (2001), Senegal and Guinea (2002), and Burkina Faso (2004).

Most epidemiologists recognize that it was in part because of weak surveillance systems in developing countries that HIV rapidly spread during the late 1970s, and was not detected until it was first identified when it began to transmit in the United States.

Failure of safety procedures/regulations

Sub-standard universal precautions and hospital regulations during the 1980s led to breaches in sterile injection practices and nosocomial infections of HIV in the former USSR and Romania, together infecting over 250 children, accompanied by high levels of hepatitis B in both patients and health workers. Likewise sub-standard universal precautions led to nosocomial outbreaks of Ebola haemorrhagic Fever in the Democratic republic of Congo in 1976 and 1995, where syringes and/or failed barrier nursing amplified the transmission to patients, health workers, and the community. Lapses in universal precautions led to nosocomial transmission of SARS in hospitals in China and Hong Kong, Singapore, Vietnam, and Canada, where outbreaks then spread from hospitals to communities.

Changes in the process of rendering the carcasses of ruminant animals for the preparation of bone meal fed to other ruminant animals are thought to have been the cause of the outbreak of bovine spongiform encephalopathy (BSE) in cattle that also led, in May 1995, to the death of a 19-year male in the United Kingdom, the first human death from what is now known to be variant Creutzfeldt-Jakob Disease (vCJD) or human Bovine Spongiform Encephalopathy (hBSE). The BSE and hBSE outbreaks demonstrate the health consequences of regulations for rendering that had changed over a 10-year period prior to 1995, inadvertently permitting rendered parts of cattle infected with the BSE-causing prion to contaminate bone meal made from rendered carcasses and used for livestock feed. The most likely source of human infection is thought to be through the consumption of contaminated meat. The BSE outbreak led to the recognition of the need for stronger government intervention along the entire 'feed to food' continuum to ensure the safety of foodstuffs for human consumption.

Population increase

The world's population more than doubled in the second half of the twentieth century, accelerating most rapidly in the developing countries of the tropics and sub-tropics. Rural-urban migration has resulted in inadequacy of water and sanitation systems, crowded living conditions and other basic infrastructure associated with population growth. In 1950, there were two urban areas in the world with populations greater than 7 million; by 1990, this number had risen to 23, and by 2005 to 30.

Population increases in Latin America resulted in breakdowns in sanitation and water systems in large coastal cities. In 1991, when cholera re-emerged in Peru after having been quiescent for approximately 100 years, it rapidly spread throughout Latin America. Thought to have originated from contaminated seafood on the Peruvian coast, the disease spread rapidly

across the South American continent, causing nearly 400 000 reported cases and over 4000 deaths in 16 countries that year. By 1995, there were more than 1 million cases and just over 10 000 deaths reported in the Americas.

Urbanization, and the subsequent crowding with sub-standard and living conditions in slum areas has likewise contributed to the re-emergence of tuberculosis and plague. The most recent serious outbreak of plague occurred in five states in India in 1994, where almost 700 suspected bubonic or pneumonic plague cases and 56 deaths were reported.

Anthropogenic activities or natural variance in climate

Deforestation that disrupts natural habitats of animals, and forces animals, searching for food, into closer contact with humans has been linked to the emergence and re-emergence of Lassa Fever in West Africa, and sine nom virus in North America. First identified in 1969 when two nurses died with a haemorrhagic fever syndrome in Nigeria, the Lassa Fever virus is now known to be transmitted to humans from human food supplies and/or the household environment contaminated by urine and/or other excreta of infected rodents. In many instances, rats invade human living spaces in search of food because rainforests, a natural habitat, have been destroyed and can no longer support their needs. Sin nombre virus is a hantavirus, first identified in an outbreak in the southwestern part of the United States in 1993. It is now known to spread from infected rodents to humans through aerosolized excreta found in dust of homes that have been invaded by rodents as they scavenge for food.

In Latin America, Chagas disease re-emerged as an important human disease after mismanagement of deforested land caused triatomine populations to move from their wild natural hosts to involve humans and domestic animals in the transmission cycle, eventually transforming the disease into an urban infection that can be transmitted by blood transfusion. Other emerging infections influenced by changing habitats of animals include Lyme borreliosis in Europe and North America, transmitted to humans who come into contact with ticks that normally feed on rodents and deer, the reservoir of *Borrelia burgdorfi* in nature.

The narrow band of desert in sub-Saharan Africa, in which epidemic *Neisseria meningitides* infections traditionally occur, has enlarged as drought spread south so that Uganda and Tanzania experience epidemic meningitis. Climate extremes, whether involving excessive rainfall or drought, can likewise displace animal species and bring them into closer contact with human settlements, or increase vector breeding sites. A 1998 outbreak of Japanese encephalitis in Papua New Guinea has been linked to extensive drought, which led to increased breeding sites for the *Culex* mosquito as rivers dried into stagnant pools. Mosquitoes then transmitted the Japanese encephalitis virus from infected pigs and or wild birds to humans. The Japanese encephalitis virus is now widespread in Southern Asia from India and Thailand to Malaysia, and as far north as Korea and Japan.

Above-normal rainfall associated with the occurrence of the warm phase of the El Niño Southern Oscillation phenomenon is thought to have caused extensive flooding in East Africa from December 1997 to March 1998, increasing the number of pooled-water breeding sites of *Aedes* mosquitoes. Mosquitoes then facilitated the transfer of the Rift Valley Fever virus from infected cattle, sheep, and/or goats to humans who had been forced to live in close proximity to animals on islands of dry land surrounded by flood water. During this period, the largest Rift Valley fever (RVF) outbreak ever reported in East Africa occurred in Kenya, Somalia, and

Tanzania. The total number of human infections in northern Kenya and southern Somalia alone was estimated at 89 000 with an estimated 478 deaths.

Civil disturbance/human displacement

Human population movements on a large-scale as a result of war, conflict, or natural catastrophe often result in crowded, unhygienic, and impoverished living conditions. This in turn heightens the risk of emergence and re-emergence of infectious diseases. In the aftermath of civil disturbance in Rwanda in 1994, over 48 000 cases of cholera and 23 800 deaths were reported within 1 month among Rwandans who had been displaced to refugee camps in Goma, Democratic Republic of Congo.

A collateral impact of war, conflict, or natural catastrophe such as earthquakes is the destruction or weakening of health systems with diminished capacity to detect, prevent, and respond to infectious disease outbreaks. One consequence of the 27-year civil war in Angola was the outbreak of Marburg haemorrhagic fever in 2004 that spread to more than 200 humans, 90 per cent of whom died. Emergence of the Marburg virus was detected late and transmission was amplified in overcrowded and understaffed health facilities where lack of investment during the war had resulted in sub-standard infection control.

Another large outbreak of Marburg virus infection was identified in late 1998 in the Democratic Republic of Congo, also a conflict-ravaged country. This emergence resulted in sporadic cases with small chains of transmission over a 2-year period in a remote area where civil war had interrupted supply lines and communication to health facilities in the region.

Human behaviour

Occupation

Throughout history, human occupations have been associated with infectious diseases. Anthrax, for example, has been called wool-sorters disease because of transmission of anthrax spores from infected animals to humans who shear sheep and other wool-producing animals. It has also been associated with butchers who come into contact with infected animals at the time of slaughter or during preparation of meat for markets. Anthrax spores infect humans either intra-dermally, causing cutaneous anthrax, or by inhalation, causing pulmonary or inhalation anthrax.

Though intensive research has failed to confirm the origins of Ebola fever outbreaks, infection is thought to occur as humans encounter animal sources, possibly infected bats and/or non human primates, somewhere in the transmission cycle. An outbreak of Ebola haemorrhagic fever in humans in 1995 was linked to a woodsman, who worked deep within the tropical rainforest making charcoal, and who is somehow thought to have become infected with the Ebola virus that he then carried back to his home village and family members. A Swiss researcher infected with the Ebola virus while searching for the cause of a major die-out of chimpanzees in a forest reserve in West Africa is thought to have become infected while conducting chimpanzee autopsies in search of the cause of death.

In 2003, a veterinarian in the Netherlands became infected with the influenza A (H7N7) virus during an investigation of influenza outbreaks in poultry and later died in acute respiratory

failure. A total of 89 humans, including the veterinarian, were confirmed to have H7N7 influenza virus infection associated with this poultry outbreak and no further deaths occurred. The majority of human infections are thought to have occurred as a result of direct contact with infected poultry; but there were three possible instances of transmission of infection from poultry workers to family members.

Mistrust and misinformation

During 2003, unsubstantiated rumours circulated in northern Nigeria that the oral polio vaccine (OPV) was unsafe and could cause infertility by vaccination of young children. Mistrust and misinformation that followed led to the government-ordered suspension of polio immunization in two northern states and substantial reductions in polio immunization coverage in those states, and a large number of others. The result was a polio outbreak across northern Nigeria that then spread to previously polio-free areas in sub-Saharan Africa. Over 70 per cent of all children worldwide who were paralyzed by polio during the following year, 2004, were living in Nigeria—or in other parts of sub-Saharan Africa that had been re-infected by polio virus genetically linked to viruses that had a Nigerian origin.

Misinformation about the safety of vaccines against pertussis, measles, and hepatitis B has likewise led to decreases in vaccine uptake among children, and in some instances industrialized country outbreaks of pertussis and measles.

Anti-infective drug prescription and use

Behaviours such as over- or under-prescribing of antibiotics by health workers, and excessive demand for antibiotics by the general population, have had a remarkable impact on the selection and survival of resistant microbes, rapidly increasing levels of microbial resistance.

The selection and spread of resistant infectious agents is paradoxically facilitated by either over or under-prescribing of drugs, and/or poor compliance to their use and unregulated sale that makes them available to any who have the ability to purchase them. In Thailand, among 307 hospitalized patients in the late 1990s, 36 per cent who were treated with anti-infective drugs did not have an infectious disease. Over-prescribing of anti-infective drugs occurs in most other countries as well. In Canada, it has been estimated of the more than 26 million people treated with anti-infective drugs, up to 50 per cent were treated inappropriately. Findings from community surveys of *Escherichia coli* in the stool samples of healthy children in China, Venezuela, and the United States suggest that although multi-resistant strains were present in each country, they were more widespread in Venezuela and China, countries where less control is maintained over antibiotic prescribing and sales.

Animal husbandry and agriculture use large amounts of anti-infective drugs, sometimes indiscriminately, resulting in the selection of resistant bacterial strains. Antibiotics are used as growth-promoting agents in animal feed in some countries, and for spraying of fruit trees, rice paddies, and flowers to avoid bacterial blights. Some of the infectious agents that infect animals freely circulate between animals and humans, providing opportunities for swapping or exchanging resistant genes, increasing the speed with which anti-infective resistance evolves in both agriculture and human populations.

From January 2005 to March 2006, 44 of 53 patients with multi-drug resistance to tuberculosis

(MDR-TB) were further diagnosed with extreme drug resistant tuberculosis (XDR-TB). All were found to be HIV-positive as well. Widespread infection with HIV provides fertile ground for the transmission of all forms of TB, including XDR-TB, facilitated by inappropriate prescribing behaviour of health workers and poor adherence to treatment regimes by patients.

Deliberate use to cause terror and harm

The potential of organisms used as weapons of biological warfare or bioterrorism was graphically illustrated in 1979 in an accident involving anthrax in Sverdlovsk, 1400 km east of Moscow, in the then Soviet Union. Attributed at first by government officials to the consumption of contaminated meat, it was later shown to have been caused by the unintentional release of anthrax spores from a Soviet military microbiology facility. It is estimated that up to 358 humans were infected and that between 45 and 199 died.

In the United States in late September 2001, the deliberate dissemination of potentially lethal anthrax spores in four known letters sent through the United States Postal Service caused massive disruption of postal services in the United States and many other countries around the world. The anthrax letters—dated 11 September 2001, and postmarked 7 days later—caused huge public alarm and prompted a massive public health response. A total of 22 persons are thought to have been infected by anthrax spores sent through the postal system; 11 developed cutaneous anthrax and the remaining 11 developed inhalation anthrax, of whom five died. Twenty of the 22 patients were exposed to work sites that were found to be contaminated with anthrax spores. Nine of them had worked in mail processing facilities through which the anthrax letters had passed.

Other bacteria, viruses, mycotic agents, and biological toxins are also considered to have the potential for deliberate use to cause harm to humans. Great concern has been expressed by many countries about the potential health consequences that could be caused by the deliberate introduction of infectious agents such as the variola virus into a human population where smallpox vaccination is no longer practised, or the plague bacillus that could potentially cause an outbreak of pneumonic plague.

Public health security: Globalization and emerging/re-emerging infectious disease agents

Emerging and re-emerging infections enter a world of increased human mobility and interdependence that facilitates the transfer of infectious agents from country to country, and from continent to continent. Infectious agents efficiently travel in humans, insects, food and animals, and can spread around the globe and emerge in new geographic areas with ease and speed. Some are transported by the flights of migratory birds. Others, such as disease-carrying mosquitoes, travel in the passenger cabin or luggage hold of jets, to cause tropical infections in temperate countries when they bite airport workers or those who live nearby. They thus threaten public health security—our collective vulnerability to acute infectious disease outbreaks (Heymann 2003).

In 2000, among 312 athletes participating in an international triathlon held in Malaysia, 33 became infected with leptospirosis and returned to their home countries during the incubation period. While leptospirosis lacks human transmissibility and therefore did not set up local foci

or transmission, another event in 2003—the outbreak of SARS, clearly demonstrates the full potential of emerging infectious agents for international spread. From a medical doctor who was infected by patients that he was treating in the Guangdong Province of China, and then unknowingly carried the newly emerged infectious agent to a Hong Kong hotel, SARS spread in individual chains of transmission from infected hotel guests to 8422 persons reported infected in North and South America, the Middle East, Europe, and Asia with a case-fatality rate of approximately 11 per cent.

During the years 1969–2003, 18 instances of airport malaria were reported to WHO—malaria infections in workers at airports or in persons who live nearby who had not travelled to malaria-endemic countries. Their infection originated from malaria-infected *anopheles* mosquitoes that had travelled from countries with endemic malaria and took a blood meal from airport workers or other persons upon landing, clearly demonstrating that insects, like humans, can transport infectious agents around the world to emerge in places where they are not endemic.

Livestock, animal products, and food can also carry infectious agents that emerge or re-emerge in non-endemic countries. Rift Valley Fever emerged in humans in Yemen and Saudi Arabia in 2000, 2 years after a major outbreak of Rift Valley Fever in East Africa. Infection has since become endemic in livestock in the Arabian Peninsula, and is thought to have been imported from East Africa in livestock traded across the Red Sea. In 1996, imported raspberries contaminated with *Cyclospora* caused an outbreak in the United States. It is hypothesized that the raspberries imported from Guatemala were contaminated when surface water was used to spray them with fungicide before harvest.

Concern about the international spread of emerging and re-emerging infections and the need for strong public health security are not new. By the fourteenth century, governments recognized the capacity for international disease transmission and legislated preventive measures, as reflected in the establishment of quarantine in the city state of Venice. Arriving ships were not permitted to dock for 40 days, in order to attempt to keep plague from entering by sea.

Many European leaders of the mid-nineteenth century, worried by the cholera pandemic of the time; threats of plague; and the weakness of quarantine measures, began to recognize that controlling the spread of infectious diseases from one nation to another required cooperation between those nations. International conventions were organized and draft covenants signed, almost all of which related to some type of quarantine regulations.

From 1851 to 1897, 10 international sanitary conferences were held among a group of 12 European countries, focusing exclusively on the containment of epidemics in their territories. The inaugural 1851 conference in Paris lasted 6 months and was followed in 1892 by the first International Sanitary Convention that dealt with cholera. Five years later, at the 10th International Sanitary Conference, a similar convention that focused on plague was signed.

New policies then emerged in the late nineteenth century, such as the obligatory telegraphic notification of first cases of cholera and plague, a model that a small group of South American nations followed when they signed the first set of international public health agreements in the Americas during the 1880s. In addition to cholera and plague, often carried by immigrants arriving from Europe, the agreements in the Americas covered yellow fever that was endemic

in much of the American region at that time, and that from time to time caused major urban epidemics.

During the following decade, 12 countries attended the First International Sanitary Convention of the American Republics in Washington, DC, leading to the creation of the Pan American Sanitary Bureau (now called the Pan American Health Organization) in 1902. Its counterpart in Europe was the Office International d'Hygiène Publique (OIHP), established in 1907, and based in Paris.

In 1951, 3 years after its founding, WHO adopted a revised version of the International Sanitary Regulations (1892) that remained focused on the control of cholera, plague and yellow fever and rooted firmly in the preceding agreements of nineteenth and twentieth centuries.

The international health regulations

In 1969 the Member States of the World Health Organization agreed to new set of regulations—the International Health Regulations (IHR)—aimed at better ensuring public health security with minimal interruption in travel and trade. In addition to requiring reporting of four infectious diseases—cholera, plague, yellow fever, and smallpox—the IHR (1969) were aimed at stopping the spread of disease by pre-established control measures at international borders. They included requirements such as yellow fever and smallpox vaccination for passengers arriving from countries where yellow fever or smallpox outbreaks had been reported, and thus provided a legal framework for global surveillance and response, with the potential to decrease the world's vulnerability to four infectious diseases that were known to cross international borders.

By 1996, it had become clear, however, that the IHR (1969) were not able to ensure public health security as had been envisioned—countries reported the occurrence of cholera, plague and yellow fever late or not at all because of fear of stigmatization and economic repercussions (smallpox had been removed from the list when it was certified eradicated in 1980). At the same time it was realized that the IHR (1969) did not meet the challenges caused by emerging and re-emerging infectious diseases and the rapid global transit of these infections, sometimes still in the incubation period, by humans, insects, animals, and goods. From 1996 until 2005, the Member States of WHO therefore undertook a process to examine and revise the IHR (1969).

The result—the IHR (2005)—provide a more up-to-date legal framework requiring reporting of any public health emergency of international concern (PHEIC), and the use of real-time evidence to recommend measures to stop their international spread. A PHEIC is defined as an extraordinary event that could spread internationally or might require a coordinated international response (World Health Organization).

Under the IHR (2005) an event is evaluated for its potential to become a PHEIC by the country in which it is occurring, using a decision tree instrument developed for this purpose (Fig. **9.17.4**). If the criteria for a PHEIC are met, an official notification must be provided to WHO. Notification is also required for even a single occurrence of a disease that would always threaten global public health security—smallpox, poliomyelitis caused by a wild-type poliovirus, human influenza caused by a new virus subtype, and SARS. In addition, there is a

national and international surveillance and response

For emerging and re-emerging infections that are able to transmit from person to person, the window of opportunity for effective intervention often closes quickly. The most important defence against their international spread is highly sensitive national surveillance systems, public health laboratories that can rapidly detect outbreaks caused by emerging and re-emerging infections, and mechanisms that permit timely containment. These are the core capacities required by the IHR (2005). The same systems that detect and contain naturally occurring outbreaks also permit detection and initial response to deliberately caused outbreaks of infectious disease, although the scale of a deliberately caused outbreak could be large, similar to an outbreak caused by an event such as an influenza pandemic.

The collaborative action required by IHR (2005) when emerging or re-emerging infections threaten to spread internationally likewise provides a framework for global surveillance and response that is a departure from previous international conventions and regulations. The IHR (2005) explicitly acknowledge that non-state sources of information about outbreaks often pre-empt official notification, especially in situations when countries may be reluctant to reveal an event in their territories. Within the framework of the IHR (2005), WHO is therefore authorized to take into account information sources other than official notifications.

Collaboration among countries for public health security in the face of emerging and re-emerging infections has been occurring since 1997 when the Global Outbreak Alert and Response Network (GOARN) was first envisaged. This collaboration now sits firmly within the framework of the IHR (2005). By design, GOARN is a network of networks that interlinks electronically, and in real time, over 140 existing laboratory and disease reporting and response networks. Together, these networks possess much of the data, technical expertise, and skills needed to keep the international community constantly alert and ready to respond to emerging diseases within countries and internationally if and when they spread across national borders.

GOARN was formalized in April 2000 and is supported by a customized artificial intelligence engine for real-time gathering of disease information, the Global Public Health Intelligence Network (GPHIN) maintained by Health Canada. This computer application heightens vigilance by continuously and systematically crawling web sites, news wires, local online newspapers, public health email services, and electronic discussion groups in six different languages in order to identify reports of outbreaks (Grein *et al.* 2000).

Other sources of information linked together in GOARN 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 by WHO and its partners in GOARN, and validated information is made public on the WHO web site.

If an outbreak of emerging or re-emerging infectious disease occurs in a country that requires international assistance to help in containment activities, as agreed upon in confidential pro-active consultation with the affected country and with experts in the network, electronic communications are used to describe the technical expertise required and to then provide

prompt assistance and support. 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.

From July 1998 to August 2001, GOARN verified 578 outbreaks in 132 countries, indicating the system's broad geographical coverage (Fig. 9.17.5). The most frequently reported outbreaks were of cholera, meningitis, haemorrhagic fever, anthrax, and viral encephalitis. During this same period, the network launched effective international cooperative containment activities in many developing countries such as Afghanistan, Bangladesh, Burkina Faso, Côte d'Ivoire, Egypt, Ethiopia, Kosovo, Sierra Leone, Sudan, Uganda, and Yemen.



Fig. 9.17.5

Sample of international epidemic response missions during the first 12 months, Global Outbreak Alert and Response Network, 1998–1999.

GOARN reached its full potential during the SARS outbreak in 2003. It was not only instrumental in detecting the outbreak, but also in coordinating an international response for the first time using real-time evidence to make recommendation for epidemic containment and control, ways of working that were later incorporated in the IHR (2005). Since the SARS outbreak, operational protocols which set out standardized procedures for the alert and verification process, communications, coordination of an epidemic response, emergency evacuation, research, monitoring, ownership of data and samples, and relations with the media have been finalized and are available on the World Wide Web (WHO). By setting out a chain of command, and bringing order to the containment response, such protocols ensure collective action as required by the IHR (2005) and help ensure public health security.

The future

The vision embraced by the IHR (2005) is of a world on the alert and ready to respond collectively to the threat of emerging and re-emerging infections that represent an acute threat to public health security (Heymann & Rodier 2001).

To achieve this vision, the IHR (2005) requires an unbroken line of defence within countries and globally, using the most up-to-date technologies of surveillance and response. If a country had to concern itself only with the domestic public health issues caused by emerging and re-emerging infections, ensuring core capacities domestically would suffice. In today's world of international travel and trade, no politically drawn borders can absolutely prevent the spread of disease, and all countries have an obligation to develop and maintain these core capacities. They also have an obligation to be part of an interconnected system engaged in risk management activities that collectively reduce international vulnerability to threats to public health security.

Adherence to the IHR (2005) requires adherence to new norms and standards for reporting and responding to emerging and re-emerging infections despite the economic consequences that may result. Their full achievement will provide the highest level of public health security possible. National core capacities as described in the IHR (2005) must be put in place within the national public health system that can detect, investigate, communicate, and contain events that threaten public health security as soon as they appear. An interconnected system must be operating at the national and international levels, engaged in specific threat and risk assessment and management activities that minimize collective vulnerability to public health events.

These two goals are interdependent and must be sustained. They involve measures that the international community must continually invest in, strive to achieve, and assess for progress. In today's mobile, interdependent, and interconnected world, threats arising from emerging and epidemic-prone diseases affect all countries. Such threats reinforce the need for shared responsibility and collective action in the face of universal vulnerability, in sectors that go well beyond health.

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