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Emerging and Re-emerging Pathogens and Diseases, and Health Consequences of a Changing Climate

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KEY CONCEPTS

- The pursuit of both natural resources and new sources of food have put people, wildlife, and disease vectors into close contact with each other, increasing the chance for disease spillover.
- Risks of emerging infectious disease are especially high where dramatic changes in land use occur.
- Changes in global temperatures may directly increase the distribution of populations of disease vectors with regard to both their latitudes and altitudes.
- Extreme weather events, such as severe flooding, droughts, or severe storms, increase the probability that infectious disease outbreaks occur.
- Geopolitical events such as military conflicts, mass migration and political unrest can promote conditions that decrease the ability to detect, control and prevent outbreaks of emerging and re-emerging diseases.
- Infectious diseases spread rapidly in closed or partially closed populations, such as military barracks, college dormitories, prisons, hospitals, nursing homes, and the urban slums of megacities.
- Poverty is associated with several conditions related to the spread of infectious diseases, e.g. lack of access to clean water, poor sanitation and lack of access to healthcare. However, factors connected to economic development may also be linked with the emergence of infectious diseases.
- New molecular diagnostic platforms, coupled with novel surveillance approaches, will continue to improve the ability to identify both new pathogens and outbreaks more quickly.

Introduction

Mass vaccination programs and effective antimicrobials have greatly diminished the morbidity and mortality attributable to infectious diseases.[1] However, even before the introduction of antibiotics and vaccination programs, the morbidity and mortality caused by infectious diseases decreased in a dramatic fashion, in large part due to the wider availability of clean water, better sanitation and increased standards of living.[2,3] These improvements in health were concentrated mostly in higher-income countries, but they occurred in low- and middle-income countries (LMIC) as well.[4] Subsequent rapid progress toward medical treatments for tuberculosis, successful vaccination programs against smallpox and polio, and large-scale programs focused on malaria, all helped encourage the medical and public health communities to think that the threat posed by infectious diseases was diminishing.[3]

Yet, infectious diseases never really disappeared as a public health problem, especially in LMIC, and diseases also continue to emerge and evolve in industrialized countries. For example, not long after the widespread introduction of penicillin, cases of penicillin-resistant *Staphylococcus aureus* were reported.[5] Decades later, resistant strains would become a major cause of morbidity and mortality both in healthcare settings and ultimately community settings. This emergence of antimicrobial resistance repeated itself many times over in the years to come, with many other antibiotics and for a wide range of pathogens. At the same time, ambitious programs to eliminate malaria suffered setbacks for a variety of reasons in various parts of the world.[6] Similarly, some mass vaccination programs failed to meet their original goals.

In the last quarter of the 20th century and into the 21st century, several new infections emerged or at least became widely recognized (see Table 4-1). Some of these diseases were not new but had not yet been appreciated, due to limitations in diagnostic testing. For example, the causative agent for Legionnaire's disease was identified after an outbreak in 1976; however, the disease had most likely caused outbreaks of atypical cases of pneumonia for years. Other newly identified pathogens like HIV and hepatitis C were associated with a dramatic increase of morbidity and mortality around the world, while other diseases like dengue emerged in new geographic locations. Other pathogens have re-emerged after decades of decline. Vaccine-preventable diseases like mumps and pertussis have also re-emerged and so has tuberculosis. In fact, there may have been more people living with tuberculosis in the first decade of the 21st century than at any time in history.[3] Finally, the increasing resistance of many pathogens to antimicrobial agents has hinted that we may enter a post-antibiotic era for some difficult-to-treat infections. This threat was highlighted by the recent spread of infections caused by highly resistant gram-negative bacteria capable of producing New Delhi metallo-B-lactamase (NDM-1) enzyme, such as *Escherichia coli* and *Klebsiella pneumoniae*.[7]

What happened? Travel increased, human behavior changed, and in some parts of the world people came into closer contact with animals, as human populations moved into new habitats. The way food was produced and transported also changed. More intensive animal farming practices made food cheaper but kept more animals in smaller spaces. Also, agricultural practices encroached into new regions, increasing the chances of spillover of pathogens.[8] Now, food is often produced hundreds if not thousands of miles from the point of consumption. The resulting product specialization, large-scale farming and production lots and global distribution enable food-based outbreaks to spread quickly around the globe,[9] and also make it difficult to determine the original source of an outbreak.

Pathogens also changed to adapt to new environments. Medical treatments opened new niches for infections (e.g. new implantable medical devices, catheters, new immunosuppressive therapies) and pathogens also adopted resistance to widely used antimicrobial agents. Finally, the concept that problems related to infectious diseases were under control may in part have helped lead to the resurgence: the lack of investment in public health and research may have decreased support for surveillance and treatment and thereby may have provided opportunities for infectious diseases to re-emerge.[10,11]

The move to de-emphasize infectious diseases as a major public health threat may have been in part due to a lack of appreciation of the interplay between infectious diseases, human history and the environment. Thus, the goal of this chapter is to give readers an appreciation of why emerging infections were a problem in the past and to

TABLE 4-1 Selected Emerging and Re-emerging Disease-Related Events, 1993–2014

1993	Hantavirus pulmonary syndrome (USA)
1994	Plague (India)
1995	Ebola fever (Zaire [Democratic Republic of Congo])
1996	New variant Creutzfeld–Jakob disease (UK)
1997	H5N1 influenza (Hong Kong)
1998	Nipah virus encephalitis (Malaysia)
1999	West Nile encephalitis (USA, Russia)
2000	Rift Valley fiver (Kenya, Saudi Arabia, Yemen)
2001	Anthrax (USA)
2002	Vancomycin-resistant *Staphylococcus aureus* (USA)
2003	Severe acute respiratory syndrome (China, Hong Kong, Canada)
2003	Monkey pox (USA)
2003	Highly virulent strain of *Clostridium difficile* (Canada, Netherlands, USA, UK)
2005	Chikungunya (Indian Ocean Islands then spreading to India and beyond)
2008	Measles outbreaks associated with low vaccination rates (European countries, USA)
2008	NDM-1 carrying Enterobacteriaceae (isolated in Sweden in traveler from India)
2009	Pandemic H1N1 influenza (beginning in Mexico and spreading internationally)
2010	Cholera (Haiti)
2011	*E. coli* O104:H4-associated hemolytic uremic syndrome (Germany and European countries)
2012	MERS-CoV (Saudi Arabia)
2012	*Exserohilum rostratum* CNS infections from contaminated steroid products (USA)
2013	Chikungunya (Caribbean)
2014	Ebola (multiple African countries and isolated cases internationally)

describe some of the current drivers of emerging infectious diseases today (see Box 4-1), with the hope that such an appreciation will help to anticipate future disease threats. Here we consider emerging infections as either new infections, ones that are increasing in incidence or geographic scope, or infections that are likely to do so.

BOX 4-1 DRIVERS OF EMERGING AND RE-EMERGING INFECTIOUS DISEASES

HUMAN–ECOSYSTEM INTERACTIONS

Changes in land use, deforestation, and irrigation
Intensification of farming and agriculture
Specialization of agriculture and foreign trade
Procurement and sale of bush meat
Crowded and diverse live-animal markets
Importation of exotic animals
Construction of dams and roads

CLIMATE, WEATHER, NATURAL DISASTERS

Sea-level rise and flooding of low-lying coastal areas
Changes in ocean surface temperatures
Extreme weather and storms
Floods
Droughts
Earthquakes
Tsunamis
Displacement of populations
Lack of utilities and infrastructure following disasters

TRAVEL

Spread of disease vectors (e.g., mosquitoes) on ships and airplanes
Passengers in confined spaces
Rapid transfer of infections to new and susceptible populations
Return home of ill travelers
Delayed diagnosis of returning travelers with infectious diseases

POVERTY

Lack of access to clean water
Poor sanitation
Housing with poor ventilation
Building materials that house disease vectors
Poor nutrition
Homelessness
Limited access to healthcare
Lack of public-health resources

GOVERNMENTAL AND GEOPOLITICAL FACTORS

Lack of investment in public health
Wars and armed conflict
Mass migration of displaced populations into crowded refugee camps
Economic and fiscal crises

BEHAVIORAL CHANGES AND EMERGING INFECTIOUS DISEASES

Vaccine avoidance and refusal
Intravenous drug use
Risky sexual activity

CROWDING, INCREASED POPULATION DENSITY

Colleges and universities
Military populations
Prisons
Nursing homes and hospitals
Megacities

MEDICAL TECHNOLOGY

Widespread use of antimicrobial agents leading to resistance
Immunosuppressive medical therapies (e.g., biologics)
Medical devices (e.g., catheters, prosthetic joints)
Transplants and transfusions

A Short History of Emerging Infectious Diseases

Human settlement and the corresponding development of agriculture provided ideal conditions for the emergence and spread of infectious diseases. Agriculture allowed people to stay in one place, and increased food production caused the population density to expand far beyond levels that could be sustained by hunting and gathering alone. This growth in population density provided a critical mass of people to sustain and spread contagious infectious diseases.[2,12] Also, some agricultural practices, specifically the domestication of animals, increased human and animal interactions, as well as interactions between different animal species. This cross-species mixing provided the ideal conditions for the evolution of new infectious diseases.[2,12] Subsequent historical developments involving trade, war and migration created a means for spreading disease outbreaks to new populations around the world.[13]

Historically, the spread of infectious diseases often followed periods of social upheaval and transitions.[14] In some cases, infectious diseases may have played a role in the course of history.[13] An epidemic decimated the population of ancient Greece, and the 'Plague of Athens', possibly caused by typhus,[2] may have determined the outcome of the Peloponnesian war and the future of the state of Athens. Similarly, the 'Justinian Plague', believed to have been caused by *Yersinia pestis*,[15] greatly affected the Byzantine Empire and devastated Constantinople.[14] Centuries later the plague spread to Europe via trade routes and resulted in an extraordinarily high mortality rate. The resulting dramatic decrease in population in Europe helped increase social mobility and may have helped lead to changes in political and economic structure.[16]

Exploration and travel also promoted the emergence of new infectious diseases into susceptible populations. For example, when the Spanish reached the Americas, they introduced smallpox and measles. These diseases had a greater impact on indigenous populations than the relatively small armies accompanying Cortez and Pizarro.[13] The exchange of emerging infections was heavily one-sided, but not one-way. For example, it is likely that Spanish explorers introduced syphilis to Europe.[2,13]

During the Industrial Revolution, particularly in Britain, cities, with their rapidly increasing populations, efficiently spread infectious diseases. As the population moved from the countryside into the cities to work in the new factories, migrants experienced over-crowding, longer working hours and a poorer diet compared to their contemporaries in rural communities. Smallpox, typhus and tuberculosis were endemic in cities. Child mortality was high from diseases like measles, mumps, pertussis and scarlet fever. Before the widespread introduction of modern sewage systems in the late 19th century, sewage often contaminated water supplies directly. Cleaner water supplies eradicated cholera in Britain and the United States, but poor sanitation still leads to the spread of cholera in many parts of the world.

Over the last several decades, improvements in technology and the standards of living for some have opened new routes for emerging infections. The resulting increase in travel now means that infections can move across continents in a matter of days rather than weeks or months. Thus, the closeness between populations and infectious diseases can no longer be measured in terms of geographic distance, and the factors that drive emerging infectious diseases in one part of the world can affect other parts of the world very quickly. Similarly, the pursuit of natural resources and sources of food have put people into close contact with new species, increasing the chance for disease spillover (Figure 4-1),[8,17] which when coupled with the ease with which both people and diseases can travel, has created an unprecedented opportunity for new diseases to emerge and spread.[14]

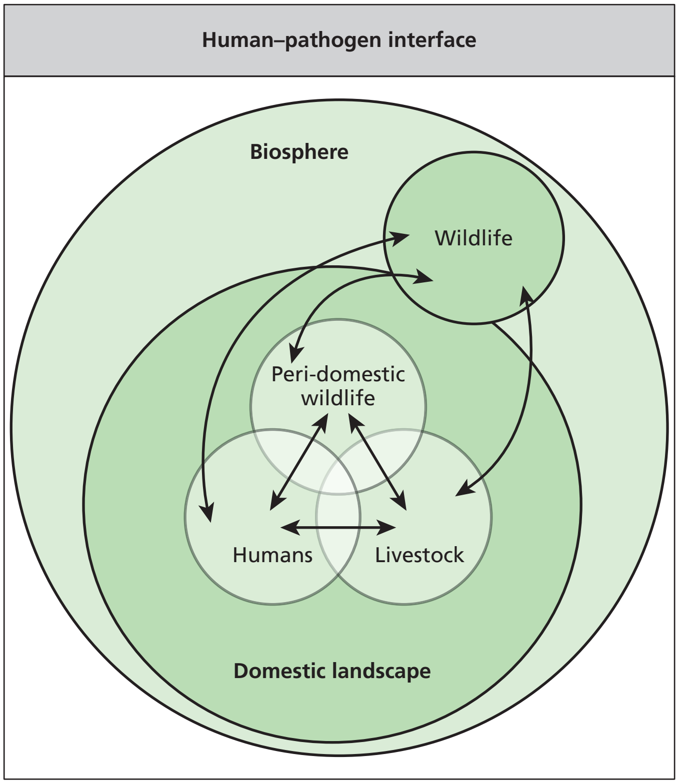

Figure 4-1 Human–pathogen interface. Pathogen flows between animals and humans can be direct, indirect, or vector-borne. Flows are dependent upon the duration, frequency and intensity of interactions. *(From Jones BA, Grace D, Kock R, et al. Proc Natl Acad Sci USA 2013; 110(21):8399–8404.)*

Human–Ecosystem Interactions and Emerging Infectious Diseases

Humans may have influenced their surroundings ever since Paleolithic times. However, the large environmental changes that increased the likelihood of humans becoming infected with new pathogens escalated when farmers started domesticating animals and tilling their fields over 10 000 years ago.[12] Even today, in some parts of the world, humans are brought very close to animals, as a result of not only farming approaches, but also processing and selling animals.[18] Situations in which multiple species live in close proximity increase the likelihood that new infections can emerge and spread to humans. In fact, a majority of all emerging and re-emerging infectious diseases are zoonotic in nature.[19,20] The regions that are at high risk for producing emerging infectious diseases feature populations that have more frequent interactions between humans and other animals.[17,20] Risks of disease emergence may be especially high where and when changes in land use occur, that is when intensified agricultural approaches spread into previously uncultivated ecosystems.[9] The emergence of Nipah virus in the 1990s in Malaysia provides an example of an emerging infectious disease associated with a change in land use. Pig farms were established close to tropical forests, and the virus spread from fruit bats to pigs and then to pig farmers.[2,21] Efforts to control this outbreak resulted in the culling of over a million pigs.[21] When forests and other habitats are fragmented by increasing human incursion and changing land use, the amount of area where humans come in contact with wildlife and disease vectors increases due to 'edge effects'. Habitat fragmentation has been associated with increased risk for Lyme disease in the northeastern USA.[9] Decreasing levels of wildlife diversity, specifically the diversity of bird species, has been associated with increasing cases of West Nile virus infection among humans. Thus, loss of biodiversity may also be an important driver of emerging infectious diseases.[8]

Intensified production of domestic animals can also increase the spread of zoonotic infectious diseases.[8] Crowded conditions and lack of free movement both compromise the health and well-being of the animals and also make animal-to-animal transmission of diseases more efficient. Antibiotics are often used to control infections and promote growth. The widespread use of antibiotics in intensive farming has introduced antibiotics into the food chain and may lead to antibiotic-resistant bacteria that could affect human health.[22]

The domestication of animals is not the only food-based risk factor for emerging infectious diseases. In some regions, the procurement and sale of bush-meat may also be a potential driver of emerging infectious diseases. Indeed, HIV may have emerged in an area in which non-human primates were used for food.[8,17] The sale and widespread distribution of such foodstuffs may amplify the risk of emerging infectious diseases related to bush-meat or bush-products, especially since such food products are often smuggled around the world, evading any sort of inspection systems. Also, some of the animals may be alive at the time of transport. Crowded and diverse animal markets in Southern China may have played an important role in the initial spread of severe acute respiratory syndrome (SARS).[18]

The smuggling of animals for pets may also contribute to the possible spread of infections. Even legal importation of exotic animals has been associated with the emergence and spread of infectious diseases because animals of different species are often kept together in close spaces during transport and distribution. For example, the outbreak of monkey pox in the USA was associated with the exotic pet trade. During this outbreak, over 70 cases were documented. These were linked to pet prairie dogs, which most likely acquired the virus from imported rodents housed in the same distribution center.[23]

Plant-based agriculture can also help drive the emergence or re-emergence of infectious diseases. The incursion of farmland into forested areas increases the likelihood of human interactions with disease vectors. In addition, some farming practices increase the likelihood of human–insect contact by supporting populations of mosquitoes. Rice farming, which involves the flooding of fields, and also irrigation practices can facilitate the growth of mosquito populations.[24] Any agricultural practice that generates standing water, including aquaculture, also helps sustain and increase mosquito populations.

Travel and Emerging Infectious Diseases

Travel is now more accessible than ever before. Over the past several decades, the costs associated with travel have decreased dramatically; at the same time the convenience and speed of travel have increased. This has created a large network of travelers around the globe, composed of more than 25 000 routes by sea and 6000 routes by air (Figure 4-2).[25] Thus, travelers provide a way for pathogens to move quickly around the world.[26] Even the act of travel itself, with passengers cramped in confined spaces (buses, airplanes, trains, ships) increases the potential for diseases, especially those spread by both droplet and airborne routes, to spread from traveler to traveler.[27]

The choice of travel destination also places some travelers at extra risk. For example, more adventurous travel, especially in rural, tropical environments, provides new opportunities to spread emerging infectious diseases, ranging from dengue to malaria and chikungunya.[26,28] However, even travel to urban environments can put travelers at risk for diseases. For example, dengue fever is becoming more common in many cities around the world.[29] Finally, even relatively local travel can spread diseases. For example, spring-break-associated travel among college students helped spread mumps during the largest USA mumps outbreak in decades.[30]

Furthermore, once travelers arrive at their destination or return home, opportunities to spread travel-acquired diseases are often realized, as infectious returning travelers come into contact with susceptible populations. When returning travelers present with travel-acquired diseases, there are often delays associated with a proper diagnosis, treatment and reporting possible cases to public health authorities. Delays are especially likely to occur if physicians do not have sufficient experience with emerging infections or do not consider such diseases in their differential diagnosis. Delays in diagnosing such diseases in returning travelers can, in some cases, generate additional cases. For example, in 2003 the SARS outbreak spread quickly around the world from Hong Kong to Canada and then to other countries, and the spread of SARS was accelerated and facilitated by international air travel.[31] More recently, international travel has facilitated the international spread of chikungunya. In two neighboring villages in Italy, over 200 autochthonously transmitted cases of chikungunya were identified and linked to a traveler who had acquired the virus while visiting relatives in India.[32] The outbreak's occurrence demonstrates how easy it may be for this disease and others to spread to Europe and beyond. Indeed, autochthonously transmitted cases of chikungunya have since been reported in France[33,34] and in the Caribbean. The laboratory-based observation that some mosquitoes in Florida are susceptible to both infection by and dissemination of chikungunya virus raises the concern that the disease could spread once introduced in the Southern USA.[35]

Finally, human travelers are not the only means by which pathogens can travel. Insects, which serve as infectious disease vectors, can also spread diseases when they are accidentally carried from one location to another. Mosquitoes, for example, can live in the holds or container vessels of ships or in cargo, such as old tires or bamboo, and then spread around the world, disembarking when the ship's cargo is unloaded at a new port.[25,33] Airplanes can also transport mosquitoes over extremely long distances. For example, air travel has been implicated in the introduction of new species of mosquitoes to Hawaii.[25]

Poverty and Emerging Infectious Diseases

Poverty is associated with several conditions related to the spread of infectious diseases: a lack of access to clean water, poor sanitation and housing with poor ventilation or building materials that house disease vectors. Poor nutrition can also facilitate the acquisition and spread of infectious diseases. Furthermore, although poverty, as a risk factor, is most commonly measured at a population level (e.g., access to clean water), poverty can also help drive the spread of infectious diseases at an individual level, even in higher-income countries. For example, homelessness has been associated with the spread of tuberculosis in several countries. The prevalence of tuberculosis, as well as hepatitis C and HIV, may be substantially higher in homeless populations.[36] Tuberculosis has also been associated with poor neighborhoods, even in higher-income countries.[37]

People living in poverty often have limited access to healthcare. Therefore, in the case of an outbreak, diagnoses can be delayed, and follow up can be difficult, leading to more opportunities for disease spread. A lack of public health infrastructure and access to medical care may delay the recognition of an emerging infectious disease outbreak, and thus delay a coordinated public health response. A lack of public health resources can also dilute the effectiveness of a public health response.[38]

Several efforts have been aimed at improving the health of populations, using interventions targeted toward improving the standard of living or via direct aid to populations living in poverty or with poor public health. Unfortunately, foreign aid, by itself, is not always associated with a decrease in infectious disease activity or outbreaks for a variety of reasons. The association between poor nations and infectious disease outbreaks involves multiple factors, making interventions difficult. For example, government corruption may make foreign interventions, which are designed to reduce the spread of infections, less effective. Specifically, up to 5% of the differences among countries in multidrug-resistant tuberculosis could be related to corruption.[39] With corruption, treatments do not necessarily go to those who need them most, or even to those with the ability to pay for them, but rather to those with specific connections. Such factors complicate strategies designed to reduce both poverty and the spread of infectious diseases associated with poverty. When countries attempt to restructure their spending in response to the loan conditions of the International Monetary Fund, the result can be a decrease in spending for public health, treatment, and surveillance.[40] For example, the implementation of reform programs of the International Monetary Fund has been associated with increased tuberculosis incidence in post-communist Eastern European and former Soviet countries.[40] While economic reforms may ultimately lead to higher standards of living and increased spending in public health, economic transitions may help fuel other factors associated with emerging infectious diseases. In fact, low- and middle-income countries, in the process of becoming more industrialized, may engage in more road construction, dam building, mining and other activities, which result in the alteration of land use and deforestation, and these changes can precipitate environmental changes, which lead to the emergence of infectious diseases.[9,17] Thus, it is possible that development efforts and aid may in some cases actually help increase the potential of infectious disease outbreaks in low- and middle-income countries.

Governmental and Geopolitical Factors Associated with Emerging Infectious Diseases

Progress in controlling infectious diseases was sometimes followed by a shift in public investment away from public health infrastructure to other spending priorities. These decisions may have been the result of the optimism that the tide had turned against infectious diseases as a major future public health threat. However, in other cases, funding was cut to ease financial pressures. In both situations, the lack of investment may have prevented future detection and compromised control efforts. For example, during the 1970s, New York City decided to cut public health funding during a fiscal crisis.[41] Unfortunately, in the following years, tuberculosis re-emerged as an important pathogen, and now a substantial burden of the disease is associated with

Flight travel paths

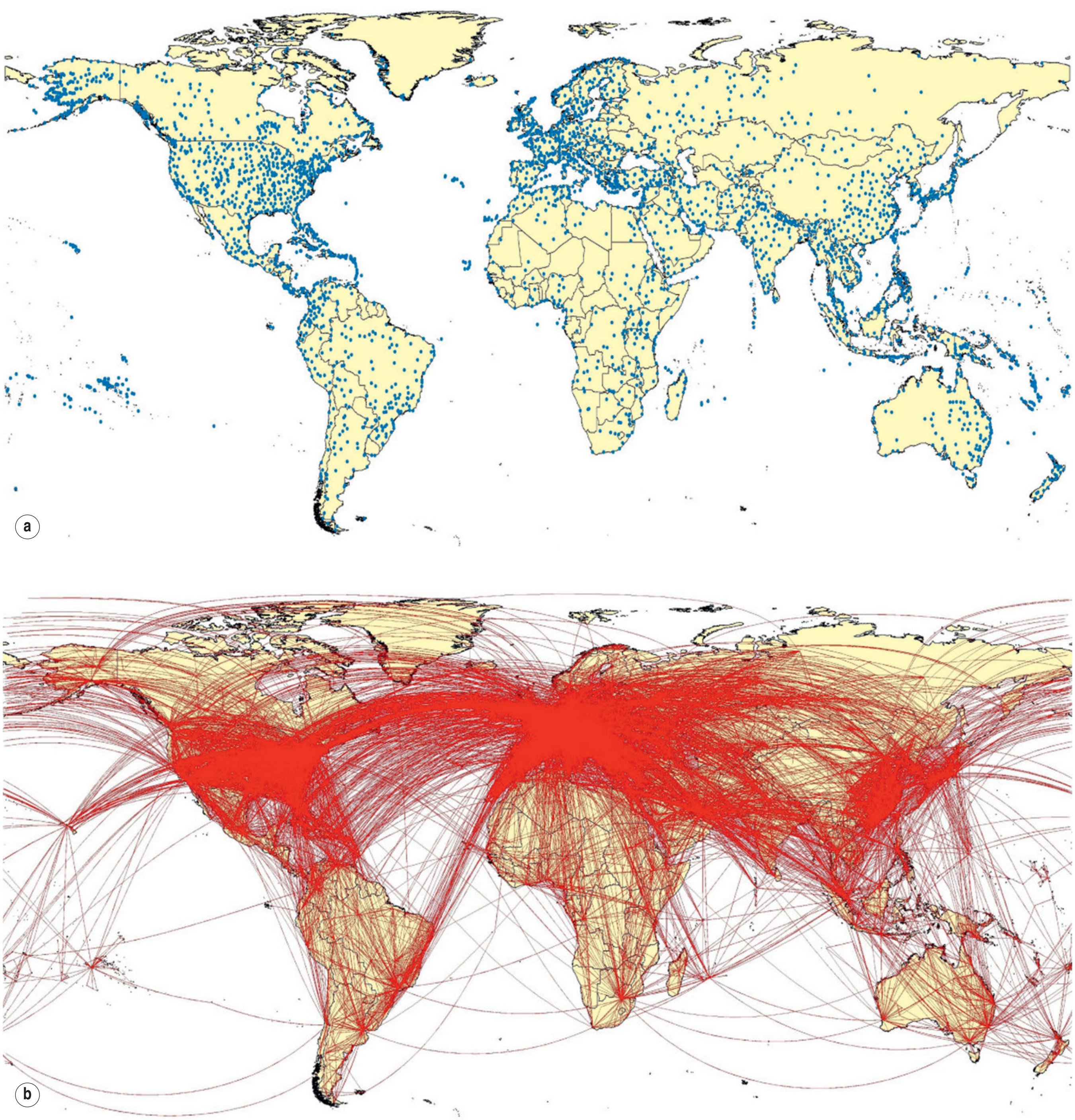

Figure 4-2 Flight travel paths. (a) The location of the 3632 airports and (b) the flight routes. *(From Huang Z, Das A, Qiu Y, et al. Web-based GIS: the vector-borne disease airline importation risk (VBD-AIR) tool. Int J Health Geogr 2012; 11:33.)*

drug resistance. The lack of public health support may have led to decreased diagnosis and treatment and even less efficient administration of treatment, and thereby facilitated the emergence of drug-resistant tuberculosis.

Another example of how political events and decisions can affect re-emerging infectious diseases occurred in the former Soviet Union in the 1990s. Following the breakup of the Soviet Union, the previous public health system became increasingly fragmented, and the result was a re-emergence of several infectious diseases, most notably, diphtheria: during the 1990s over 150 000 cases were reported, making it the largest diphtheria epidemic since the 1950s.[42] Tuberculosis rates dramatically increased,[2] and reported rates of syphilis were also very high.[43] Between 1990 and 1994 all-cause age-adjusted mortality increased by more than 30%, and infectious diseases accounted for approximately 5% of this increase.[44]

Wars and other armed conflicts represent another potential driver of emerging infectious diseases.[45] For example, wars can disrupt vaccination programs.[46] Conflicts can also disrupt disease prevention efforts, strategies and necessary supplies to protect against or control for malaria.[47] Displaced populations, fleeing from conflicts, often crowd into refugee camps, and such camps can facilitate the spread of re-emerging infectious diseases such as measles.[48]

Economic crises can also impact the transmission of communicable diseases and thus the spread of emerging infectious diseases. During recessions, worse infectious disease outcomes have been reported.[49] In Thailand increasing measles, malaria and diarrhea in children, and dengue in adults were associated with a 30% decrease in gross national product during the 1997 financial crisis.[50] In contrast, the economic recession in 2009 in the USA was associated with an unexpected decline in tuberculosis cases.[51] Thus, the relationship between funding and health outcomes is difficult to interpret in the short term by examining disease rates in a single country. However, if recessions exacerbate poverty and undermine public health efforts, such financial shocks will hamper efforts to detect and control outbreaks when they occur.

Behavioral Changes and Emerging Infectious Diseases

While some outbreaks are driven by the choices made by policy makers and government officials, others are driven by individual choices. Despite the availability of vaccines, in many cases parents are choosing not to vaccinate their children. These decisions to avoid vaccines have been linked to outbreaks of vaccine-preventable diseases and in some cases, for example, the re-emergence of measles and pertussis.[52,53] From a spatial perspective, cases of vaccine-preventable diseases cluster with areas of lower vaccination and high rates of non-medical vaccination exemptions.[52] At times, vaccination decisions are enabled by policy choices that make it easier for parents to refuse vaccination, but in other instances parents go to great lengths to avoid vaccination. Misconceptions about the safety of the vaccines drive many of the decisions.[54] Internationally, misperceptions regarding vaccine safety are an important public health problem. In fact, during the 1980s, concerns about risks in part led to significantly reduced vaccination levels in the Soviet Union, and these lower levels helped drive a diphtheria outbreak that occurred in both Russia and the newly independent states.[42]

Behavioral changes have also been linked to the emergence and re-emergence of sexually transmitted infections. While syphilis was once a major cause of morbidity, it had been reasonably well controlled due to expanded treatment efforts and public health interventions. In fact, syphilis was once pegged as a disease that had the potential to be eradicated.[43] Yet in the past several years the number of cases of syphilis has increased dramatically, and the disease has re-emerged.[55] Why? Syphilis is straightforward to diagnose and treat. One reason for the re-emergence of syphilis relates to a behavioral change associated with an emergent technology: the Internet has been used to facilitate sexual encounters. Often these encounters are anonymous, and thus risky by nature.[56] In addition, the specific websites designed to facilitate these encounters dramatically increase the potential number and diversity of partners any user can identify. While the Internet has made it easier to find sexual partners, it has complicated the process of contact-tracing for public health officials, a cornerstone of public health interventions for sexually transmitted infections. And while syphilis is not resistant to treatment, another sexually transmitted infection, gonorrhea, is now resistant to a number of antimicrobials,[57]and as treatment becomes more and more difficult, the infection may re-emerge and become even harder to control than in past decades, given the increasingly complicated sexual networks in several communities around the world.

Crowding, Population Density and Emerging Infectious Diseases

Many emerging or re-emerging diseases spread rapidly in closed or partially closed populations. The best examples of such populations include military recruits and college students living in dormitories. Prisons are also ideal environments for spreading infections. Not only are these populations placed in close contact with one another, by training, working and often sleeping in close quarters (e.g., barracks and/or dormitories), but also these settings bring people with different levels of immunity together. Historically, especially in the pre-vaccine era, military recruits were frequently involved in outbreaks of emerging and re-emerging infectious diseases. Although vaccination coverage is extremely high in most military populations, outbreaks of emerging infectious diseases still occur. Adenovirus strains have caused severe pneumonia in military populations.[58] From a historical perspective, the influenza pandemics of 1968 and especially 1918 were dramatic examples of infectious diseases that spread rapidly in military populations, and subsequently military-associated travel may have helped to distribute the disease to civilian populations. Intermittent meningitis outbreaks have been associated with college campuses. However, in recent years, college and university students have been associated with outbreaks of several re-emerging infections. For example, mumps outbreaks in several countries have been associated with college students.[30] As long as people live in close proximity, with varying levels of immunity and frequent mixing, such settings will continue to be efficient population-based incubators for emerging infectious diseases around the world.

Hospitals and nursing homes are other relatively crowded environments ideal for spreading infectious diseases. In fact, SARS was greatly amplified in hospital settings, spreading both to other patients and to healthcare workers.[59,60] Over the past several decades, the hospital environment has created a new ecological niche for the emergence of several antimicrobial-resistant pathogens. Examples include methicillin-resistant *Staph. aureus* (MRSA)[61] and vancomycin-resistant enterococcus (VRE).[62] Although *Clostridium difficile* is not resistant to antimicrobials per se, it has certainly re-emerged over the past decade, in part due to the widespread use of antimicrobial therapy.[63] Cases of *C. difficile* have also emerged among pediatric populations.[64] While cases of MRSA first appeared in healthcare settings, they now occur in community settings,[65] and so too have cases of *C. difficile*. These cases are occurring even in the absence of prior antimicrobial therapy, and without exposure to healthcare environments.[63] Finally, one of the most alarming developments, with respect to antibiotic resistance, is the recent emergence and spread of multidrug-resistant gram-negative bacteria around the world. Many of these have extremely limited treatment options. Gram-negative bacteria that produce the NMD-1 enzyme are a prime example.[7] Although these are thought to have emerged from the Indian subcontinent, cases have occurred around the world, and may be introduced to new healthcare systems from returning travelers who are seeking medical attention. Once established in healthcare settings, these infections could potentially spread widely.

All of the previously mentioned cases of crowding refer to specific examples of institution-based crowding. However, the greatest potential for crowding to support the emergence and spread of new infections is the increasingly dense urbanization that is resulting in the development of 'megacities' in low- and middle-income countries. These large cities are often composed of over 10 000 000 inhabitants. Megacities, with their poverty, poor sanitation, lack of infrastructure and high population densities, are perfect breeding grounds for infectious diseases, particularly sewage-related water-borne diseases and diseases that spread person-to-person.[3] However, urban environments are also becoming increasingly suited for mosquito-borne illnesses like dengue.[29] The populations at greatest risk for acquiring emerging infections are those that live on the edges of these megacities, in the peri-urban areas. People living in these areas are less likely to live in homes with concrete floors, have access to clean water, waste removal and medical services.[66] For example, in regions where malaria is endemic, the urban prevalence of malaria is much lower in central parts of cities than in the surrounding peri-urban areas.[67]

Medical Technology and Emerging Infectious Diseases

Over the last several decades, multiple new therapeutic approaches in organ transplantation, the treatment of autoimmune diseases and also cancer have been developed. Many of these therapies lead directly to a diminution of the patient's immune response and thus increase the risk that a patient will develop a serious infection after their treatment. Thus, these medical advances have resulted in the emergence and re-emergence of new or previously uncommon pathogens. Cytotoxic therapies used to treat malignancies were not designed to specifically suppress the immune system by therapeutic intent. In practice, however, they do indeed cause prolonged periods of immunosuppression, and as a result many patients have developed a broad range of unusual infections, and many of the new pathogens are fungal.[68] In the field of organ transplantation, both for solid organ transplantation and hematopoietic transplantation, previously rare fungal infections are now much more common among patients receiving transplants.[69] Often, as a prophylaxis is used to protect against one type of infection, a pathogen resistant to the prophylaxis emerges. For example, infections due to zygomycosis have increased following the widespread use of voriconazole administration to treat *Aspergillus*.[70]

A new of class of drugs often referred to as 'biologics' is extremely effective in treating connective tissue diseases. The most common are the medications that selectively inhibit tumor necrosis factor-alpha. However, by inhibiting tumor necrosis factor they inhibit granuloma formation and maintenance, and thus have been associated with a wide range of infections, including tuberculosis, herpes zoster and a host of opportunistic infections.[71] As these biologics come off patent, their use will become more widespread; cost is currently one of the major limiting factors to their use in many parts of the world.

Other therapies also provide opportunities for new pathogens to emerge and become more common. For example, the increased use of parenteral nutrition has contributed to bloodstream infections, especially those caused by *Candida* species.[72] The widespread introduction of venous and urinary catheters created new opportunities for bloodstream infections. Indeed, urinary infections associated with catheters are often associated with antimicrobial-resistant pathogens. Catheters are certainly not the only medical devices to cause infection. The introduction of almost any new medical device has subsequently spawned a new type of device-related infection. Thus with the continued growth of implantable devices, new infections will certainly emerge that previously did not exist. Given that these devices are deployed in healthcare settings, they can become infected with emerging antimicrobial-resistant pathogens.

The increased sharing of blood and tissues over the past few decades has also played a large role in the spread of infectious diseases. Prior to the identification of the causative agents of both HIV and hepatitis C, transfusions helped spread these diseases.[73] In addition, concentrated, pooled blood products can facilitate the spread of these emerging pathogens. The safety of the blood supply has increased dramatically since the 1980s, however, pathogens that cannot yet be detected or that are not screened for remain a public health threat. Organ transplants pose an additional threat of spreading infectious diseases.[74]

Climate, Weather, Natural Disasters and Emerging Infectious Diseases

The term 'climate' describes long-term trends in temperature, precipitation, wind strength, humidity, sunshine and cloud cover, and the term 'weather' records the same parameters but on a short-term day-to-day or a week-to-week basis. According to the Intergovernmental Panel on Climate Change, 'Warming of the climate system is unequivocal, and since the 1950s, many of the observed changes are unprecedented over decades to millennia'.[75] However, climate fluctuates over different time scales, from the decadal through the centennial, to the millennial and the million-year spans of geological time. Over the past several decades, both the atmosphere and the oceans have warmed (Figure 4-3).[75] Temperature ultimately drives many other climate variables; however, the relationship between climate change and emerging infectious diseases is not a simple linear correspondence between rising temperatures and the increasing incidence of disease. Although changes in global temperatures may directly shift the distribution of populations of disease vectors, with regard to their latitudes and altitudes. For example, tick populations, an important driver of some emerging and re-emerging infectious diseases, have readjusted to warming temperatures and are now present at higher latitudes in Sweden; some models predict that the same may happen in Canada and the USA.[76,77]

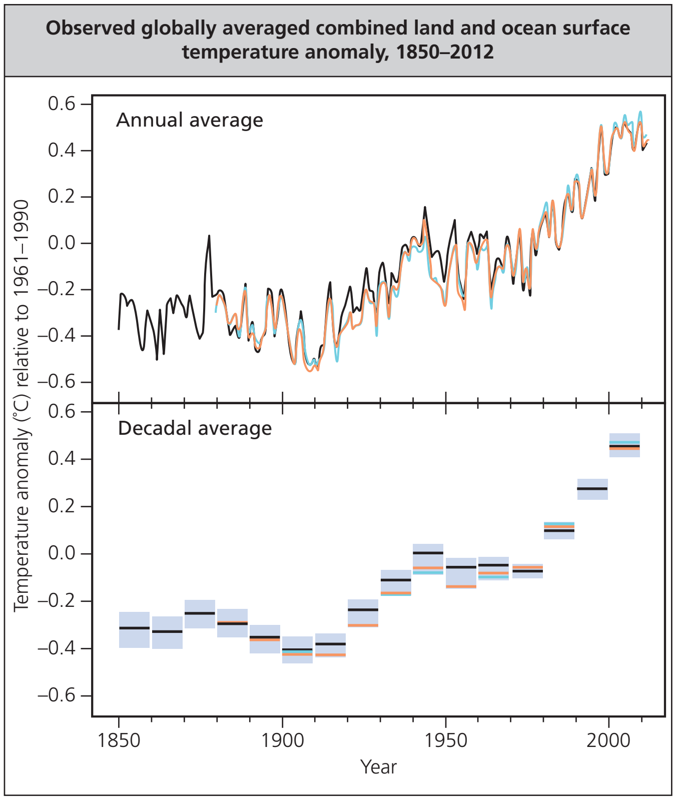

Figure 4-3 Observed globally averaged combined land and ocean surface temperature anomaly, 1850–2012. Adapted from the IPCC's Summary Report for Policy Makers (2013). Although this temperature rise begins in 1850, at the end of a naturally cold period in the Earth's environmental history known as the 'Little Ice Age', the steepness of the increase in global temperatures is unprecedented throughout geological time. *(From IPCC, www.ipcc.ch/.)*

Warming can cause rising sea levels, and consequent flooding of low-lying coastal areas can increase the breeding grounds available for mosquitoes, resulting in a rise in diseases such as malaria, dengue and yellow fever.[78] Flooding can also overwhelm coastal sewage systems, causing an outflow of sewage into the surrounding regions. Warming ocean waters may have a direct effect on cholera and other sewage-related infections because bacterial populations of *Vibrio cholera* may increase with rising sea-surface temperatures.[79] Evidence from an epidemic that started in Peru and spread north along the South American coast in 1991, showed that the *V. cholera* bacteria can attach to plankton and spread disease, particularly during planktonic blooms, such as those that occur during the relatively short-term, periodic El Niño climatic events.[80] Cholera data from 1980 to 2001 show a close correspondence with the increasing intensity of El Niño Southern Oscillation and the associated weather extremes in the Pacific, which are driven by these events.[81]

Longer-term climate change may also be increasing the intensity of more extreme weather events. Recent trends show storms of increasing severity.[82] Unexpected thunderstorms can cause increased rainfall, and the resulting deluge can overwhelm sewage systems and cause sewage or contaminated water to pollute drinking water supplies, leading to outbreaks of water-borne infectious diseases. For example, viral infections, caused by norovirus and rotavirus, have been reported after storms, as well as bacterial infections caused by *Vibrio* spp. and *Leptospira* spp.[83] Outbreaks of *E. coli* O157:H7 can also occur after heavy rains. In addition, the pools left behind after heavy rains can serve as breeding sites for mosquitoes. Finally, heavy rainfall can drive rodents from their burrows and into areas where they might come into closer contact with humans. In 1993, early and heavy rains produced a dramatic increase in local rodent populations, which was associated with an outbreak of Hantavirus pulmonary syndrome in the southwestern USA.[2]

Even local environmental change, driven by changing seasonal weather, can dramatically increase the populations of disease vectors. In addition to floods, droughts can also cause vector populations to increase, while also causing food shortages and weakening the resistance of the local population to disease, particularly in low- and middle-income countries. In some cases, drought will reduce the natural predators of rodents, such as owls and hawks, which normally keep rodent populations in check. Even smaller-scale droughts can cause stagnant pools of water to develop in place of rivers and streams, and these water collections can serve as ideal breeding ponds for mosquitoes. Storing water in anticipation of drought conditions can also provide breeding locations for mosquitoes. Drought-like conditions helped to drive the emergence of the West Nile virus in North America.[84] After the introduction of the virus it spread quickly across the continent (Figure 4-4). Drought may have been a contributing factor to the explosion of cases of chikungunya in East Africa that subsequently spread to countries around the Indian Ocean.[85,86] This outbreak caused hundreds of thousands of cases around the world and has also generated other outbreaks thousands of miles away.

When an environmental disaster such as severe flooding or drought, earthquake, tsunami, or severe storm occurs, several disease-spreading events converge: the displacement and migration of victims, the travel of aid workers, increasing poverty and a lack of utilities and infrastructure (electricity, clean water and sewage disposal facilities). Displaced residents are often weakened as a result of a suspension of their food supply and healthcare. A lack of access to clean water and disruption in sanitation can increase the chance that, if a pathogen is introduced, it will spread quickly and cause an outbreak. A recent example of such an outbreak associated with a natural disaster occurred in 2010, after an earthquake in Haiti. A visitor sponsored by the UN introduced cholera, and it spread quickly across Haiti.[87]

Approximate geographic distribution of West Nile virus in the Americas, from 1999 to September 2004

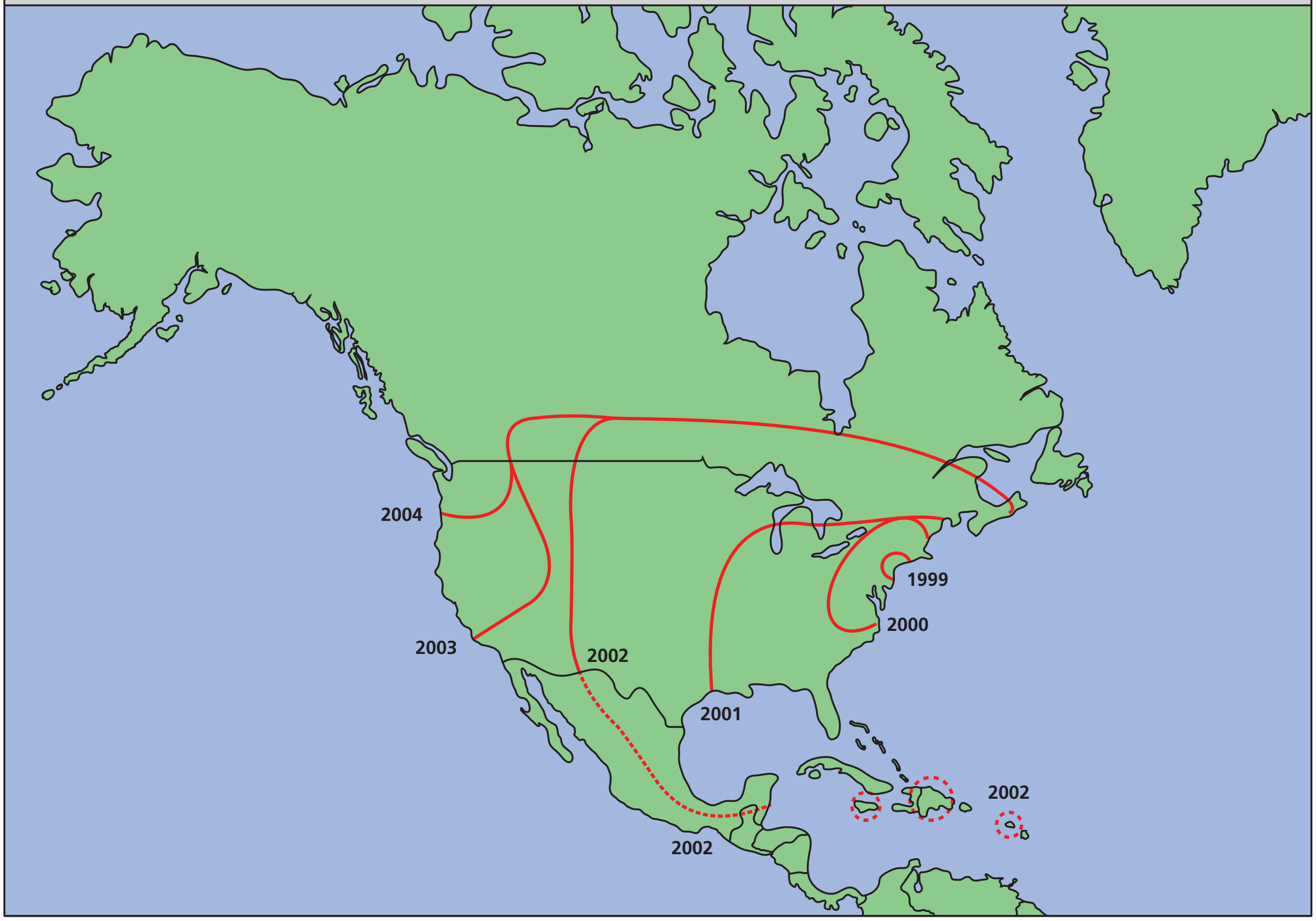

Figure 4-4 Approximate geographic distribution of West Nile virus in the Americas, from 1999 to September 2004. Placement of solid lines are based upon serologic data from dead birds, while the dashed lines are based upon serologic studies of birds and horses. *(From Mackenzie JS, Gubler DJ, Petersen LR. Emerging flaviviruses: the spread and resurgence of Japanese encephalitis, West Nile and dengue viruses. Nat Med 2004;10(12 Suppl):S98-109.)*

Finally, infectious diseases often have seasonal periodicity; some infections peak during the summer and some during the winter. Many of these diseases are driven by changes in weather, specifically humidity and temperature.[88] Vector-borne diseases usually peak in the summer: particularly mosquito-borne infections in temperate climatic zones, such as West Nile, St Louis and La Crosse encephalitis, and also tick-borne infections. Other infections that peak in the summer are skin and soft tissue infections[89] and also legionellosis.[90] In contrast, most viral respiratory diseases peak in the winter months, such as influenza and respiratory syncytial virus (RSV). In addition, gastrointestinal viral infections spike during winter months.[88] Global climate changes may make these seasonal patterns more pronounced and result in an associated increase in morbidity and mortality.

Detecting Emerging Pathogens and Outbreaks

Although new technologies have provided additional opportunities for infectious diseases to emerge and re-emerge, technological advances over this same time period have provided new approaches to identify novel pathogens, detect disease activity and coordinate disease control. For example, diagnostic tests have improved dramatically, allowing us to detect previously unknown pathogens. While it took approximately 2 years to identify the virus that caused acquired immune deficiency syndrome (AIDS), the virus responsible for SARS was identified in approximately 2 weeks. In addition, linking data from different laboratories over large geographic distances has dramatically changed the way potential food-related outbreaks are detected and traced. For example, PulseNet USA is a molecular surveillance network that has been of assistance in numerous food-borne outbreaks[91] and similar networks exist or are under development in countries around the world. New molecular diagnostic platforms, coupled with increased surveillance efforts to detect new pathogens in both animals and humans, will continue to improve the ability to identify new pathogens more quickly.[92] In addition, the promise of point-of-care testing may dramatically reduce the time it takes to rule in or rule out specific pathogens in the field, without sending specimens to reference laboratories.[93]

In response to the threat of emerging infectious diseases, many international cooperative efforts were initiated to build networks to enhance surveillance activities. An example is the World Health Organization's Global Outbreak Alert and Response Network, which unites several distinct networks to gather information about diseases in real-time, in order to detect and verify outbreaks around the world.[94] Other transnational networks focus on specific disease threats. For example, the European Centre for Disease Prevention and Control's VBORNTE is a network of public health and medical entomologists, which is dedicated to arthropod vector surveillance within the European Union.[33]

Since the 1990s, public health professionals have made several attempts to develop international surveillance networks to provide health alerts regarding infectious diseases around the world. One such program, which is not part of any governmental agency, is the electronic mail service, ProMED-mail.[95] It was the ProMED-mail listserv which helped provide an alert from a member of the listserv to the international medical community, regarding the existence of the disease that would later be identified as SARS. New generations of disease-surveillance Web applications, such as Health-Map, EpiSPIDER and BioCaster, combine data from different sources to produce a global view of emerging infectious disease threats as they occur.[92,96] These programs mine, filter, aggregate and visualize information about outbreaks in near-real time. Furthermore, new approaches to disease surveillance use data harvested from the Internet and social media sources;[97,98] these approaches may help supplement traditional forms of disease surveillance. Finally, the near ubiquity of cell phones around the world may provide a new platform, both to understand how diseases are spread and also to help coordinate disease control activities.[93,99]

Conclusion

Despite the optimism that infectious diseases would be of mostly historical interest, it appears much more likely that emerging and re-emerging infections will continue to be a part of our future. As the historian William H. McNeill wrote in the 1970s, not long after some had started to de-emphasize the future importance of infectious diseases, 'Ingenuity, knowledge, and organization alter but cannot cancel humanity's vulnerability to invasion by parasitic forms of life. Infectious disease which antedated the emergence of humankind will last as long as humanity itself, and will surely remain, as it has been hitherto, one of the fundamental parameters and determinants of human history.'[13] Just 10 years after SARS emerged, a new coronavirus also associated with a respiratory infection in humans, MERS-CoV has appeared.[100] While the ultimate impact of this new infection is not clear, given that 335 emerging infectious disease-related events occurred between 1940 and 2004 alone,[19] it is most likely that new infections will emerge and that old ones will continue to re-emerge and spread. The Ebola outbreak that began in 2013 in Guinea and spread to other Western African countries in 2014 highlights many important drivers of emerging infectious diseases discussed in this chapter.

In 2014 this Ebola outbreak became the largest and most geographically diverse outbreak to date. Changes in land use and deforestation increased the probability of spread to humans.[101] Extreme poverty and lack of public health infrastructure, in part due to years of civil conflict and lack of development, facilitated the spread of the disease. Locally relevant cultural issues, such as burial practices contributed to intra-family and community spread. In addition, the disease was introduced to more urban environments where crowding and poverty further helped spread the disease.[101] As travel-related cases outside of Africa show, human mobility is important in spreading infectious disease. Finally, the global public health response to the emerging Ebola crisis was slow and initially ineffectual. Despite a better understanding of the drivers of emerging infections, they will continue to emerge until we can address the root causes.

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