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The twentieth century was a landmark in the history of mankind as a result of the widespread control and eradication of infectious diseases that historically had been the scourge of humans. The advent and effective use of new drugs, vaccines, insecticides, treatment and prevention strategies during and following World War II reinforced public health programs already in place, and provided the tools needed to bring many of the worst diseases under control. Smallpox was eradicated using a mass vaccination strategy. By the late 1960s, the “war on infectious diseases” was declared won by leading experts in the field and by the Surgeon General of the United States (Patlak, 1996).

Unfortunately, the major successes in controlling infectious diseases in the 1950s and 1960s was followed by two coincident global trends that would have an impact on the dramatic re-emergence of infectious diseases in the waning years of the twentieth century. The first was the redirection of the resources that were once used to control infectious diseases to other public health priorities, such as the “War on Cancer” in the early 1970s. The perception that infectious diseases were no longer a problem led to decreased resources, widespread deterioration of public health infrastructure to deal with infectious diseases, and complacency among government and public health officials as well as the public (Smolinski et al., 2003). This trend included medical education with a de-emphasis on preventive medicine and a strong focus on curative medicine in medical schools. Today, training in preventive medicine is not included in the curriculum of most medical schools in the US.

The second trend was the sharply increasing and unprecedented rate of human population growth following World War II that has continued for 60 years. Increasing human numbers have been a principal factor leading to uncontrolled...
urbanization, changes in agriculture, land use and animal husbandry practices, and accelerated globalization, all of which have been major and inter-related drivers of the re-emergence of epidemic infectious diseases (Gubler, 1998a).

The first evidence of the re-emergence of infectious disease occurred in the 1970s, but the process greatly accelerated in the latter two decades of the twentieth century. Old diseases that were once effectively controlled began to reappear in epidemic form – for example, dengue, Japanese encephalitis, West Nile Virus, epidemic polyarthritis, yellow fever, measles, plague, cholera, tuberculosis, leishmaniasis, malaria, etc. In addition, numerous newly recognized diseases began to cause epidemics, such as HIV/AIDS, the hemorrhagic fevers (Marburg, Ebola, Lassa, hantavirus, Crimean-Congo, arenaviruses, dengue and yellow fever), avian influenza, Hendra and Nipah encephalitis, severe acute respiratory syndrome (SARS), Lyme disease, ehrlichiosis, and others. In addition to those factors mentioned above, resistance of bacterial pathogens to antibiotics, drug resistance in malaria parasites, insecticide resistance in mosquitoes, new medical technology (e.g. organ transplantation) and immunosuppression by drugs and disease (AIDS), and ecologic encroachment by humans and animals have all played a role in the emergence/re-emergence of infectious diseases as a global public health problem (Gubler, 1998a, 2002; Smolinski et al., 2003). In 2002, an estimated 26 percent of deaths worldwide were attributable to infectious and parasitic diseases (Fauci et al., 2005); 24 percent of the global burden of disease, as measured by disability adjusted life years (DALYs), was caused by infectious diseases (World Health Organization, 2004).

A unique feature of the twentieth century re-emergence of infectious diseases has been the rapid global spread of some infectious agents, such as SARS, avian influenza, West Nile Virus, and dengue. This global spread is tied directly to modern transportation and globalization, both of which are directly dependent on the major urban centers of the world. In the past 50 years the global human population has exploded, and nearly all of that growth has occurred in the cities of the developing world. Here, the majority of the urban population typically lives in substandard housing with no electricity, water, waste management, or sewage systems. This creates ideal conditions for increased mosquito-, rodent-, water- and food-borne infectious diseases, as well as for sexually transmitted and communicable diseases. The global airline network connects these cities, providing the ideal mechanism for transporting exotic pathogens to new geographic locations. This chapter reviews the contribution of urbanization, both directly and indirectly, to the twentieth century re-emergence of infectious diseases, focusing on dengue/dengue hemorrhagic fever as a case study.

The role of urbanization in infectious diseases

In his seminal book *Plagues and Peoples*, McNeil (1976) described how the development of major urban centers, and the successive stages of regional, and
eventually global, trade linkages via new trade routes such as the Silk Road connecting the Middle East with Asia, explain historical patterns of the emergence of plagues and, indeed, the outcome of a number of pivotal events in history. Thus the relationship between urbanization and infectious diseases is an ancient one, of which the current phase is in some ways (but not all) a continuation of this story. The story is largely one of a dynamic in which the human populations of cities grow large and dense enough to insure a constant “crop” of susceptible individuals not exposed in previous outbreaks, fueling an epidemic cycle as well as providing the social-ecologic conditions for endemic persistence of a succession of infectious diseases. A significant fraction of the “susceptibles” is contributed by the flow of rural migrants, as well as urban natives born subsequent to previous outbreaks – a demographic pattern that today involves much higher numbers of migrants. This dynamic is elaborated upon by the expansion of networks of cities linked by land and sea through the movement of people, their associated animals, and commodities, providing new opportunities for pathogen dispersal. Cities, at least where adequate resources and political stability exist, have responded with the development of social institutions (hygienic laws, customs, and behaviors) and physical infrastructure (health-care, sanitation and waste management systems, etc.). Thus, the historic as well as the present-day dynamics of human infectious diseases largely reflect the ecological and evolutionary interplay of microparasites, the proportion of susceptible individuals in a population, and cultural adaptation. An underlying complication is the continuous evolution (and co-evolution) of humans, along with their domestic animals, and pathogens – with the occasional addition of new pathogens that have jumped the species’ barrier (e.g. between apes and humans as in the case of HIV) and become successfully established in the human population.

Adding to the complexity today, and resulting in a new era of infectious disease emergence qualitatively different from that of the past, is the fact that the ecological theater in which this age-old co-evolutionary play is performed has been changing at an unprecedented pace. As a result, not only is there a need to restore investment in infectious disease prevention; new perspectives and models are also needed to understand and predict epidemic disease emergence, and to develop preventive measures that take into account the new social ecology of modern urbanization. A “social ecological systems” perspective, in which cities and their surroundings are seen as so-called “coupled human-natural systems,” is one new way of thinking that has been helpful to explain patterns of disease emergence in relation to urbanization (Wilcox and Colwell, 2005; Wilcox and Gubler, 2005). A graphical representation of this perspective is shown in Figure 4.1, which illustrates the linkage of human systems on a regional scale with natural systems, such as ecological communities and ultimately host-parasite complexes, on successively smaller ecological scales. Changes at the level of the regional environment, such as population growth, cascade down through these successively smaller scales to facilitate the emergence or re-emergence of
infectious diseases. This coupled system thus “sends” the diseases in the opposite direction, up through the system to potentially impact public health on a regional or even global scale.

**Current urban demographic trends**

While the process of urbanization has been going on for all of recorded human history, its pace has dramatically increased in the past hundred years. From 1900 to 1950 the world’s urban population increased from approximately 220 million to 732 million, and then from 1950 to 2005 to about 3.2 billion. By 2030, demographers project the number will be about 4.9 billion. Sometime in 2005, for the first time in history, there were more people living in cities than in the countryside. By 2030, about 60 percent of the world’s population will be living in cities (United Nations, 2006). In 1800, Beijing was the only city with a population of over a million people. From 1800 to 1990, the average size of
the world’s hundred largest cities grew from around 200,000 to over 5 million (Hardoy et al., 2001). There now are more than 40 cities with populations of at least 5 million, and 19 with more than 10 million. The latter are referred to as megacities, the list of which has grown and will continue to do so dramatically in the coming decades (see Table 4.1).

These are actually no longer discrete metropolitan areas surrounded by well-defined rural areas, but urban agglomerations that typically include the original city, now represented as a central urban zone, surrounded by a mix of suburbs, semi-urban, and semi-rural areas, all of which are interlinked. These are in turn connected (via the central city) to a global transportation network facilitating the rapid flow of people, vectors, and pathogens globally. Some urban agglomerations,
like Tokyo, Mexico City, New York, and the Ruhr, are composed of more
than one central city and one municipal government, but in many ways func-
tion like a single social ecological entity. The population of Tokyo, Yokohama,
Kawasaki, and Saitama is more than 34 million. The population of Mexico City,
Nezahualcoyotl, Ecatepec, and Naucalpan is more than 22 million. Seoul can be
thought of as including Bucheon, Goyan, Incheon, Seongnam, and Suweon, with
a total population of about 22 million. Not only has uncontrolled urbanization
produced “cities” with population sizes unimaginable two generations ago, it has
also created a new geography in which large, small, and medium human settle-
ments across large regions have coalesced to create regional landscapes qualita-
tively different from those of the past. A similar growth pattern is unfolding in
hundreds of smaller urban areas throughout the developing and developed world.

Thus, cities like Bangkok are now either referred to as the original municipality,
currently with around 6 million people, or as “greater” Bangkok, which encom-
passes the surrounding districts with which the urban “habitat” of the original
administrative unit is now contiguous. Such contiguous municipalities effectively
constitute a single pool of humans – and a potential disease reservoir – which,
in the case of Bangkok, now exceeds 10 million people. Even if the physical
infrastructure and thus urban human density are not contiguous, it often becomes
effectively so from a human pathogen’s standpoint. The connectivity and mixing
of people made possible by the modern transportation infrastructure and commu-
uter lifestyle makes this so.

Nearly 500 cities now have population sizes approaching or exceeding
500,000. This is just above what mathematical epidemiology has found to be
the critical population size for disease persistence and recurrent epidemics – a
key transition point beyond which the trend of increasing infectious disease
re-emergence or emergence is much more difficult to reverse, as is described
further below.

Most of the fastest growing of these cities are in the developing tropical zones,
where climate, environmental, and social ecological conditions are favorable for
the transmission of pathogens responsible for the vast majority of old and new
infectious diseases. While these conditions and the disease patterns are an inte-
gral part of the history of the development of human settlements and civilization,
that the scale and magnitude of the present era of human-induced environmental
change is unprecedented is starkly illustrated by the figures on urban popula-
tion growth in developing countries during the past half-century. From 1950 to
2005, the urban population of the developing nations increased from just over
308 million to about 2.25 billion (United Nations, 2006). Most of that growth
has resulted from immigration from rural areas, with many people bringing their
rural lifestyle to the city. Figure 4.2 illustrates the growth of urban populations
from 1950 to 2030, and shows that the largest increase has been in the low- and
moderate-income countries of the developing world.
Risk parameters associated with urbanization

How urban social ecology affects emerging disease risk, especially the underlying mechanisms and dynamics involving environmental, human behavioral, and other factors, is poorly understood. However, a number of the parameters affecting risk are known. The risk for urban infectious disease outbreaks is greatest not only where the population density is highest, but also where people, public infrastructure, and public services are poor, and where access to medical care and basic public health programs does not keep pace with population growth. This includes cities in many of the same countries in the low- to moderate-income category just described, which typically are severely overcrowded. Poor neighborhoods lack safe and adequate housing, as well as reliable clean water, sewage disposal, and waste management. Public health is usually underfunded, and surveillance is non-existent or primitive. Generally, the supply of trained medical and public health professionals is insufficient to meet basic public needs. And because all the districts and neighborhoods in a large urban area are linked by modern transportation systems, pathogens can circulate with ease. Ironically, the construction of modern transportation systems intended to support modernization and economic development ensures the mixing of infected and susceptible people at a historically unprecedented rate. Many large urban complexes in developing Asia, for example, where highway and mass transit systems were lacking a decade ago, either now have them or soon will. Moreover, these are
linked to transportation networks connecting even the most distantly separated urban centers. So the possibility now exists that an infectious disease outbreak within a neighborhood will spread readily not only throughout the city and to the surrounding areas, but also across the country and beyond national borders. This is of course exactly the scenario describing the near pandemic of SARS in 2003. Once this novel pathogen, whose source may have been fruit bats in Southern China, emerged near the rapidly growing Guangzhou in Guangdong Province (China), it easily spread to Hong Kong by surface transportation, and to Singapore, Vietnam, and even Toronto by infected air travelers, in barely a few days. In 2004, approximately a billion people traveled by air, with an ever-increasing number of them going to and from fast-growing cities in the tropical developing world. From 1983 to 1994, the number of air passengers leaving the United States doubled from about 20 million to 40 million, and more than half went to tropical countries. With modern laboratory analyses, it has been possible to track these epidemics across the urban hubs of common world travel and trade routes.

Although the global spread of epidemic pathogens tends to occur episodically, serious disease-causing pathogens now regularly erupt in cities and spread outward to the surrounding less densely populated areas of the country. In today’s booming urban economic centers of Asia, like Guangzhou (approximately 9.5 million in the metropolitan area), Ho Chi Minh City (about 5.4 million), and Bangkok, much of the labor force is almost constantly on the move to and from cities and the country. The magnitude of human movement in and out of cities in developing countries cannot be overstated. A significant proportion (often the majority) of the urban population is of non-native origin and migrants. These people immigrating to the urban centers seeking economic opportunity still call “home” the small cities, towns, and villages of their origin, often because it is where their wives, children, parents, and grandparents live. On holidays like the New Year they travel from the city to their homes en masse. Each individual who travels home is capable of spreading a disease contracted in the city, and vice versa. Not long after the SARS outbreak in Southern China, and when the pathogen was apparently not yet contained, tens of millions of people took a holiday from work to travel home for several weeks during the Chinese New Year. Even with its highly centralized authority, the Chinese Government was largely powerless to control this annual mass migration. Fortunately, in this case, the disease was nonetheless contained or self-limiting.

As already mentioned, a critical population size is required to sustain an epidemic and for diseases to become endemic, the size depending on characteristics intrinsic to a pathogen. For example, this figure is about 250,000 for measles (Black, 1966; Anderson et al., 1992). For this and a number of other common diseases, relatively isolated cities of less than a few hundred thousand or fewer people cannot generate a sufficiently large and constant flow of susceptible (immunologically naïve) people to fuel epidemics. Those that do arise as the result of an imported pathogen quite simply “burn out” quickly. For example,
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a number of Pacific Islands with small populations and limited tourism have had only limited outbreaks of dengue even though they have the *Aedes* mosquito vectors. Of course today, given the exponential growth in human mobility provided by modern transportation, even geographically isolated cities or human populations are becoming less and less biologically isolated. As this level of connectivity lowers the barriers to pathogen dispersal, the population size thresholds that once limited their continual transmission effectively cease to exist.

Even with effective family planning programs in place, demographic momentum ensures growth in most developing countries will continue until the middle of this century and, as illustrated by the Chinese New Year holiday example above, the capacity to restrict human movement is quite limited in most countries even after an epidemic has started, let alone before. Human population growth and mobility will remain a potent factor underlying disease emergence and re-emergence, as it has for the past three decades. This is clearly suggested for dengue in most Asian countries, where the mosquito vectors have been generally widespread and abundant.

Improved vector control could alter this situation in the future. However, eliminating the mosquitoes like *A. aegypti*, the primary vector for the pathogens responsible for several important emerging diseases, across large geographic areas or even single cities, likely is no longer possible. Today’s urban conglomerations consist of tens of thousands and in some cases even millions of households, virtually every one potentially harboring this highly domestic mosquito. Just as with human mobility, the movement of commodities – between villages, provinces, cities, and countries – consisting of materials capable of harboring eggs, larvae, or adult mosquitoes has grown exponentially. Even if a mosquito population can be extinguished within a semi-urban village on a city’s outskirts, or eliminated from an urban district, its absence will be only temporary. The constant influx of mosquito propagules insures the “empty patch” of domestic habitat will not stay unoccupied and unexploited for long. For example, a recent study of *A. aegypti* movement in Thailand and Puerto Rico (Harrington et al., 2005) showed that individual mosquitoes commonly dispersed actively only as far as adjacent households. Inter-village dispersal (that is, active flight of up to half a kilometer) was found to be rare. Yet passive long-distance dispersal via hitch-hiking on human transport was deduced to be common, based on genetic evidence demonstrating the ecological connectivity between populations.

In light of these and other recent research findings, it’s clear today’s sprawling and globally interconnected urban landscapes, and the limited effectiveness and ecological risks associated with insecticides, requires new approaches to mosquito vector control. Fortunately, disease control, and even prevention, can be accomplished without completely eliminating the vector, so long as its abundance and biting success is reduced. Keeping mosquito abundance below certain levels by managing the environment and influencing the frequency with which humans are bitten through various efforts can decrease epidemic frequency and severity,
as well as preventing pathogens like dengue from expanding its endemic cycle geographically. Disease ecology theory suggests the rate of spread of an infection, including whether this rate is high enough to initially spark an epidemic, is sensitive to both mosquito density and herd immunity in the human population. In disease endemic regions, pathogens like dengue viruses circulate via “silent transmission” in the human population, erupting episodically due to the interaction of a variety of dynamic factors, including the proportion of susceptible people, seasonal changes in mosquito abundance and survival, and viral evolution.

Dengue and other emerging arbovirus diseases

About 177 pathogens are recognized as re-emerging or emerging, of which 73 percent are estimated to be zoonotic (Woolhouse and Gowtage-Sequeria, 2005) – that is, they are maintained in transmission cycles that involve domestic and/or wild animals, but can infect humans. Many, like dengue, are arboviral diseases, a term that describes a virus that requires a blood-sucking (hematophagous) arthropod, like a mosquito or tick, to complete its lifecycle. Except for dengue, which has fully adapted to an *A. aegypti*–human–*A. aegypti* cycle in tropical urban settings, all arboviruses have a non-human reservoir host, like a bird, rodent, or monkey. Of the more than 534 registered zoonotic and arboviruses, about 130 have been documented to cause illness in humans. Those of public health significance belong to three families: *Flaviviridae* (e.g. dengue fever, yellow fever, West Nile Virus), *Togaviridae* (e.g. Chikungunya fever, Ross River virus), and *Bunyaviridae* (Rift Valley fever, California encephalitis) (Gubler, 2002). The past few decades have seen a significant increase in the frequency, geographic spread, and virulence of a number of arboviral diseases. Table 4.2 provides a selective list of urban arboviral diseases that have public health importance. As vector-borne diseases require warm climates and moisture to thrive, they emerge more readily in tropical climates. However, many arthropod vectors are active during the summer but can “over-winter” in temperate climates.

Dengue fever as a classic case study of the impact of urbanization

Dengue fever is an old disease, and is the classic case study of the recent re-emergence of a globally significant disease that originated as a zoonosis. Its historical pattern of emergence provides many lessons for containing the global spread of other, more recently recognized, arboviral diseases with the potential for becoming major urban public health threats. The first reports of illness clinically compatible with dengue date back to a Chinese medical encyclopedia first published in AD 265 and last edited during
the Northern Sung Dynasty in AD 992. Epidemics of dengue-like illness were reported in 1635 in the Caribbean, and in 1699 in Panama. By the end of the eighteenth century the viruses and their vectors apparently had a worldwide distribution, with epidemics of dengue-like illness being reported in Batavia (Jakarta) in Indonesia (1779), Cairo in Egypt (1779), and Philadelphia in Pennsylvania, USA (1780) (Gubler, 1997). It should be noted that these were not confirmed dengue epidemics, because the viruses were not isolated until 1943–44. However, clinically and epidemiologically, the disease was compatible with dengue.

The historical evolution of dengue to become the most important arboviral disease of humans as we enter the twenty-first century is closely tied to the evolution of urbanization and commerce (globalized trade). The primitive cycle of dengue viruses involved canopy-dwelling mosquitoes and non-human primates in the rainforests of Asia, and possibly Africa. Humans who entered the forests to hunt, cut wood, or for other activities were exposed to the viruses through the

| Table 4.2 Urban emerging infectious diseases of public health importance |
|---------------------------------------------------------------|
| Family/virus | Vector | Vertebrate host | Ecology | Disease in humans | Geographic distribution |
|---------------|--------|-----------------|---------|-------------------|------------------------|
| **Togaviridae** |        |                 |         |                   |                        |
| *Chikungunya* | Mosquitoes | Human, primates | U, S, R | SFI               | Africa, Asia           |
| **Ross River** | Mosquitoes | Human, primates | R, S, U | SFI               | Australia, South Pacific |
| **Mayaro**    | Mosquitoes | Birds           | R, S, U | SFI               | South America          |
| **Flaviviridae** |        |                 |         |                   |                        |
| *Dengue 1–4*  | Mosquitoes | Human, primates | U, S, R | SFI, HF           | Worldwide in tropics    |
| *Yellow fever*| Mosquitoes | Human, primates | R, S, U | SFI, HF           | Africa, South America   |
| *Japanese encephalitis* | Mosquitoes | Birds, pigs     | R, S, U | SFI, ME           | Asia, Pacific          |
| *St Louis encephalitis* | Mosquitoes | Birds           | R, S, U | SFI, ME           | Americas               |
| **West Nile Virus** | Mosquitoes | Birds           | R, S, U | SFI, ME           | Africa, Asia, Europe, US |
| **Bunyaviridae** |        |                 |         |                   |                        |
| *Oropouche*   | Midges  | ?               | R, S, U | SFI               | Central and South America |

U, urban; S, suburban; R, rural; SFI, systemic febrile illness; ME, meningoencephalitis; HF, hemorrhagic fever
Source: Gubler (2002).
bite of infected mosquitoes. With an incubation period of up to 14 days, people became ill (and infectious) after they returned to their village outside the forest, thus exposing peridomestic mosquitoes in the villages to the virus. These latter mosquitoes, such as *A. albopictus*, transmitted epidemics, but because of the small human populations in the villages the infections soon died out and transmission ceased until another virus was introduced. These epidemics were thus very infrequent and sporadic.

In the seventeenth, eighteenth, and nineteenth centuries, as global trade and the shipping industry developed, port cities sprouted on all continents, followed by the building of inland cities and larger port cities. The water barrels carried on sailing vessels were frequently infested with mosquitoes, and it was not uncommon for the ships to maintain active transmission of diseases like dengue and yellow fever among the mosquitoes and crew members (Gubler, 1997). When the ships docked at a port city, both the mosquitoes and the viruses went ashore with the crew. Thus were mosquitoes and viruses imported to and established in port cities around the world.

The history of the spread of *A. aegypti* provides a classic example. Although a feral mosquito in Africa, it was introduced to the villages and cities of West Africa, where it adapted to breeding in stored water containers. From there it was taken, along with yellow fever, to the Americas during the slave trade in the sixteenth and seventeenth centuries, infesting port and inland cities. Even the temperate United States was infested, with the mosquito being maintained in the port cities of the Gulf Coast during the winter and expanding up the rivers and waterways to inland cities during the summer months (Gubler, 1997). The epidemics of dengue and yellow fever in cities like Philadelphia were the direct result of this kind of commerce. From the Americas, *A. aegypti* spread to the Pacific and Asia by the same means. This mosquito ultimately became highly adapted to humans and the urban environment, infesting most tropical cities of the world, and became the most efficient epidemic vector of urban dengue and yellow fever (Gubler, 1989, 1998b).

As noted above, by the late eighteenth century dengue viruses had a worldwide distribution in the tropics. Because the viruses were dependent on sailing vessels for geographic spread, however, epidemics were infrequent, often with periods of 10–40 years with no epidemic activity. Once a virus was introduced to a new region, however, it would move from country to country within that region at a much faster pace. This was the status of the disease at the beginning of World War II.

The war in the Pacific and Asian Theaters initiated the twentieth-century pandemic of dengue (Gubler, 1998b). Both the Allied and Japanese armies put hundreds of thousands of susceptible troops into the area. The movement of those troops, along with war materials, was responsible for all four dengue virus serotypes and *A. aegypti* mosquitoes being spread throughout the region. By the end of the war, dengue was hyperendemic (the co-circulation of multiple virus serotypes) in most countries of Asia.
In the years following World War II, an economic boom began in Asia that is continuing today. It was this dramatic economic development, combined with unprecedented population growth, that was the primary driving force of uncontrolled urbanization that has occurred in most Asian cities in the past 50 years. The influx of people, primarily from rural areas, led to rapid and uncontrolled urban growth. Forced to live in inadequate housing in areas where there was no water, sewage, electricity, or waste management, people had to store water in containers, which made ideal larval habitats for *A. aegypti* mosquitoes. The large mosquito populations living in intimate association with crowded human populations similarly provided ideal conditions for epidemic transmission of the dengue virus. It was in this setting in the 1950s and 1960s that the much more serious and sometimes fatal form of dengue, dengue hemorrhagic fever (DHF), emerged in epidemic form. By 1970, DHF was a leading cause of hospitalization and death among children in Southeast Asia. In the latter two decades of the twentieth century, epidemic DHF spread throughout Asia, east to China and Taiwan, and west to the Indian subcontinent.

Urbanization was occurring in other parts of the world as well, especially in the Americas. Fortunately, however, dengue and yellow fever had been effectively controlled in the 1950s and 1960s in the Americas by the *A. aegypti* eradication program initiated in 1946, which focused on larval mosquito control using a combination of environmental management and DDT. Because there were no epidemics of dengue and yellow fever, however, this program was disbanded in the early 1970s (Gubler, 1989; Gubler and Trent, 1994). Thus began the reinvansion of tropical American countries by *A. Aegypti* – but this time there were much larger cities to host them. By the beginning of the twenty-first century, Mexico and most of the Caribbean, South and Central American countries had been re-colonized by this mosquito.

The era of jet travel and modern transportation began in the 1960s, but accelerated in the 1970s and 1980s. This provided the ideal mechanism for the hyperendemic dengue melting pot of Southeast Asia to seed the rest of the world with dengue viruses. The viruses first moved into the Pacific Islands in the early 1970s, and into the Americas in the late 1970s. The 1980s and 1990s saw the whole of the tropical world become hyperendemic, resulting in greatly increased frequency of epidemic dengue fever and the emergence of DHF in the Pacific and Americas (Gubler, 1997). As shown by the maps in Figure 4.3, in 1970 dengue was either hypoendemic with only one virus serotype circulating, or non-endemic in most countries of South and Central America, the Caribbean and West Africa; only Southeast Asia was hyperendemic with all four serotypes co-circulating. Today, the whole of the tropical world is hyperendemic, with all four virus serotypes co-circulating throughout the Americas, across tropical Africa, South Asia, Southeast Asia, Australasia, and Oceania. As a result, the epidemics have become more frequent, and larger, on a global level. In 2006, approximately 2.5–3 billion people live in areas at risk for dengue, which infects an estimated 50–100 million
persons per year, with 500,000 cases of DHF and 20,000–25,000 deaths (Gubler, 1998b; World Health Organization, 1999).

As can be seen in Figure 4.4, the increased incidence of DF/DHF in the past 50 years closely tracks global population growth, most of which is urban population growth. In Thailand, the annual number and frequency of dengue cases closely tracks the historic population increase across the country and in Bangkok.

Figure 4.5 shows that the increase in dengue cases in Bangkok closely tracks population growth, and can therefore be projected to increase for at least several decades under current conditions. Moreover, dengue frequency in terms of
the proportion of months with reported cases tends to increase sharply for provinces exceeding about 500,000 in population size (Wearing and Rohani, 2006). Population growth is a surrogate measure of urbanization and all its attendant social-ecological factors that facilitate disease emergence.

One recent study documented how dengue epidemics travel in a wave out from Bangkok at an average rate of 148 km per month (Cummings et al., 2004). Bangkok serves as a regional “epicenter” for major epidemics in Thailand on a 3- to 5-year cycle (Nisalak et al., 2003). These patterns, being uncovered through the accumulation of increasingly detailed data and more sophisticated molecular and statistical research tools, are probably representative of what is occurring in all the cities of tropical developing countries. These tropical urban centers are the spawning grounds for epidemic dengue (Gubler, 2004a).

The key to understanding the recent major resurgence of dengue, along with most of the other 177 or more emerging infectious diseases, requires an appreciation of dynamics of a “coupled human–natural system” mentioned earlier, seen as
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an inherent characteristic of urban ecosystems when viewed from a social ecological perspective (Wilcox and Colwell, 2005). Thus, this complex situation can be simplified somewhat by considering it from the standpoint of how human society – in this case in the form of poorly or ill-guided public policy with regard to public health, urbanization, and globalization – and nature interact. “Nature” here refers to the ecological and associated evolutionary processes represented by viral (and vector) dispersal, genetic change, inter-serotype and serotype–host interaction occurring across spatial scales involving virus–mosquito–human interactions in a single village or urban neighborhood to the regional and global level, with urban expansion and global transport as the dominant influences. Based on this perspective, the re-emergence of dengue and similar diseases can be described as follows.

In the first half of the twentieth century public health measures focused on vector control, and were very effective in controlling dengue and other *A. aegypti*-borne diseases such as yellow fever. Beginning in the second half of the twentieth century, and especially during the latter 30 years, rapid, uncontrolled urbanization in tropical regions of the developing world combined with exponentially increasing global transport of people, animals, and commodities developed

Figure 4.5 Historical and projected growth in dengue cases and urban population in Bangkok. Population growth serves as a surrogate or indicator of a wide range of social-ecological factors accompanying urbanization. Dashed line represents projected dengue cases assuming current circumstances, such as *per capita* levels of vector-control efforts, remain constant. Source: Wilcox (unpublished); based on historic and projected population size of greater Bangkok and dengue case data for the Queen Sirikit National Institute of Child Health in Bangkok, published in Nisalak *et al.* (2003). Projected future cases, year 2000 on, were estimated by linear extrapolation from least-squares fitted regression for peak years and trough years as a function of population size.
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into dominant social-ecological forces, as already noted above. A growing lack of effective mosquito control in crowded urban centers and the increasing movement of viruses via modern transportation facilitated increasing hyperendemicity in large urban centers in the tropics. The result has been epidemic cycles shortened from a 10- to 40-year to a 3- to 5-year cycle, as the case data for Vietnam and Thailand show in Figure 4.6.

Finally, dengue provides the classic model of how the geographic spread of an infectious disease, a principal characteristic by which many viral diseases are classified as emerging, can be revealed by the tracking of a specific viral genetic strain on a map. Before 1989 DHF was common in Southeast Asia, but rare on the Indian subcontinent, despite the circulation of all four serotypes. After 1989, regular epidemics of DHF were reported on the Indian subcontinent and Sri Lanka.

Figure 4.6 The dynamics of dengue. Dengue outbreaks in Thailand and Vietnam now occur on a 3- to 5-year cycle instead of the 10- to 40-year prior historical pattern. Source: Gubler (2004a).
The change did not appear to be due to a general increase in viral transmission, but to a change in virus subtype (Lanciotti et al., 1994; Messer et al., 2003). The majority of people with severe disease were infected with a new subtype of DENV-3, which was clearly derived from the pre-DHF epidemic DENV-3 strain, most likely via genetic drift and selection (Bennett et al., 2003). While the exact processes by which epidemic DHF arose in Sri Lanka are not fully understood, it is clear that the DENV-3 strain associated with DHF in Sri Lanka was derived from the strain previously circulating in Sri Lanka, and was not the same as the DENV-3 circulating in the Southeast Asia region. It appears this Indian subcontinent subtype then spread from South Asia to East Africa (Gubler et al., 1986; Messer et al., 2003). Genetic studies show the DENV-3 subtype III viruses currently found in Latin America are also closely related to isolates found in East Africa and South Asia. Figure 4.7 illustrates the most likely route of the global spread of DENV-3, subtype III from South Asia to East Africa and Central and South America, and, although based on global population movement data, it is likely that the American DENV-3 was introduced from Asia.

Two other arboviral diseases, yellow fever and Chikungunya fever, whose emergence appears to be following a pattern disturbingly similar to the early re-emergence of dengue, also have a transmission cycle in urban areas similar to dengue, being transmitted by *A. aegypti* and *A. albopictus*. Changes in the transmission dynamics of both are also associated with social ecological changes accompanying urbanization, along with regional environmental change and globalization.

Chikungunya is Swahili for “that which bends up,” and the name comes from the muscle and joint symptoms of the diseases, which can be debilitating and last for weeks or months. People with Chikungunya experience a range of other symptoms, such as fever, headache, fatigue, nausea, vomiting, and skin rash. Like dengue and yellow fever, the Chikungunya virus exists in a natural cycle involving mosquitoes and monkeys in the rain forests of Africa. It was first isolated in Tanzania in 1953, and has since been identified in epidemics in western, central and southern Africa, and in a number of Asian countries, such as Indonesia, the Philippines, Thailand, Myanmar, and India. In 2005 and 2006 there were numerous epidemics in India and the islands off the east coast of Africa. A large epidemic in the heavily populated Indian state of Andhra Pradesh spread to neighboring states with fatalities in a number of cities, including Udaipur, Chittorgarh, and Bhilwara. By the time this chapter was going to press 1.39 million cases had been reported across 13 Indian states (NVBDCP, 2006). Currently, Chikungunya fever is most likely spread by infected travelers, but it has been endemic in Asia for decades, and has the potential to become an urban disease globally.

Yellow fever was the most important urban infectious disease in the Americas until the twentieth century. The *A. aegypti* eradication program noted above eliminated the mosquito and the disease throughout most of the Americas (Gubler, 2004b). Endemic in Africa and South America, the first recorded outbreak of
Figure 4.7  Global spread of dengue virus 3 (DENV-3). Subtyping studies show the likely spread of a single subtype of dengue virus 3 from its origin on the Indian subcontinent to East Africa and Latin America. Source: Messer et al. (2003).
yellow fever in the Western Hemisphere occurred in 1648, and over the next 400 years epidemics were recorded across much of South and Central America, and as far north as New York City (Carter and Frost, 1931). Once Walter Reed and his colleagues had determined that *A. aegypti* spread yellow fever outbreaks, control focused on destroying the mosquito in the larval stage in domestic water-storage containers, and killing adult mosquitoes with insecticides – usually DDT. In 1901, William Gorgas developed the first effective control program in Havana, Cuba, which in 1904 was replicated in Panama. Over the next few years, programs were initiated in Rio de Janeiro in Brazil, Vera Cruz in Mexico, and Guayaquil in Ecuador. In 1937 a live-attenuated vaccine was developed, which was used in West Africa but not in the Americas. Nevertheless, successful mosquito control in the Americas worked to eliminate urban epidemics of yellow fever (Gubler, 2004b). With the re-expansion of *A. aegypti* across its former geographic range in Latin America, however, it has been dengue that has re-emerged most dramatically.

Today, yellow fever persists in three kinds of transmission cycles (Table 4.3). These cycles illustrate the process by which social-ecological factors, such as settlement patterns (including the urban expansion into rural zones and agriculture communities into forests), produce a landscape continuum from natural habitat to urban habitat. Arboviruses, because of their capability for relatively

| Type                          | Transmission cycle                                                                 |
|-------------------------------|-----------------------------------------------------------------------------------|
| Sylvatic or jungle yellow fever | This is a disease of the rainforest in which the virus is transmitted between monkeys and wild mosquitoes; it is seen only rarely in people, in those working in logging or other activities in the rainforest |
| Intermediate yellow fever     | This occurs in “zones of emergence,” like savannah areas of Africa during the rainy season, where there is increased contact between humans and semi-domestic mosquitoes; even if a number of villages are involved simultaneously, outbreaks affect only relatively small populations |
| Urban yellow fever             | This involves domestic *A. aegypti* mosquitoes and produces the largest and most dangerous epidemics in cities of tropical Africa (between 15º north and 10º south of the equator); it is less common than dengue, possibly because both viruses compete for the same vector and hosts |
rapid evolution (aided by a parallel domestication process exhibited by mosquitoes like *A. aegypti*), have the potential over time to “move” across this landscape to become major public health threats for urban areas.

At present, 33 countries in Africa with a total population of 468 million are at risk for yellow fever. Since 2000, 18 countries in Africa have reported yellow fever outbreaks, 13 of them in West Africa (World Health Organization, 2006). Given the inadequacies of the health system in these countries, it is likely that the number of reported cases is well below the actual number. Most people infected with yellow fever have no symptoms or only mild symptoms, and are not likely to see a physician who would then report their case to public health authorities. In endemic areas there also is a shortage of laboratories capable of performing virologic analyses. The major threat of epidemic yellow fever, however, is in the Americas, where over 300 million people live in urban areas infected with *A. aegypti* (Gubler, 2004b). So far yellow fever has not taken hold in Asia, but if urban yellow fever epidemics begin to occur, as in the Americas, a major global public health emergency will occur, because all of the Asia-Pacific region is at high risk (Gubler, 2004b).

**What the future holds**

What can we learn from historical and recent experience, and what does a social-ecological perspective reveal that can help with the challenges ahead in controlling diseases in an increasingly urbanized world? First, one-dimensional vector control measures and technological quick fixes will not work. The *Aedes* mosquito cannot be completely eliminated from any of today’s cities in the tropics. Nor can effective vaccines be developed for every infectious disease that is a potential public health problem. Integrated multi-level disease prevention and control programs will be necessary (Gubler, 1989). However, if complacency prevails after these approaches achieve success, as it did when control programs against *A. aegypti* were disbanded and merged with other public health programs, prevention programs will again fail (Gubler, 1989, 1998a, 2005).

Moreover, a top-down approach and methods, based on a limited or inadequate understanding of mosquito ecology, evolution, and urban social ecology, will fail. This lesson can be learned from the flawed strategy of using ultra-low volume (ULV) insecticides to kill adult mosquitoes that replaced previous successful programs that targeted mosquito larvae in water containers (Gubler, 1989). ULV is a top-down reactive strategy, which relies heavily on prompt physician reporting of cases before widespread spraying is initiated. Space-spraying requires direct contact of pesticide with the adult mosquito. It does not penetrate inside houses or kill mosquito larvae in water containers, where the mosquitoes thrive. Within a few hours of spraying, *A. aegypti* is again feeding on and infecting humans.
Surveillance and public education should be constant and based on a bottom-up community participation and community ownership approach. Between outbreaks, it should be expected that the index of suspicion for primary care medical providers and public awareness will fall (Gubler, 1989). Public health professionals should stress the professional obligation to be aware of and report cases. Public education health messages should continue when there are no outbreaks, otherwise epidemics will proceed without public health attention until they are at near peak level. In the case of a mosquito-borne disease like dengue, at that point spraying is not likely to be effective. The consequence of this public health laxness in the Americas was that *A. aegypti* and dengue both reappeared and spread in the 1970s and 1980s in more frequent and longer epidemics (Gubler, 1989, 2005).

Prevention and control begin with recognizing the potential for a particular arthropod-borne disease in a given environment and understanding the specific conditions that promote its transmission and spread. For about a century it has been known that *A. aegypti* thrives in water containers, and public health prevention effectively targeted open-water reservoirs in population centers. That is still the case today, but the difference is that human population centers are an order of magnitude larger, resulting in more frequent and larger epidemics. Controlling breeding sites today requires the help of the community and the people who live in the homes where transmission occurs (Gubler, 1989). These interventions thus require public planning and education, as well as investment. Even financially-strapped local governments can do a better job through public education and outreach, while they work on and invest in more long-term expensive projects to improve water and sewage infrastructure.

Another lesson is to continue effective immunization programs, even when case incidence is low. African countries did not maintain their mass vaccination programs for yellow fever. There are many reasons for this, including financial constraints and civil instability, but keeping up and modernizing those programs might have prevented the resurgence of yellow fever.

Continuous, active public health surveillance with the assistance of modern laboratory virology must be the mainstay for effective tracking of dengue and other emerging arboviral diseases (Gubler, 1998). Active surveillance usually depends on mandatory reporting of suspected cases by diligent primary care health providers to public health agencies. Active surveillance also requires modern laboratory diagnostic methods, which may not be readily available in many developing countries. In these instances, a productive strategy is to develop ongoing partnerships with scientists and laboratories in developed nations. Fortunately, some of these features are beginning to be integrated within region-wide programs employing interdisciplinary approaches based on a largely social-ecological perspective, also called an "ecosystem approach" or "eco-bio-social approach," as in the case of a recent initiative aimed at controlling dengue in tropical developing countries (IDRC, 2006).
There is an immediate need for frontline medical professionals to be better educated in emerging diseases, and for modern laboratory-based epidemiological surveillance in endemic areas. This includes training primary care medical professionals to accurately diagnose patients that present with the symptoms of infectious diseases and promptly notify cases to public health departments. Tropical areas need up-to-date public health laboratories capable of accurately diagnosing disease. This includes the capability of doing genetic subtyping, which requires sophisticated training of laboratory personnel and is relatively costly. There also needs to be better sharing of surveillance information; this is a foundation stone for coordinating the prevention of epidemics across regions at-risk, and it helps link local government agencies to international NGOs. After being free of the disease since 1981, even Cuba, with its strong, centralized government health system, has experienced a re-emergence of dengue in the past 10 years. So while national attention to public health is essential, top-down planning and funding has limitations. Community partnerships with government agencies are not only a key part of the solution to overcoming short resources, they are also essential to sustaining disease control activities over the long term.

References

Anderson, R.M., May, R.M. and Anderson, B. (1992). Infectious Diseases of Humans: Dynamics and Control. New York: Oxford University Press.

Bennett, S.N., Holmes, E.C., Chirivella, M. et al. (2003). Selection-driven evolution of emergent dengue virus. Molecular Biology and Evolution 20(10), 1650–1658.

Black, F.L. (1966). Measles endemicity in insular populations: critical community size and its evolutionary implication. Journal of Theoretical Biology 11, 207–211.

Carter, H.R. and Frost, W.H. (1931). Yellow fever. In: L.A. Carter and W.H. Frost (eds), An Epidemiological and Historical Study of its Place of Origin. Baltimore: Waverly Press.

Cummings, D.A.T., Irizar, R.A., Huang, N.E. et al. (2004). Travelling waves in the occurrence of dengue hemorrhagic fever in Thailand. Nature 427, 344–347.

Fauci, A.S., Touchette, N.A. and Folkers, G.K. (2005). Emerging infectious diseases: a 10-year perspective from the National Institute of Allergy and Infectious Diseases. Emerging Infectious Diseases 11(4), 519–525.

Gubler, D.J. (1989). Aedes aegypti and Aedes aegypti-borne disease control in the 1990s: top down or bottom up? American Journal of Tropical Medicine and Hygiene 40, 571–578.

Gubler, D.J. (1997). Dengue and dengue hemorrhagic fever: its history and resurgence as a global public health problem. In: D.J. Gubler and G. Kuno (eds), Dengue and Dengue Hemorrhagic Fever. London: CAB International, pp. 1–22.

Gubler, D.J. (1998a). Dengue and dengue hemorrhagic fever. Clinical Microbiology Reviews 11(3), 480–496.

Gubler, D.J. (1998b). Resurgent vector-borne diseases as a global health problem. Emerging Infectious Diseases 4, 442–450.

Gubler, D.J. (2002). The global emergence/resurgence of arboviral diseases as public health problems. Archives of Medical Research 33, 330–342.
Gubler, D.J. (2004a). Cities spawn epidemic dengue viruses. *Nature Medicine* **10**(2), 129–130.

Gubler, D.J. (2004b). The changing epidemiology of yellow fever and dengue, 1900 to 2003: full circle? *Comparative Immunology Microbiology and Infectious Diseases* **27**(5), 319–330.

Gubler, D.J. 2005. The emergence of epidemic dengue fever and dengue hemorrhagic fever in the Americas: a case of failed public health policy. *Pan-American Journal of Public Health* **17**(4), 221–224.

Gubler, D.J. and Meltzer, M. (1999). The impact of dengue/dengue hemorrhagic fever on the developing world. *Advances in Virus Research* **53**, 35–70.

Gubler, D.J. and Trent, D.W. (1994). Emergence of epidemic dengue/dengue hemorrhagic fever as a public health problem in the Americas. *Infectious Agents and Disease* **2**, 383–393.

Gubler, D.J., Sather, G.E., Kuno, G. and Cabral, A.J.R. (1986). Dengue 3 transmission in Africa. *American Journal of Tropical Medicine and Hygiene* **35**, 1280–1284.

Hardoy, J.E., Mitlin, D. and Satterthwaite, D. (2001). *Environmental Problems in an Urbanizing World: Finding Solutions for Cities in Africa, Asia, and Latin America*. London: Earthscan Publications Ltd.

Harrington, L.C., Scott, T.W., Lerdthusness, K. et al. (2005). Dispersal of the dengue vector *Aedes aegypti* within and between rural communities. *American Journal of Tropical Medicine and Hygiene* **72**(2), 209–220.

IDRC (2006). Eco-biosocial Research on Dengue in Asia: Understanding Ecosystem Dynamics for Better-Informed Dengue Prevention. Available at: the International Development Research Center website, http://www.idrc.ca/en-ev-88137-201-1-DO_TOPIC.html (accessed 21 December 2006).

Lanciotti, R.S., Lewis, J.G., Gubler, D.J. and Trent, D.W. (1994). Molecular evolution and epidemiology of dengue-3 viruses. *Journal of General Virology* **75**, 65–75.

McNeil, W.H. (1976). *Plagues and Peoples*. New York: Doubleday.

Messer, W.B., Gubler, D.J., Harris, E. et al. (2003). Emergence and global spread of a dengue serotype 3, subtype III virus. *Emerging Infectious Diseases* **9**(7), 800–809.

NVBDCP (2006) *Chikungunya Fever Situation in the Country during 2006* (as on 03.01.2007). Available at: the National Vector-Borne Disease Control Program, Government of India website, http://www.namp.gov.in/Chikun-cases.html (accessed 5 January 2007).

Nisalak, A., Endy, T.P., Nimmanitya, S. et al. (2003). Serotype-specific dengue virus circulation and dengue disease in Bangkok, Thailand, from 1973 to 1999. *American Journal of Tropical Medicine and Hygiene* **68**, 191–202.

Patlak, M. (1996). Book reopened on infectious diseases {electronic version}. *FDA Consumer Magazine* **30**(3).

Smolinski, M.S., Hamburg, M.A. and Lederberg, J. (eds). (2003). *Microbial Threats to Health: Emergence, Detection, and Response*. Washington, DC: Institute of Medicine, National Academies Press.

United Nations (2002). *World Urbanization Prospects: The 2001 Revision*. New York: United Nations.

United Nations, Department of Economic and Social Affairs (2006). *World Urbanization Prospects: The 2005 Revision Population Database*. Available at: the United Nations, Department of Economic and Social Affairs website, http://esa.un.org/unup/ (accessed 21 December 2005).

United Nations Population Fund (2001). *The State of World Population 2001*. Available at: the United Nations Population Fund website, http://www.unfpa.org/swp/2001/english/tables.html (accessed 21 December 2006).
Urbanization and the Social Ecology of Emerging Infectious Diseases

Wearing, H.J. and Rohani, P. (2006). Ecological and immunological determinants of dengue epidemics. Proceedings of the National Academy of Sciences 103(31), 11,802–11,807.

Wilcox, B.A. and Colwell, R.R. (2005). Emerging and re-emerging infectious diseases: biocomplexity as an interdisciplinary paradigm. EcoHealth 2(4), 244–257.

Wilcox, B.A. and Gubler, D.J. (2005). Disease ecology and the global emergence of zoonotic pathogens. Environmental Health & Preventive Medicine 10(5), 263–272.

Woolhouse, M.E.J. and Gowtage-Sequeria, S. (2005). Host range and emerging and reemerging pathogens. Emerging Infectious Diseases 11(12), 1842–1847.

World Bank (2002). World Development Report 2002: Building Institutions for Markets. New York: Oxford University Press for the World Bank.

World Health Organization (2004). The World Health Report 2004 – Changing History. Geneva: World Health Organization.

World Health Organization (2006). Epidemiological Trends and Current Situation of Yellow Fever. Available at: the World Health Organization website, http://www.who.int/csr/disease/yellowfev/surveillance/en/index.html (accessed 29 October 2006).

World Health Organization, Regional Office for Southeast Asia, New Delhi (1999). Prevention and Control of Dengue and Dengue Hemorrhagic Fever: A Comprehensive Guideline. Geneva: World Health Organization, pp. 1–137.