

# The Global Threat of Emergent/Re-emergent Vector-Borne Diseases

Duane J. Gubler

**Abstract** The past 30 years has witnessed a dramatic re-emergence of epidemic vector-borne diseases throughout much of the world. Factors contributing to this are many, but the principal drivers have been complacency and de-emphasis of infectious diseases in public health policy, increased population growth, uncontrolled urbanization without concomitant attention to water and waste management, increased globalization and the ease with which modern air transport can quickly spread pathogens and their vectors. The re-emergence of parasitic, bacterial and viral vector-borne pathogens is described. This re-emergence increases the current and future need for preventative measures to contain disease outbreaks and for international cooperation and collaboration to constantly monitor the outbreak of these debilitating and deadly diseases.

**Keywords** Dengue · West Nile · Yellow fever · Plague · Lyme disease · Vector-borne diseases · Mosquitoes · Ticks · Urbanization · Globalization

## Introduction

At the beginning of the 20th century, epidemic vector-borne diseases were among the most important global public health problems (Gubler 1998, 2002a). Diseases such as yellow fever (YF), dengue fever (DF), plague, louse-borne Typhus, malaria,

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D.J. Gubler (✉)

Program in Emerging Infections Diseases, Duke-Nus Graduate Medical School, 8 College Road, Singapore 169857

Department of Tropical Medicine, Medical Microbiology and Pharmacology, Asia-Pacific Institute Tropical Medicine and Infectious Diseases, John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI 96813, USA

e-mail: dgubler@hawaii.edu

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etc., caused explosive epidemics affecting thousands of people. Subsequently, other vector-borne diseases were identified as major causes of disease in both humans and domestic animals. As the natural history of these diseases became better understood, prevention and control measures, primarily directed at the arthropod vectors, were highly successful in controlling disease transmission. Effective prevention and control accelerated in the post-World War II years with the advent of new insecticides, drugs, and vaccines. By the 1960s, the majority of important vector-borne diseases had been effectively controlled in most parts of the world, and those that were not yet controlled were targeted for more intensive programs using new vaccines, drugs, and insecticides.

Unfortunately, “success led to failure”; some of the successful programs, such as the *Aedes aegypti* eradication program that effectively controlled epidemic YF and DF throughout the American tropics for over 40 years, and the global malaria eradication program that effectively controlled malaria in Asian and American countries, were disbanded in the 1970s because the diseases were no longer major public health problems (Gubler 1989, 2004; Gubler and Wilson 2005; IOM 1992). Additionally, residual insecticides were replaced with less effective chemicals used as space sprays to control adult mosquitoes. The 1970s ushered in a 25-year period characterized by decreasing resources for infectious diseases, decay of the public health infrastructure to control vector-borne diseases, and a general perception that vector-borne diseases were no longer important public health problems. Coincident with this period of complacency, however, was the development of global trends that have contributed to the reemergence of epidemic infectious diseases in general, and vector-borne diseases in particular, in the past 25 years. In addition to the emergence of newly recognized diseases, there was increased incidence and geographic expansion of well-known diseases that were once effectively controlled (Gubler 1989, 1998; IOM 1992, 2003; Mahy and Murphy 2005). This paper will briefly review the changing epidemiology of several of the most important vector-borne diseases and discuss the lessons learned from this global reemergence.

## **The Reemergence of Epidemic Vector-Borne Diseases As Public Health Problems**

The earliest indications that epidemic vector-borne diseases might reemerge came in the early 1970s. Subsequent warnings were ignored by public health officials and policy makers because of competing priorities for limited resources (Gubler 1980, 1987, 1989; IOM 1992). The 1980s ushered in a period with increased epidemic vector-borne disease activity associated with expanding geographic distribution of both the vectors and the pathogens via modern transportation and globalization. It was not until the Institute of Medicine (IOM) report on emerging infectious diseases that policy makers took notice (IOM 1992), and not until after the 1994 plague epidemic in India that new resources were allocated to emerging infectious diseases (Fritz et al. 1996; WHO 1994).

Parasitic, bacterial, and viral pathogens may be transmitted by blood-sucking arthropods. Mosquitoes, which primarily transmit parasitic and viral diseases, are the most important arthropod vectors; ticks, which primarily transmit bacteria and viruses, are next in importance.

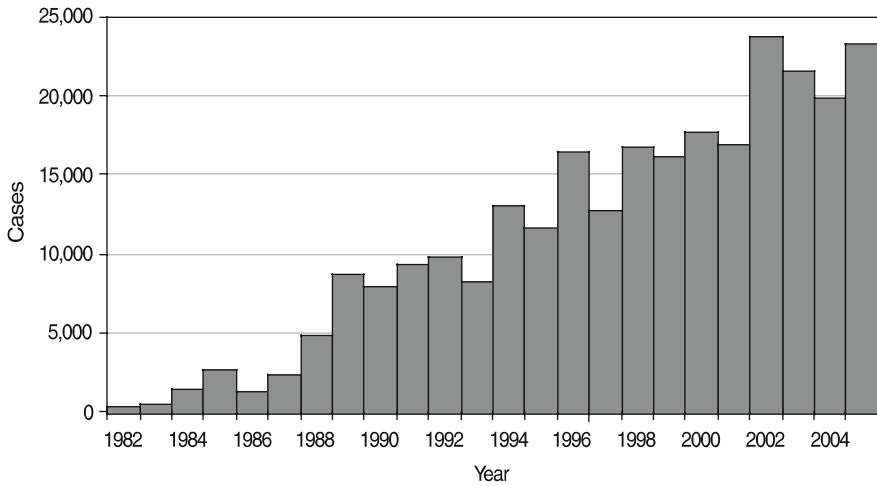
## Parasitic Diseases

Of the parasitic infections transmitted by arthropods, malaria is by far the most important, although there has also been a reemergence of leishmaniasis and African trypanosomiasis. The principal problem area for malaria is Africa, where 95% of all global cases occur, most of them in children under five years of age (Gubler and Wilson 2005). This disease is dealt with elsewhere and will not be considered further here.

## Bacterial Diseases

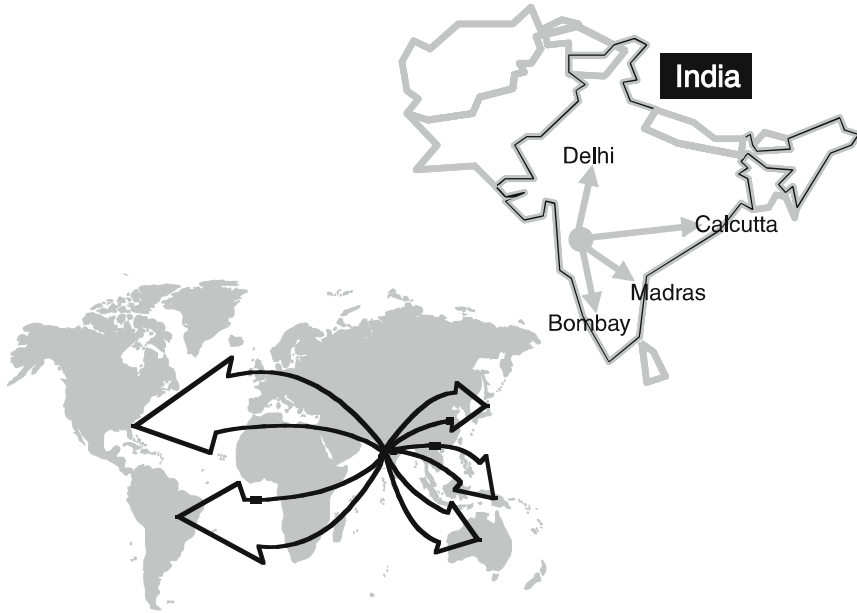
Two newly recognized vector-borne bacterial diseases, Lyme disease, caused by *Borrelia burgdorferi*, and ehrlichiosis, caused by *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, and *Ehrlichia ewingii*, have emerged as important public health problems in the past three decades (Dumler et al. 2007; Steere et al. 2004). Both have small rodents as their natural vertebrate reservoir host, with hard ticks as their principal vectors. Both diseases are found primarily in temperate regions of the world, where emergence has been associated with environmental change. Figure 1 shows the dramatic increase in reported cases of Lyme disease in the United States since the Centers for Disease Control and Prevention (CDC) began surveillance in 1982. The increased transmission in the United States is directly related to reforestation of the northeastern United States, allowing the mouse and deer populations to increase unchecked, which in turn has allowed the tick population to increase. A final factor has been the trend in recent decades to build houses in woodlots where humans share the ecology with deer, mice, and ticks; thus most transmission to humans in the northeastern United States where the majority of cases of Lyme disease occur, is residential (Steere et al. 2004).

Plague, caused by *Yersinia pestis*, is the most important reemergent bacterial vector-borne disease. The current global increase in case reports of plague is primarily due to outbreaks in Africa. However, it is the potential of plague to cause explosive epidemics of pneumonic disease, transmitted person-to-person and with high mortality that makes it important as a reemergent infectious disease and as a potential bioterrorist threat. This was illustrated in 1994 when an outbreak of plague occurred in Surat, Gujarat, India (WHO 1994). Although this was a small outbreak (most likely less than 50 cases) that should have been a relatively unimportant local public health event, it became a global public health emergency. The reasons for this are complicated and beyond the scope of this article, but it is a



**Fig. 1** Reported Lyme disease cases by year, United States, 1982–2005. Source: Adapted from Gubler (1998) and CDC (2006), courtesy, Division of Vector-Borne Infectious Diseases, CDC, Fort Collins, CO

classic case of “success breeding failure.” Briefly, because the Indian Health Service had successfully controlled epidemic plague in India for over 30 years (the last confirmed human plague case prior to 1994 was in 1966), laboratory, clinical, and epidemiologic capacity to diagnose and control plague had deteriorated. Thus, when the Surat outbreak occurred, the clinical and laboratory diagnosis was confused, creating lack of confidence in public health agencies and ultimately panic when it was finally announced that the disease was pneumonic plague. Within a few weeks in early October 1994, an estimated 500,000 people fled Surat, a city of about 2 million people at that time. Many of these people traveled to other urban areas in India, and within days, newspapers were reporting plague cases in other cities. The World Health Organization implemented Article 11 of the International Health Regulations (WHO 1983) for the first time in 33 years because it was thought that people with pneumonic plague might board airplanes in India and transport the disease to other urban centers around the world (Fig. 2). Many countries stopped air travel and trade with India and most implemented enhanced surveillance for imported plague cases via airplane travel. This was the first global emerging infectious disease epidemic that impacted the global economy since infectious diseases were controlled in the 1950s. It is estimated that this small outbreak cost India US\$3 billion (John 1999) and the global economy US\$5–\$6 billion. Fortunately, there were no cases of plague exported from India (Fritz et al. 1996), but this epidemic was the “wake-up call” that modern transportation and globalization were major drivers of pandemic infectious diseases. It was this epidemic that helped stimulate in the first funding of CDC’s Emerging Infectious Disease Program.



**Fig. 2** Suspected spread of pneumonic plague from India, 1994. Source: Courtesy, Division of Vector-Borne Infectious Diseases, CDC, Fort Collins, CO

### Arboviral Diseases

Of the vector-borne diseases, it is the arboviruses that have become the most important causes of reemerging epidemic disease (Gubler 1996, 2002a). In 2007, there are few places on Earth where there is no risk of infection with one or more of these viral diseases, most of which are transmitted by mosquitoes. The more important reemerging epidemic arboviral diseases are presented in Table 1. They include members

**Table 1** Emergent/Re-emergent arboviral diseases of humans

- 
- Dengue hemorrhagic fever
  - Yellow fever
  - West Nile fever
  - Japanese encephalitis
  - Chikungunya
  - Rift valley fever
  - Alkumra fever (Kysanui forest disease)
  - Venezuelan equine encephalitis
  - Epidemic polyarthritis
  - Barmah forest
  - Oropouche
  - California encephalitis
  - Crimean-Congo hemorrhagic fever
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of three families (*Togaviridae*, *Flaviviridae*, and *Bunyaviridae*). Three diseases – dengue fever, West Nile, and yellow fever – will be discussed as case studies to illustrate the changing epidemiology of arboviral diseases.

### ***West Nile Virus***

West Nile virus (WNV) (*Flaviviridae*, genus *Flavivirus*), an African virus, belongs to the<sup>1</sup> Japanese encephalitis virus (JEV) sero-group, which includes a number of closely related viruses, including JEV in Asia, St. Louis encephalitis virus in the Americas, and Murray Valley encephalitis virus in Australia. All have a similar transmission cycle involving birds as the natural vertebrate hosts and *Culex* species mosquitoes as the enzootic/epizootic vectors, and all cause severe and fatal neurologic disease in humans and domestic animals, which are generally thought to be incidental hosts, as well as in birds.

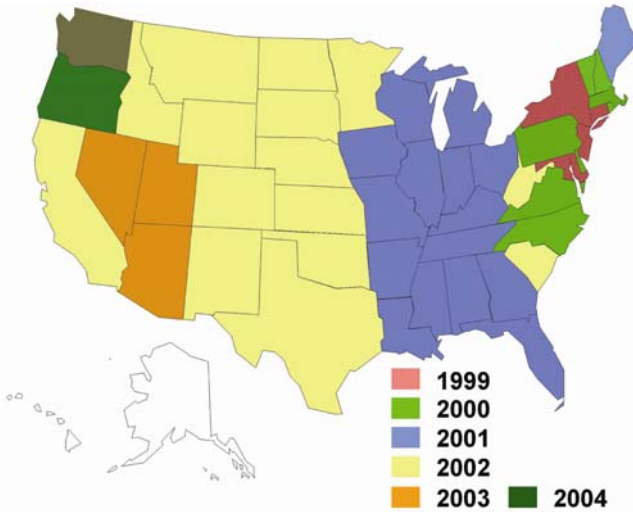
The clinical illness associated with WNV in humans ranges from asymptomatic infection to viral syndrome to neurologic disease (Hayes and Gubler 2006), but historically it has been considered among the least virulent of the Japanese encephalitis sero-group viruses (Hayes 1988); recent epidemics, however, have changed that perception.

From the time WNV was first isolated from the blood of a febrile patient in the West Nile province of Uganda in 1937 (Smithburn et al. 1940) until the fall of 1999, it was considered relatively unimportant as a human and animal pathogen. The virus was enzootic throughout Africa, West and Central Asia, the Middle East, and the Mediterranean, with occasional extension into Europe (Hayes 1988). A subtype of WNV (Kunjin) is also found in Australia (Hall et al. 2002). A characteristic of WNV epidemiology during this 62-year history (1937–1999) was that it caused epidemics only occasionally, and the illness in humans, horses, and birds was generally either asymptomatic or mild; neurologic disease and death were rare (Marfin and Gubler 2001; Murgue et al. 2001, 2002).

In late August 1999, an astute physician in Queens, New York, identified a cluster of elderly patients with viral encephalitis (Asnis et al. 2000). Because of the age group involved and the clinical presentation, these cases were initially thought to be St. Louis encephalitis, but subsequent serologic and virologic investigation showed them to be caused by WNV (Lanciotti et al. 1999). The epidemic investigation, which focused only on neurologic disease, identified 62 cases with 7 (11%) deaths, all of them in New York City (Nash et al. 2001). Epidemiologic studies, however, showed widespread transmission throughout New York City, with thousands of infections (Montashari et al. 2001; Nash et al. 2001). The virus caused a high fatality rate in birds, especially those in the family *Corvidae* (Komar 2003). Genetic sequence of the infecting virus suggested it was imported from the Middle East, most likely from Israel (Lanciotti et al. 1999). Although it will never be known for sure, epidemiologic and virologic evidence suggests the virus was introduced in

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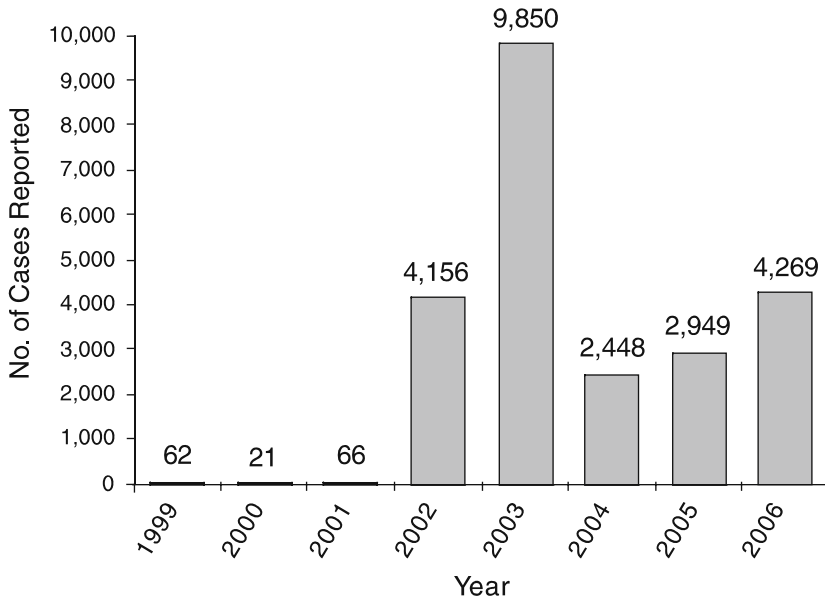


**Fig. 3** The spread of West Nile virus through the United States, 1999–2004

the spring or early summer of 1999, most likely via infected humans arriving from Israel, which was experiencing an epidemic of WNV in Tel Aviv at the time (Giladi et al. 2001; Marfin and Gubler 2001).

Over the next five years, WNV rapidly moved westward across the United States to the west coast (Fig. 3), north into Canada, and south into Mexico, the Caribbean, and Central America. In 2002, it caused the largest epidemic of meningoencephalitis in U.S. history with nearly 3,000 cases of neurologic disease and 284 deaths. That same year, there was a large epizootic in equines with over 14,500 cases of neurologic disease and a case fatality rate of nearly 30% (Campbell et al. 2002). The epidemic curve for human cases in the United States is shown in Fig. 4. In 2003, another large epidemic occurred, but the epicenter of transmission was in the plains states and the majority of the reported cases were not neurologic disease (Hayes and Gubler 2006). Since 2003, the virus has persisted with seasonal transmission during the summer months, but at a lower level; the majority of cases have been in the plains and western states.

WNV was first detected south of the U.S. border in 2001 when a human case of neuro-invasive disease was reported in the Cayman Islands (Campbell et al. 2002), and birds collected in Jamaica in early 2002 were positive for WNV-neutralizing antibodies (Komar and Clark 2006). In 2002, WNV activity was reported in birds and/or equines in Mexico (in six states) and on the Caribbean islands of Hispaniola (Greater Antilles) and Guadeloupe (Lesser Antilles). Most likely, the virus was also present in Mexico in 2001, since a cow with WNV-neutralizing antibody was detected in the southern state of Chiapas in July of 2001 (Ulloa et al. 2003). In 2003, the virus was detected in 22 states of Mexico; in Belize, Guatemala, and El Salvador in Central America; and in Cuba, Puerto Rico, and the Bahamas in the Caribbean. In 2004, WNV activity was reported from northern Colombia, Trinidad,



**Fig. 4** Epidemic West Nile virus in the United States, 1999–2006, reported to CDC as of May 2, 2007. Source: CDC (2007)

and Venezuela, the first reported activity in South America; in 2006, Argentina reported WNV transmission (Komar and Clark 2006; Morales et al. 2006).

Migratory birds have likely played an important role in the spread of WNV in the western hemisphere (Owen et al. 2006; Rappole et al. 2000). This conclusion is supported by data on the movement of WNV in migratory birds in the Old World (Malkinson et al. 2002). Moreover, the westward movement of WNV across the United States and Canada can best be explained by introduction via migratory birds that fly south to Central and South America in the fall and north from those areas in the spring. Thus, the yearly movement westward in 2000, 2001, 2002, 2003, and 2004 shows very good correlation with the Atlantic, Mississippi, Central, and Pacific flyways of migratory birds (Figs. 3 and 5). After introduction to an area, local dispersion of WNV likely occurred via movement of resident birds, which often fly significant distances. Interestingly, the major epidemic in each region of the country occurred the following year after introduction, with the exception of the 1999 New York outbreak.

The emergence of a WNV strain with greater epidemic potential and virulence was likely a major factor in the spread of WNV in both the Old and the New Worlds (Marfin and Gubler 2001). The first evidence of this new strain of WNV was in North Africa in 1994, when an epidemic/epizootic of serologically confirmed WNV occurred in Algeria; of 50 cases with neurologic disease 20 (40%) were diagnosed as encephalitis and 8 (16%) died (Murgue et al. 2002). Over the next 5 years, epidemics/epizootics occurred in Morocco, Romania, Tunisia, Israel, Italy, and Russia, as well as jumping the Atlantic and causing the epidemic in Queens, New York (Fig. 6).





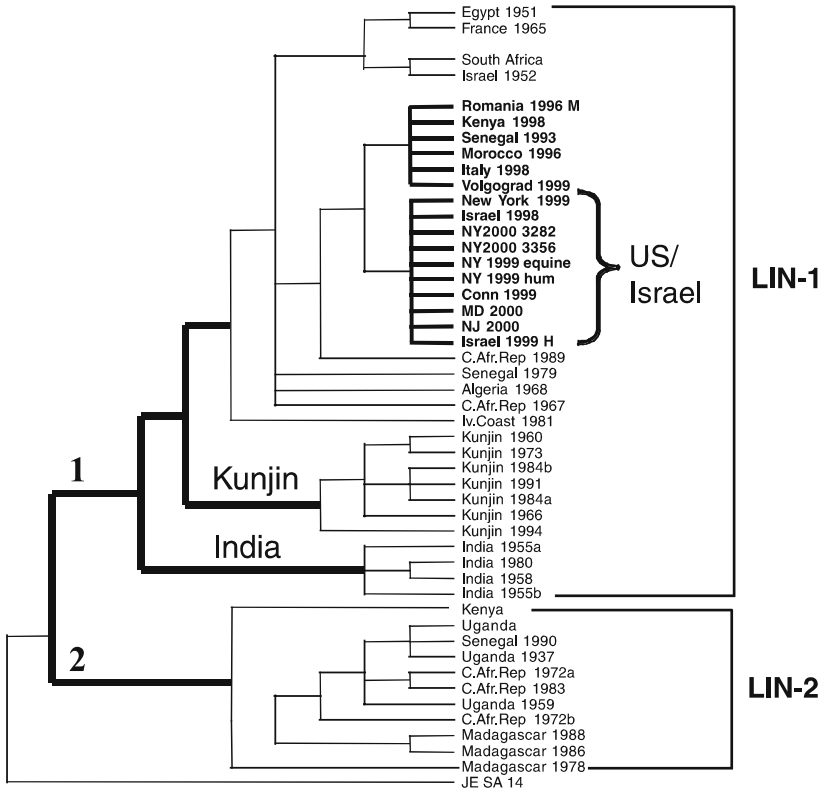
**Fig. 5** Migratory bird flyways in the western hemisphere. In the fall birds fly south to areas in tropical America where they spend the winter. In the spring, they fly north again, potentially carrying the virus with them each way. Source: Reprinted from Gubler (2007a)



**Fig. 6** Epidemics caused by West Nile virus, 1937–2007. The red stars indicate epidemics that have occurred since 1994 and have been associated with severe and fatal neurologic disease in humans, birds, and/or equines. Source: Reprinted from Gubler (2007a)

All of these epidemics/epizootics were unique from earlier epidemics in that they were associated with a much higher rate of severe and fatal neurologic disease in humans, equines, and/or birds. This virus most likely had better fitness and caused higher viremias in susceptible hosts, allowing it to take advantage of modern transportation and globalization to spread, first in the Mediterranean region and Europe, and then to the western hemisphere. This speculation is supported by sequence data documenting that the viruses isolated from these recent epidemics/epizootics are closely related genetically, most likely having a common origin; all belonged to the same clade (Lanciotti et al. 1999, 2002) (Fig. 7). Moreover, experimental infection of birds has documented that viruses in this clade, represented by the New York 1999 isolate, have greater virulence than virus strains isolated earlier (Brault et al. 2004; Langevin et al. 2005).

The broad vertebrate host and vector range of WNV was another important factor in the successful spread of epidemic/epizootic WNV transmission. The virus has been isolated from 62 species of mosquitoes, 317 species of birds, and more than



**Fig. 7** Phylogenetic tree of West Nile viruses based on sequence of the envelope gene. Viruses isolated during recent epidemics all belong to the same clade, suggesting a common origin. Source: Reprinted from Gubler (2007a)

30 species of non-avian hosts since it entered the U.S. in 1999 (CDC 2007, unpublished data). The non-avian vertebrate hosts include rodents, bats, canines, felines, ungulates, and reptiles, in addition to equines and humans. It is unknown what role any of these non-avian species play in the transmission cycle of WNV, but the fact that so many mammal and opportunistic blood-feeding mosquitoes have been found infected suggests that there may be secondary transmission cycles involving mammals and mammal-feeding mosquitoes, putting humans and domestic animals at higher risk for infection.

### ***Dengue/Dengue Hemorrhagic Fever***

The dengue viruses (DENVs) are also members of the family *Flaviviridae*; there are four<sup>2</sup> dengue serotypes (DENV-1, DENV-2, DENV-3, DENV-4), which make up the dengue complex within the genus *Flavivirus*. While the DENVs have a primitive sylvatic maintenance cycle involving lower primates and canopy-dwelling mosquitoes in Asia and Africa, they have also established an endemic/epidemic cycle involving the highly domesticated *Ae. aegypti* mosquito and humans in the large urban centers of the tropics. They have become completely adapted to humans and current evidence suggests that the sylvatic cycle is not a major factor in the current emergence of epidemic disease (Gubler 1997; Rico-Hesse 1990).

The DENVs cause a spectrum of illness in humans ranging from inapparent infection and mild febrile illness to classic DF to severe and fatal hemorrhagic disease (WHO 1997). All age groups are affected, but in endemic areas, most illness is seen in children, who tend to have either a mild viral syndrome or the more severe dengue hemorrhagic fever (DHF), a vascular leak syndrome. DENV infection has also been associated with severe and fatal neurologic disease and massive hemorrhaging with organ failure (Sumarmo et al. 1983).

Dengue is an old disease; the principal urban vector, *Aedes aegypti*, and the viruses were spread around the world as commerce and the shipping industry expanded in the 17th, 18th, and 19th centuries. Major epidemics of DF occurred as port cities were urbanized and became infested with *Ae. aegypti*. Because the viruses depended on the shipping industry for spread, however, epidemics in different geographic regions were sporadic, occurring at 10–40-year intervals. The disease pattern changed with the ecological disruption in Southeast Asia during and after World War II. The economic development, population growth and uncontrolled urbanization in the post-war years created ideal conditions for increased transmission and spread of urban mosquito-borne diseases, initiating a global pandemic of dengue. With increased epidemic transmission, and the movement of people within and between countries, hyperendemicity (the co-circulation of multiple DENV serotypes) developed in Southeast Asian cities, and epidemic DHF, a newly described disease, emerged (Gubler 1997; Halstead 1980; WHO 1997).

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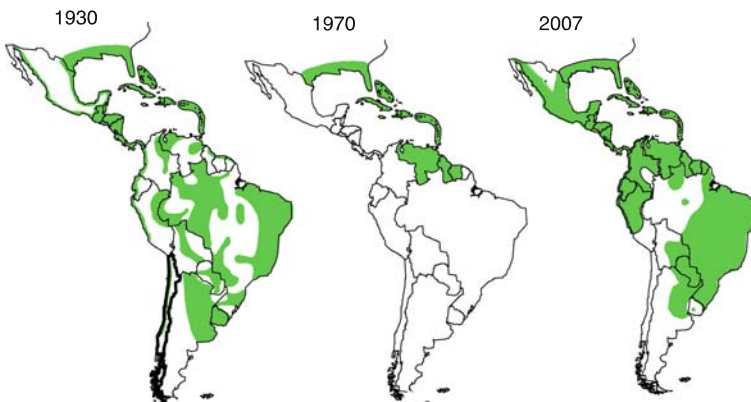
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By the mid-1970s, DHF had become a leading cause of hospitalization and death among children in the region (WHO 1997, 2000). In the 1980s and 1990s, dengue transmission in Asia further intensified; epidemic DHF increased in frequency and expanded geographically west into India, Pakistan, Sri Lanka, and the Maldives, and east into China (Gubler 1997). At the same time, the geographic distribution of epidemic DHF was expanding into the Pacific islands in the 1970s and 1980s and to the American tropics in the 1980s and 1990s (Gubler 1989, 1993, 1997; Gubler and Trent 1994; Halstead 1992).

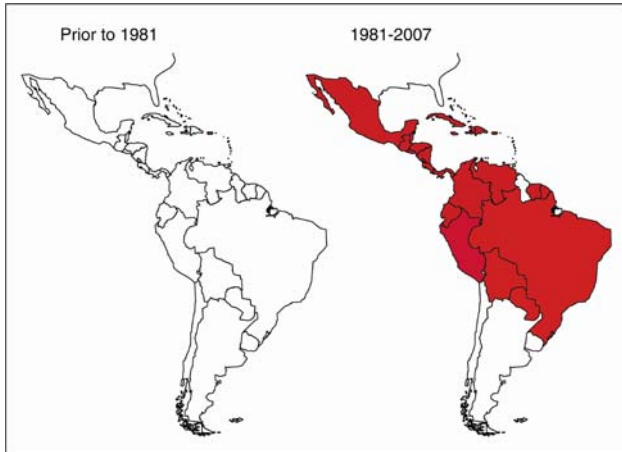
Epidemiologic changes in the Americas have been the most dramatic. In the 1950s, 1960s, and most of the 1970s, epidemic dengue was rare in the American region because the principal mosquito vector, *Aedes aegypti*, had been eradicated from most of Central and South America (Gubler 1989; Gubler and Trent 1994; Schliessman and Calheiros 1974). The eradication program was discontinued in the early 1970s, and the mosquito then began to reinvade those countries from which it had been eliminated. By the 1990s, *Aedes aegypti* had regained the geographic distribution it had before eradication was initiated (Fig. 8). This was another classic case of “success breeding failure.”

Epidemic dengue invariably followed after reinfestation of a country by *Aedes aegypti*. By the 1980s, the American region was experiencing major epidemics of DF in countries that had been free of the disease for more than 35 years (Gubler 1989, 1993; Gubler and Trent 1994; Pinheiro 1989). With the introduction of new viruses and increased epidemic activity came the development of hyperendemicity in American countries and the emergence of epidemic DHF, much as had occurred in Southeast Asia 25 years earlier (Gubler 1989). From 1981 to 2006, 28 American countries reported laboratory-confirmed DHF (Gubler 2002b) (Fig. 9).

While Africa has not yet had a major epidemic of DHF, sporadic cases of severe disease have occurred as epidemic DF has increased in the past 25 years. Before the



**Fig. 8** Distribution of *Aedes aegypti* in American countries in 1930, 1970, and 2007. Source: Courtesy, Division of Vector-Borne Infectious Diseases, CDC, Fort Collins, CO; adapted from Gubler (1998)



**Fig. 9** Countries reporting confirmed DHF prior to 1981 and 1981–2007. Source: Courtesy, Division of Vector-Borne Infectious Diseases, CDC, Fort Collins, CO; adapted from Gubler (1998)

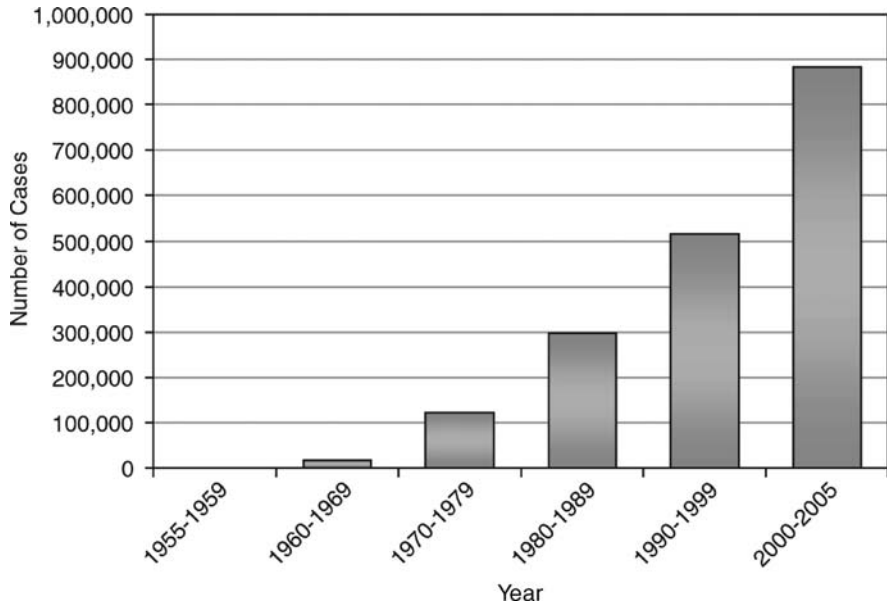
1980s, little was known of the distribution of DENVs in Africa (Carey et al. 1971). Since then, however, major epidemics caused by all four serotypes have occurred in both East and West Africa (Gubler 1997; Monath 1994).

In 2007, dengue viruses and *Ae. aegypti* mosquitoes have a worldwide distribution in the tropics with 2.5–3.0 billion people living in dengue-endemic areas. Currently, DF causes more illness and death than any other arboviral disease of humans. The number of cases of DF/DHF reported to the World Health Organization (WHO) has increased dramatically in the past 3 decades (Fig. 10). Each year, an estimated 100 million dengue infections and several hundred thousand cases of DHF occur, depending on epidemic activity (Gubler 1997, 2002b, 2004; WHO 2000).

### ***Yellow Fever***

Yellow fever virus (YFV) was the first arbovirus to be isolated and the first shown to be<sup>3</sup> transmitted by an arthropod. It is the type species of the family (*Flaviviridae*: genus *Flavivirus*) (Gubler et al. 2007b). Its natural home is the rainforests of sub-Saharan Africa where it is maintained in a cycle involving lower primates and canopy-dwelling mosquitoes (Monath 1988). It was transported to the western hemisphere with the slave trade in the 1600s and became adapted to an urban cycle involving humans and *Aedes aegypti* mosquitoes, similar to dengue. It also established a sylvatic monkey cycle in the rain forests of the Amazon basin similar to the one in Africa.

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**Fig. 10** Mean annual global reported cases of DEN/DHF to the World Health Organization, by decade, 1955–2005. Source: Adapted from MacKenzie et al. (2004)

The first recorded epidemic of YF occurred in 1648 and was followed by numerous epidemics in port cities of the New World, as far north as Boston (Monath 1988). Urban epidemic transmission was effectively controlled in the Americas in the 1950s, 1960s, and 1970s by the *Aedes aegypti* eradication program (see earlier discussion) (Gubler 1989; Schliessman and Calheiros 1974) (Fig. 8). The last known urban epidemic occurred in Brazil in 1942 (Monath 1988). In Francophone countries of West Africa, YF was controlled by mass vaccination programs. The result was the disappearance of major urban epidemics of YF in both Africa and the Americas. In the mid-1980s, however, the urban disease reemerged in West Africa, with major epidemics in Nigeria and increased transmission in other countries (Gubler 2004; Monath 1988; Nasidi et al. 1989; Robertson et al. 1996). Kenya experienced its first epidemic in history in 1993 (Sanders et al. 1998). In the Americas, the reinfestation of most Central and South American countries by *Aedes aegypti* has put the urban centers of the American tropics at the highest risk for epidemic urban YF in more than 60 years (Gubler 2008b). Thus, the disease continues to be an important public health problem in both Africa and the Americas.

The reemergence of epidemic YF in the past 30 years has not been as dramatic as that of DF/DHF. While there has been increased epidemic activity in both Africa and the Americas, the outbreaks have been limited and mostly associated with sylvatic cycles. Of concern is that several of the outbreaks in the Americas have occurred in or in close proximity to urban areas where *Aedes aegypti* occurs, greatly increasing the risk of urban transmission (Gubler 2004; Van der Stuyft et al. 1999). Additionally, the recent increase in ecotourism without proper immunization

has increased the risk of YF being introduced to urban areas where *Aedes aegypti* occurs (CDC 2000).

Currently, the threat is that YFV will become urbanized in the American tropics and spread geographically much as DENVs have done over the past 25 years. The biggest concern is that it will be introduced to the Asia-Pacific region, where there are approximately 1.8 billion people living in large urban centers under crowded conditions in intimate association with large populations of *Aedes aegypti* mosquitoes, thus creating ideal conditions for increased urban transmission. While there is an effective, safe, and economical vaccine for YF, its supply is limited and it would take months to increase production to the point where adequate doses could be produced. By then YFV would likely be widely distributed in the region.

If YF was introduced to the Asia-Pacific, the initial cases would most likely be misdiagnosed as DHF, leptospirosis, rickettsiosis, hantavirus disease, or malaria, thus potentially allowing it to spread and become established in widespread areas before it was identified. Thus, YF virus could be introduced and become established in Asia-Pacific countries weeks to months before it was recognized. Even after it is diagnosed, it is not likely that an effective control program could be mounted because most countries in the region do not have effective *Aedes aegypti* control programs. Once recognized as YF, it would likely cause overreaction and panic on the part of the press, the public, and health officials. Regardless of whether YF virus caused a major epidemic in this region, there would be a major public health emergency, creating social disruption and great economic loss to all countries of the region, making the Indian plague epidemic of 1994 (Fritz et al. 1996; John 1999; WHO 1994) and the 2003 SARS epidemic (Drosten et al. 2003) pale by comparison.

It is not known whether YFV would become established in Asia (Downs and Shope 1974; Gubler 2004; Monath 1989). YFV was most likely introduced sporadically to the Pacific and Asia in the past (Usinger 1944), but secondary transmission has never been documented. There are several possible explanations why there have not been YF epidemics in the Asia-Pacific region (Monath 1989). First, logistics: during the time when major YF epidemics were occurring in the Americas, the virus and the mosquitoes depended on ocean vessels to be transported to new geographical locations. The probabilities of the virus being introduced to Asia were low because the Panama Canal had not been built, and there was not as much commerce between Caribbean, Central and South American countries and Asia, as there was with the United States and Europe. Moreover, YF epidemics were not common in East Africa, thus decreasing the probability of introduction to India. Second, the high heterotypic flavivirus antibody (DENV-1, DENV-2, DENV-3, DENV-4, JEV, and many other flaviviruses of lesser importance) rates in Asian populations, while not protecting against YF infection, could possibly modulate the infection and down-regulate viremia and clinical expression, as has been shown in monkeys (Theiler and Anderson 1975), thus decreasing the likelihood of secondary transmission by mosquitoes. Third, there has been some suggestion that Asian strains of *Aedes aegypti* mosquitoes are less susceptible to YFV than American strains (Gubler et al. 1982). Finally, it is possible that evolutionary exclusion may prevent YFV from becoming established in areas where closely related flaviviruses are endemic.

Most likely, a combination of these factors has contributed to preventing YF from becoming established in Asia in the past.

The reason why urban YF has not occurred in the American tropics, despite the high risk in recent years, is not known. As noted for Asia, the high seroprevalance rates for the DENVs and other flaviviruses in most Central and South American countries could down-regulate viremia and illness, thus decreasing the risk of secondary transmission and clinical diagnosis. Additionally, the enzootic YFV may require adaptation to *Aedes aegypti* and humans, before becoming highly transmissible in the urban environment. If it does become adapted, however, it is important to remember that the logistic and demographic factors that influence arbovirus spread at the beginning of the 21st century are very different from past centuries. First, tens of millions of people travel by jet airplane between the cities of tropical America and the Asia-Pacific region every year; this provides the ideal mechanism for people incubating YFV to transport it to new geographic locations. There has been an increase in ecotourism in recent years, and since 1996, at least six tourists have died in the United States and Europe as a result of infection with YFV acquired during travel to YF endemic countries without vaccination (CDC 2000; Gubler 2004; Gubler and Wilson 2005). If urban epidemic transmission of YF begins in the Americas, there could be thousands of YFV infected people traveling to Asia-Pacific countries where *Aedes aegypti* exposure is high, thus dramatically increasing the probability that epidemic YF transmission will occur in Asia.

## **Why Has There Been Such a Dramatic Resurgence of Vector-Borne Diseases?**

The dramatic global reemergence of epidemic vector-borne diseases in the past 25 years is<sup>4</sup> closely tied to global demographic, economic, and societal trends that have been evolving over the past 50 years. Complacency and deemphasis of infectious diseases as public health problems in the 1970s and 1980s resulted in a redirection of resources and ultimately to a decay of the public health infrastructure required to control these diseases. Coincident with this trend, unprecedented population growth, primarily in the cities of the developing world, facilitated transmission and geographic spread. This uncontrolled urbanization and crowding resulted in a deterioration in housing accompanied by a lack of basic services (e.g., water, sewer, and waste management). Population growth has been a major driver of environmental change in rural areas as well (e.g., deforestation, agriculture land use, and animal husbandry practice changes). All of these changes contributed to increased incidence of vector-borne infectious diseases.

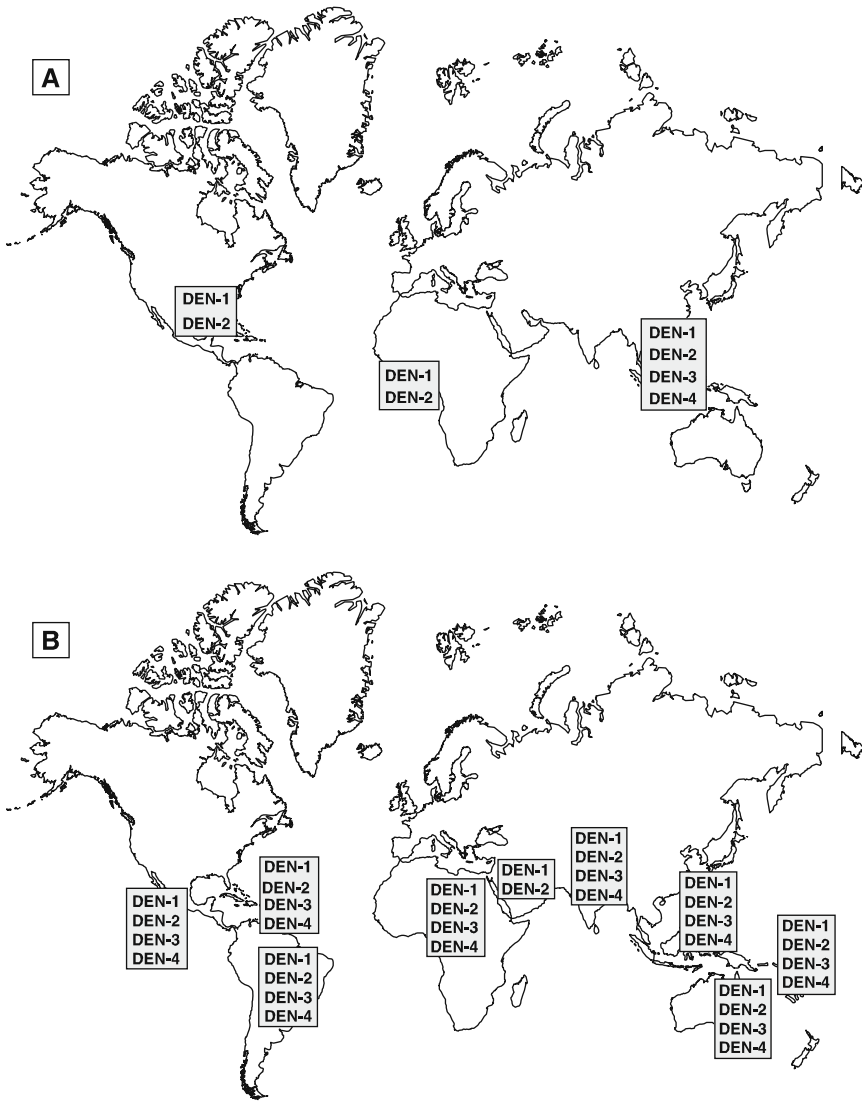
Many urban agglomerations (population >5 million) have emerged in the past 50 years, and most have an international airport through which millions of passengers pass every year (Wilcox et al. 2007). In addition, globalization has insured an

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equally dramatic increase in the movement of animals and commodities between population centers. The jet airplane provides the ideal mechanism by which pathogens of all kinds move around the world in infected humans, vertebrate host animals, and vectors. A classic example of how urbanization combined with globalization has influenced the geographic expansion of disease is illustrated by the DENVs (Fig. 11). In 1970, only Southeast Asian countries were hyperendemic with



**Fig. 11** The global distribution of dengue virus serotypes, (a) 1970 and (b) 2007. Source: Adapted from Mackenzie et al. (2004)

multiple virus serotypes co-circulating, as a result of World War II. The rest of the tropical world was hypopendemic with only a single DENV serotype circulating, or nonendemic (Fig. 11a). In 2007, the whole of the tropical world is hyperendemic as a direct result of urbanization, lack of mosquito control, and increased movement of viruses in people via modern transportation (Fig. 11b). The result has been increased frequency of larger epidemics, and the emergence of the severe and fatal form of disease, DHF, in most tropical areas of the world. Globalization and modern transportation were also responsible for the recent spread of WNV to and throughout the western hemisphere (Fig. 6). Increased transmission is a major driver of genetic change in all of these viruses, which can result in virus strains with greater virulence or epidemic potential being spread around the globe. The concern is that YF or RVF will be the next vector-borne diseases to spread because of globalization and modern transportation.

There are many other vector-borne diseases that have the potential for geographic spread. As an illustration of movement of infectious disease pathogens, Table 2 lists some of the exotic diseases introduced into the United States in recent years. It should be noted that the majority of these pathogens are vector-borne, zoonotic, and viruses. In addition, five species of exotic mosquitoes have been introduced and have become established in the country in the past 25 years. Some of the more important epidemic vector-borne diseases affecting humans at the beginning of the new millennium and which have the potential to spread via modern transportation are shown in Table 3. Again, it should be noted that most are zoonotic viral diseases. There is reason to believe that, sooner or later, one or more known or unknown pathogens will cause devastating epidemic disease.

**Table 2** Exotic infectious diseases that have recently been introduced to the United States

Diseases	Autochthonous transmission
• West Nile fever	Yes
• Yellow fever	No
• Mayaro fever	No
• Dengue fever	Yes
• Chikungunya	No
• SARS	No
• Monkeypox	Yes
• CJD/BSE	No
• HIV/AIDS	Yes
• Lassa fever	No
• Malaria	Yes
• Leishmaniasis	Yes
• Chagas disease	Yes
• Cyclospora	Yes
• Cholera	No

**Table 3** Principal epidemic vector-borne diseases affecting humans at the beginning of the twenty first century

- 
- Malaria
  - Plague
  - Leishmaniasis
  - African trypanosomiasis
  - Relapsing fever
  - Yellow fever
  - Dengue fever and dengue hemorrhagic fever
  - West Nile encephalitis
  - Japanese encephalitis
  - Rift valley fever
  - Venezuelan equine encephalitis
  - Chikungunya
  - Epidemic polyarthritis
  - Other arboviruses
  - Zoonoses
- 

## Lessons Learned and Challenges to Reverse the Trend

At the dawn of the 21st century, epidemic infectious diseases have come “full circle” in that<sup>5</sup> many of the diseases that caused epidemics in the early 1900s, and which were effectively controlled in the middle part of the 20th century, have reemerged to become major public health problems. Complacency and competing priorities for limited resources have resulted in inadequate resources to continue prevention and control programs when there is no apparent disease problem. Only when an epidemic occurs do policy makers respond by implementing emergency response plans, but by then it is usually too late to have any impact on transmission.

In today’s world of modern transportation and globalization, we have learned to expect the unexpected: that old diseases will reemerge and new diseases will emerge, and that modern transportation and globalization will disperse them around the world. Once introduced and established, it is unlikely that zoonotic disease agents can be eliminated from an area.

We have learned that international cooperation and collaboration are critical to developing and maintaining effective early warning disease detection and emergency response systems. Unfortunately, while elaborate epidemic preparedness and response plans are often drawn up, these plans are most often not implemented until it is too late to impact disease transmission because the decision to declare an emergency is one that often has important political and economic implications. As a result, public health problems that should remain localized have the potential to become more widespread because of modern transportation and the mobility of people.

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We have learned that we must emphasize prevention. Local public health infrastructure must be rebuilt and maintained in order to contain disease outbreaks as local public health events instead of letting them spread around the world via modern transportation. The public and the press require accurate and reliable information in order to prevent panic and overreaction.

We have learned that most newly emergent infectious diseases will likely be caused by zoonotic pathogens, and those that cause major regional or global epidemics that impact the global economy will likely originate in Asia. This has been the case for the past 25 years, and demographic, societal, and economic trends suggest this trend will continue for the indefinite future (Table 4). Thus, it is projected that most of the world's population growth will occur in the cities of Asia in the next 25 years, and most of the world's economic growth will occur in Asian countries. Changes in animal husbandry and agricultural practices, combined with regional human behavior and cultural practices, and increased trade, will all facilitate the emergence of exotic zoonotic pathogens in a region where people from rural areas continue to migrate to large urban centers, and from which the movement of people, animals, and commodities increase the risk of dispersal via modern transportation and globalization.

Finally, if we hope to reverse the trend of emerging and reemerging infectious diseases, the movement of pathogens and arthropod vectors via modern transportation must be addressed. This problem has important political and economic implications, but if it is not dealt with, the long-term costs will far exceed those required to proactively address the problem. Local public health infrastructure, including laboratory and epidemiologic capacity, must be developed in all countries, but especially in those tropical developing countries where new diseases may emerge. Effective laboratory-based, active disease surveillance systems are needed in every country, as are public health personnel that can respond rapidly and effectively to control epidemic transmission before it spreads. We need new tools (vaccines, drugs, insecticides, diagnostic tests, etc.), and finally, we need to better understand the ecology of newly emerging diseases in order to develop effective prevention strategies; drugs or vaccines will likely not be developed for most of these pathogens.

**Table 4** Pathogens of tomorrow: From whence they will come?

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From Asia and Animals

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- Human population growth
  - Urbanization
  - Environmental change
  - Animal husbandry
  - Agricultural practices
  - Human behaviour
  - Cultural practices
  - Economic growth
  - Trade
-

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