

The Global Pandemic of Dengue/Dengue Haemorrhagic Fever: Current Status and Prospects for the Future

D J Gubler,*^{Sc D}

Abstract

Dengue/dengue haemorrhagic fever has been one of the most important resurgent tropical diseases in the past 17 years, with expanding geographic distribution of both the viruses and the mosquito vectors, increased frequency of epidemics, the development of hyperendemicity (co-circulation of multiple virus serotypes) and the emergence of dengue haemorrhagic fever in new areas. This paper briefly reviews the changing epidemiology of dengue, discusses some of the factors responsible for the recent resurgence, and reviews the current options for reversing the trend of emergent disease.

Ann Acad Med Singapore 1998; 27:227-34

Key words: *Aedes aegypti*, Arboviruses, Emerging diseases, Mosquitoes

Introduction

The world has experienced unprecedented population growth in the past 50 years that continues unabated in the waning years of the 20th century. It is projected that by the year 2025, the global population will be 8.3 billion people, and by 2050, 10 billion people.¹ Most of the recent population increase has occurred in urban centres of developing countries, which has resulted in uncontrolled and unplanned urbanisation, especially in the tropics. Projections indicate that this trend will continue with 95% of population growth in the next 25 to 30 years occurring in developing countries (World Resources Institute, 1996). Moreover, it is estimated that by the year 2000, 39% of the global population will live in urban areas and this will increase to 56% by the year 2025.²

Coincident with these demographic changes has been societal changes that have had a marked influence on the movement of commerce and people. The automobile has greatly increased the mobility of humans and commodities within cities and countries, and the jet plane has done the same for regional and intercontinental movement of goods and people. While these changes reflect economic progress and have increased the standard of living in some respects, they have also had some disastrous effects on public health, especially in tropical developing countries of the world. The global resur-

gence of epidemic dengue fever and the emergence of dengue haemorrhagic fever are directly related to these changes. This paper will review the changing epidemiology of dengue, some of the factors thought to be responsible for the dramatic increase in disease incidence and prospects for reversing the trend of emergent disease in the future.

Natural History

Dengue fever/dengue haemorrhagic fever (DEN/DHF) are caused by infection with dengue viruses. There are four closely related virus serotypes, DEN-1, DEN-2, DEN-3, and DEN-4, which show extensive cross-reactivity in serologic tests, but do not provide cross-protective immunity.³ Thus, persons living in an endemic area can be infected with three and probably all four of the dengue serotypes during their lifetime.

Dengue viruses are transmitted by female *Aedes* (*Stegomyia*) species of mosquitoes.⁴ *Aedes aegypti*, the principal urban vector, is a small black and white, highly domesticated mosquito that prefers to lay its eggs in artificial water containers commonly found in urban areas of the tropics. Containers found in and around the home, such as those used for water storage, flower vases, old automobile tyres, buckets and various plastic containers, and other junk that collect rainwater are examples. The adult mosquitoes are highly adapted to living with humans

* Director

Division of Vector-Borne Infectious Diseases

National Center for Infectious Diseases

Centers for Disease Control and Prevention

Public Health Service, US Department of Health and Human Services

Address for Reprints: Dr Duane J Gubler, Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Public Health Service, US Department of Health and Human Services, PO Box 2087, Fort Collins, CO 80522, USA.

and are rarely noticed, preferring to rest indoors and to feed on humans during daylight hours in an unobtrusive and often undetected way.

Mosquitoes become infected with dengue viruses by ingesting virus with the blood meal when feeding on persons acutely ill with dengue. From the lumen of the midgut, the virus infects the epithelial cells, passes into the body cavity and over a period of 8 to 12 days, depending on temperature and other environmental factors, infects other tissues of the mosquito, including the salivary glands. Once the salivary glands are infected, the mosquito becomes infective and can transmit the virus when it takes another blood meal.

Human infection with dengue viruses occurs when a person is bitten by an infective mosquito. After a period of incubation lasting 3 to 14 days (average 4 to 6 days), the person may experience acute onset of fever accompanied by a variety of nonspecific signs and symptoms.⁴ During this acute febrile period, which may be as short as 2 days and as long as 10 days, a viraemia occurs, which may vary in magnitude and duration.^{5,6} If uninfected *Aedes aegypti* mosquitoes bite the ill person during this febrile viraemic stage, those mosquitoes may become infected and subsequently transmit the virus to other, uninfected persons after the extrinsic incubation period of 8 to 12 days noted above.³

Clinical Presentation

In humans, dengue virus infection of all four virus serotypes causes a spectrum of illness ranging from inapparent or mild febrile illness to severe and fatal haemorrhagic disease.⁷ Clinical presentation in both children and adults may vary in severity, depending on the strain and serotypes of the infecting virus, and the immune status, age and the genetic background of the patient.^{3,7-9} In dengue endemic areas, acute dengue infections may be clinically nonspecific, especially in children, who often present with signs and symptoms of a viral syndrome. The differential diagnosis of dengue during the acute phase of illness includes measles, rubella, influenza, typhoid, leptospirosis, malaria, other viral haemorrhagic fevers, and any other diseases that may present in the acute phase as a nonspecific viral syndrome.

Classic dengue fever is primarily a disease of older children and adults; it is characterised by sudden onset, fever, and one or more of a number of nonspecific signs and symptoms such as frontal headache, retro-orbital pain, myalgias, arthralgias, nausea and vomiting, weakness, and rash.^{3,4,7} Anorexia, altered taste sensation and mild sore throat are not uncommon. Clinical laboratory findings associated with dengue fever include leukopenia and in some patients, thrombocytopenia and elevated liver enzymes. Haemorrhagic manifestations may occur, skin haemorrhages being the most common. Den-

gue fever is generally self-limiting and rarely fatal; the acute illness usually lasts 3 to 7 days. Convalescence, however, may be prolonged for weeks with the patient exhibiting weakness and depression. No permanent sequelae are known, and immunity to the infecting virus serotype is lifelong.

DHF is primarily a disease of children under the age of 15 years in Asia, although it may occur in older children and adults in other areas.⁷ Like dengue fever, it is characterised by sudden onset of fever and nonspecific signs and symptoms; it is difficult to distinguish DHF from dengue fever and other illnesses during the acute stage. The critical stage in DHF occurs at the time of defervescence when the patient develops a vascular leak syndrome with signs of circulatory failure and haemorrhagic manifestations, primarily skin haemorrhages. Thrombocytopenia ($\leq 100\,000/\text{mm}^3$) and elevated haematocrit are prominent features. DHF can be a very dramatic disease; the patient's condition may deteriorate very rapidly with onset of shock and death if the plasma leakage is not detected and corrected with fluid replacement therapy. Leukopenia, thrombocytopenia, and haemoconcentration are constant findings; hepatomegaly and elevated liver enzyme levels are common. Risk factors for developing severe haemorrhagic disease are not fully understood, but as noted above, include the strain and serotype of the infecting dengue virus and the immune status, age, and genetic background of the patient.^{3,7-9} The differential diagnosis of DHF includes the same diseases noted above for classic dengue fever.

Geographic Distribution and Incidence

Dengue fever is an old disease and has had a global distribution in the tropics for over 200 years. Epidemic DHF first occurred in Southeast Asian countries in the 1950s and 1960s, and currently, is a leading cause of hospitalisation and death among children in that region.⁷ Epidemic DHF spread to the South Pacific islands in the 1970s, and reached the Caribbean Basin in the 1980s.¹⁰⁻¹² The pattern of severe haemorrhagic disease evolved in the American region in the 1980s and 1990s in a manner similar to the way it did in Southeast Asia in the 1960s and 1970s.^{12,13} The disease is now a major public health problem in the Caribbean islands, Central and South America, where a recent study has shown that dengue fever has an economic impact of the same order of magnitude as malaria, tuberculosis, sexually transmitted diseases (excluding AIDS), hepatitis, the childhood cluster (polio, measles, pertussis and diphtheria), and the tropical cluster (schistosomiasis, filariasis, Chagas disease, leishmaniasis and onchocerciasis).¹⁴

In 1998, dengue fever and *Aedes aegypti* mosquitoes have a worldwide distribution in tropical areas of the world; over 2.5 billion people live in dengue-endemic areas (Fig. 1).^{8,10,15} The current known geographic distri-

bution of the various dengue virus serotypes is shown in Figure 2, and reflects the development of hyperendemicity (the co-circulation of multiple virus serotypes in a country) in most tropical areas of the world in the past 15 to 20 years. Surveillance for DEN/DHF is passive in most endemic countries, relying on physicians to report disease to the health ministry; only severe cases are typically reported to the World Health Organization. Thus, only the tip of the iceberg is reported, making DEN/DHF one of the most under-reported tropical infectious diseases in the past 20 years; dengue fever is often reported as malaria. Even so, approximately four times as many DHF cases were reported from 1981 to 1995 than in the previous 30 years (Fig. 3). DEN/DHF is currently the most important arboviral disease affecting humans; it is estimated that more than 100 million cases of dengue fever and 500 000 cases of DHF occur each year, depending on epidemic activity.^{10,16,17} The average case fatality rate of DHF is 5%.

Changing Epidemiology of Dengue

The global epidemiology of dengue viruses first began to change with the ecological disruption in Southeast Asia during and following World War II.^{3,18} During the war, existing water systems were destroyed, and water storage was increased for domestic use as well as for fire

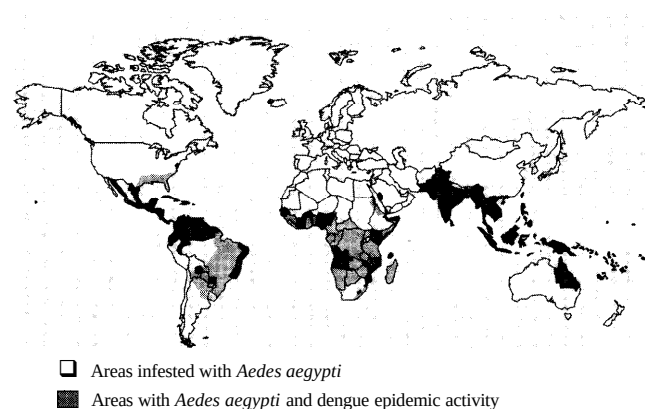


Fig. 1. World distribution of dengue and the principal epidemic vector, *Aedes aegypti*, 1998.

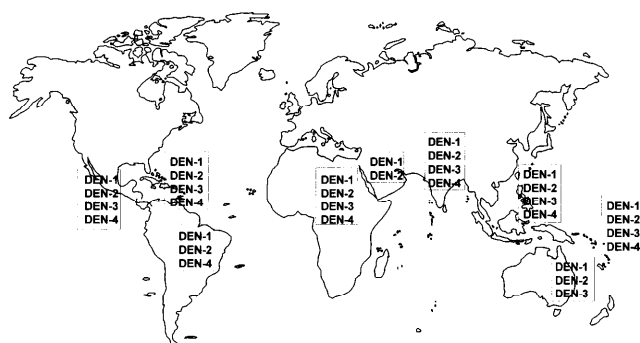
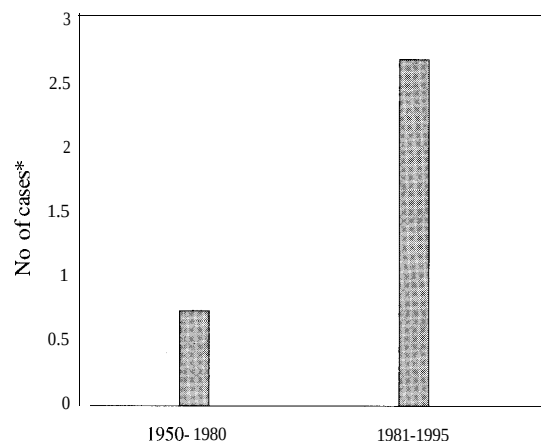


Fig. 2. Known global distribution of the four dengue virus serotypes, 1998.



* Millions of cases

Fig. 3. Cases of dengue haemorrhagic fever reported to World Health Organization, 1950 to 1980 and 1981 to 1995.

control. War equipment was moved frequently between cities and countries, and large amounts were also left behind. This material collected rainwater and, along with water storage containers, made ideal larval habitats for the principal vector mosquito, *Aedes aegypti*. The movement of war materials resulted in the transport of mosquitoes and their eggs to new geographic areas. The result of these ecological changes was a greatly expanded geographic distribution and increased population densities of *Aedes aegypti*. In addition, hundreds of thousands of Japanese and Allied soldiers, most of them susceptible to dengue virus infection, were constantly transferred between countries in Asia and the Pacific. This provided a mechanism for movement of dengue viruses between cities, countries and other regions, as well for providing susceptible individuals for epidemic transmission. The war years were thus responsible for creating the conditions (hyperendemicity and high densities of *Aedes aegypti*) for the emergence of epidemic DHF in Southeast Asia.

In the years following World War II, an unprecedented urbanisation of Southeast Asia began, with millions of people moving to the cities of the region. Urban centres in most countries expanded rapidly in an uncontrolled and unplanned fashion. Housing was inadequate for large numbers of people, and water, sewer and waste management systems deteriorated. The *Aedes aegypti* populations and dengue viruses thrived in this new ecological setting, with increased transmission and increased frequency of dengue epidemics occurring in the indigenous children as the adult populations became immune to the viruses. Moreover, an economic expansion began in the region that continues today. This led to continued urbanisation and increased movement of people (and with them, dengue viruses) between cities and countries. Those countries that did not already have multiple virus serotypes co-circulating, quickly became

hyperendemic. The viruses, often all four serotypes, were (and still are) maintained in a human-*Aedes aegypti*-human transmission cycle in most urban centres of Southeast Asia. The result of these changes was dramatically increased dengue transmission and the emergence of DHF. In every country where the disease emerged as a major public health problem, it evolved in a similar manner, first as sporadic cases of DHF occurring for several years, ultimately culminating in a major epidemic. Following the first epidemic, a pattern of epidemic activity was established, with epidemics occurring every 3 to 5 years. Characteristically, succeeding epidemics became progressively larger as a result of geographic expansion of DHF within the country.

From the mid-1950s to the 1970s, epidemic DHF was localised in a few Southeast Asian countries. The 1980s and 1990s saw a dramatic geographic expansion of epidemic DHF, west into India, Pakistan, Sri Lanka and the Maldives Islands and east into the People's Republic of China (Fig. 4). There was also a resurgence of disease in Singapore, which had effectively controlled DHF for nearly 20 years; in 1996, Singapore experienced its largest outbreak in history.

Epidemic dengue fever re-emerged as a public health problem in the Americas in the late 1970s after a 40-year quiescence, which was due to an *Aedes aegypti* eradication programme initiated by the Pan American Health Organization (PAHO) in 1946 to prevent urban epidemics of yellow fever.^{19,20} The programme was successful and eradication was achieved in most countries of the region. Unfortunately, the programme was discontinued in the early 1970s, and failure to eradicate *Aedes aegypti* from all countries of the region resulted in repeated reinfestations by this mosquito of those countries that had achieved eradication. During the 1970s, support for *Aedes aegypti* surveillance and control programmes waned, and they were merged with malaria control programmes in many countries. By the end of the 1980s, *Aedes aegypti* had reinfested much of the area from which it had been eradicated in the 1950s and 1960s (Fig.

5).^{3,21,22} The reinfestation of the region has continued during the 1990s, and in 1997, *Aedes aegypti* has a distribution similar to that in the 1930s, before eradication was initiated (Fig. 5).

The expanding geographic distribution of *Aedes aegypti* in the Americas during the 1970s and 1980s coincided with increased movement of dengue viruses both into, and within the region.^{12,13} Prior to 1977, only DEN-2 and DEN-3 viruses were known to be present in the Americas, although DEN-1 and DEN-3 were probably present in the early 1940s.^{12,13,23,24} A characteristic of dengue in the Americas from the 1950s through the early 1980s was nonendemicity (no viruses present) or hypoendemicity (only a single serotype was present) in a country.^{12,13,21,23,25}

DEN-1 was re-introduced to the American region in 1977, with epidemics in Jamaica and Cuba; this serotype subsequently spread throughout the Caribbean Islands, Mexico, Texas, Central America and northern South America, causing major or minor epidemics over the next 4 years.^{12,13,21} In 1981, DEN-4 was introduced into the eastern Caribbean Islands, and like DEN-1, this serotype also spread rapidly to other islands in the Caribbean, and to Mexico, Central America and northern South America, causing major or minor epidemics, many of them in countries that had experienced recent DEN-1 epidemics.^{12,13} Some of these outbreaks (Suriname, 1982; Mexico, 1984; Puerto Rico, 1986; El Salvador, 1987) were associated with the first documented emergence of DHF, occurring in small numbers or sporadically for the most part.^{12,13}

Also in 1981, a new strain of DEN-2 was introduced into Cuba from Southeast Asia.²⁶⁻²⁸ Unlike the DEN-1 and DEN-4 epidemics, the 1981 Cuban DEN-2 epidemic was associated with thousands of cases of severe haemorrhagic disease (Fig. 6); this was the first major DHF epidemic in the Americas.²⁶ Although the viruses isolated in Cuba have not been made available for objective study, DEN-2 viruses isolated from patients exposed to infection in Jamaica at the time of and shortly after the Cuban epidemic (Gubler DJ, unpublished data)

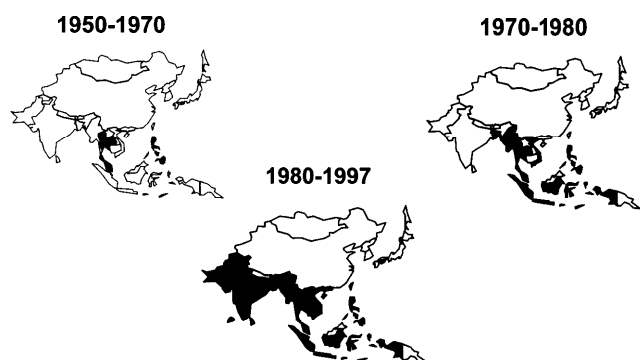


Fig. 4. The geographic spread of epidemic dengue haemorrhagic fever in Asia, 1950 to 1997.

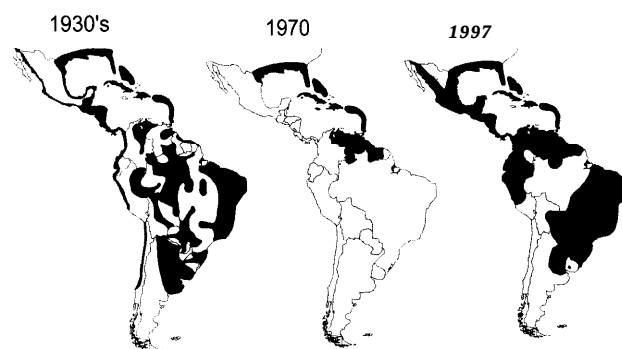
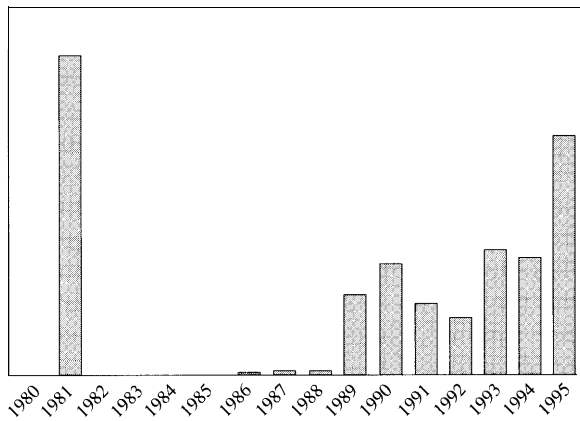


Fig. 5. Geographic distribution of *Aedes aegypti* in the Americas, 1930, 1970 and 1998.



Data from PAHO

Fig. 6. Cases of dengue haemorrhagic fever reported to the Pan American Health Organization, 1980 to 1995.

were sequenced and the data suggest that the virus causing the epidemic was a new strain introduced from Asia, most likely from Viet Nam, where several thousand Cuban aid personnel were working at the time,²⁸ (Gubler DJ, unpublished data).

The second major epidemic of DHF in the Americas, also thought to be caused by this new strain of DEN-2, occurred in Venezuela in 1989 to 1990 with over 6000 cases and 73 deaths.²⁹ Epidemic DHF of variable intensity caused by this genotype of DEN-2, subsequently occurred in Colombia (1990), Brazil (1992 and 1994), French Guiana (1992), Puerto Rico (1994) and Mexico (1995), but none of these epidemics were of the same magnitude and severity as the Cuban epidemic of 1981. Other outbreaks involving this genotype of DEN-2 did not cause DHF, even though they had been recently preceded by DEN-1 and/or DEN-4 outbreaks.

In 1994, a new strain of DEN-3 was introduced into the American region, causing a major epidemic of DEN / DHF in Nicaragua and a small outbreak associated with classical dengue fever in Panama.³⁰ This virus, which was shown to be genetically distinct from the DEN-3 that previously occurred in the Americas³¹ (Lanciotti R, Quiros I, Clark GG and Gubler DJ, unpublished data), apparently was also a recent introduction from Asia; it spread throughout Central America and Mexico in 1995, causing major epidemics. Surprisingly by December, 1997, it has yet to be detected in the Caribbean islands or South America.

The sequence of events associated with the changing epidemiology of dengue in the Americas in the 1970s, 1980s, and 1990s was nearly identical to that which occurred in Southeast Asia in the 1950s, 1960s, and 1970s.^{12,13} Thus, re-invasion of Central and South America by *Aedes aegypti* in the 1970s and 1980s, combined with increased urbanisation, increased movement of people

and with them, dengue viruses, resulted in most countries evolving from nonendemicity (no viruses present), or hypoendemicity (one virus present) to hyperendemicity (multiple virus serotypes co-circulating). This resulted in increased frequency of epidemic activity and the emergence of DHF as a major public health problem. Several countries (Cuba, Venezuela, Brazil, and Nicaragua) have had major epidemics of DHF in recent years. Moreover, outbreaks with sporadic or small numbers of cases of DHF have occurred in many countries throughout the region. In 1980, DHF was not considered endemic in any American country. Between 1981 and 1997, however, there was a dramatic emergence of DHF, with 23 countries reporting laboratory-confirmed DHF that met the WHO case definition (Fig. 7). This disease is now endemic in most of those countries where multiple dengue virus serotypes co-circulate, and the numbers of cases reported to PAHO have increased dramatically (Fig. 6). If the disease pattern continues to evolve in the Americas as it did in Southeast Asia, the first 10 years of the 21st century will bring more frequent and larger epidemics of DHF.^{12,13}

Surveillance for dengue in Africa has been poor during this century, and epidemics, when they have occurred, were often initially reported as malaria. Although surveillance has not improved, laboratory-confirmed reports of epidemic dengue fever have increased dramatically since 1980 (Fig. 8). Limited outbreaks have occurred in West Africa, but the most recent epidemic activity has occurred in East Africa and the Middle East.²⁵ All four dengue serotypes have been involved, and although sporadic cases of disease clinically compatible with DHF have been reported in some epidemics of dengue fever, DHF in its epidemic form, has not yet occurred in Africa or the Middle East.

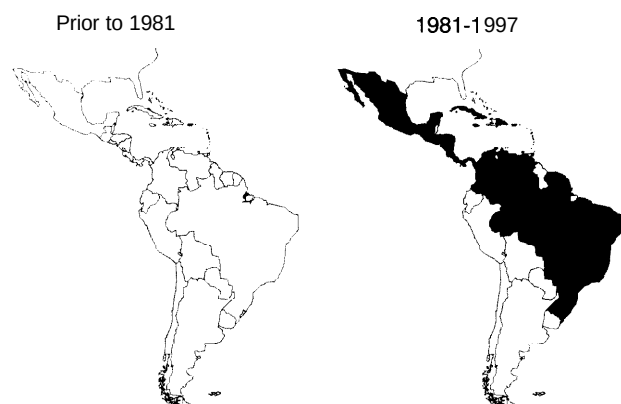


Fig. 7. The geographic spread of dengue haemorrhagic fever in the Americas, prior 1981, and 1981 to 1997.

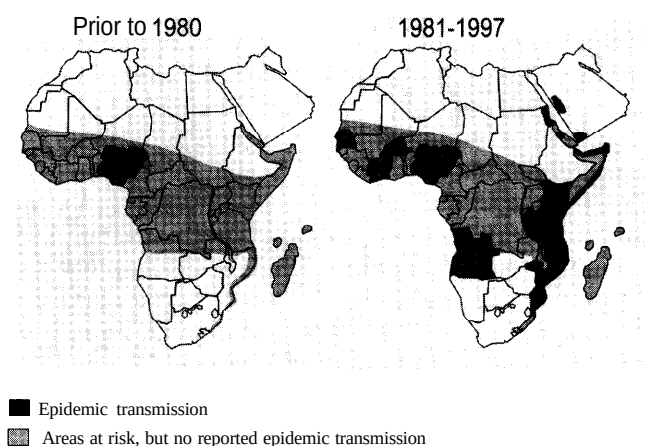


Fig. 8. The geographic distribution of reported dengue fever epidemics in Africa, prior to 1980 and 1981 to present.

Factors Responsible for the Global Resurgence of Dengue

The reasons for the dramatic resurgence of epidemic DEN/DHF in the waning years of the 20th century are complex and not fully understood, but are most likely associated with demographic and societal changes that have occurred over the past 50 years as noted above.^{10,25} The most important demographic change has been the unprecedented population growth, primarily in tropical developing countries. Coincident with this has been uncontrolled and unplanned urbanisation in these same countries. These changes have resulted in large, crowded human populations living in urban centres in substandard housing with inadequate water, sewer and waste management systems. Most consumer goods are now packaged in non-biodegradable plastic or cellophane, which is discarded into the environment, where it collects rain water and provides ideal larval habitats for the vector mosquito. Also, used automobile tyres make ideal mosquito larval habitats, and the numbers have increased dramatically in the past 20 years, along with the numbers of automobiles; tyres are very difficult to dispose of from the environment. All of these factors have contributed to the expanded geographic distribution and increased population densities of the principal mosquito vector, *Aedes aegypti*.

Another contributing factor has been the lack of effective *Aedes aegypti* mosquito control in most dengue-endemic countries of the world. Emphasis for the past 25 years has been placed on ultra-low volume space sprays of insecticide for adult mosquito control.²² This has been shown to be ineffective in controlling *Aedes aegypti*.^{22,32,33} Thus, hundreds of millions of people in urban centres of the tropics are living in intimate association with large populations of an efficient epidemic mosquito vector of dengue viruses, providing ideal conditions for increased transmission of urban mosquito-borne disease such as dengue.

The automobile has increased the mobility of people within and between population centres in a country, enhancing the ability of dengue viruses to spread locally in infected persons or in mosquitoes, and thus the development and maintenance of multiple virus serotypes (hyperendemicity) in a country or region. The jet plane has had a similar impact on the rapid and efficient movement of people, and has changed global demographics. It also provides the ideal mechanism for dengue viruses to move with ease between countries and continents in persons incubating the viruses. The reinfestation of the American tropics by *Aedes aegypti*, placed at risk for dengue infection, large numbers of susceptible individuals living in permissive urban areas. The numerous epidemics and increased transmission of dengue that subsequently occurred there, in Asia, the Pacific and Africa, provided increased opportunity for the viruses to move between countries, both within and between the regions, and have resulted in a constant exchange of dengue viruses and other pathogens and the development of global hyperendemicity (Fig. 2). An illustration of the increased human air travel is seen in US Department of Transportation data. From 1983 to 1994, the number of international departures from US airports doubled from 20 to nearly 40 million with over 50% of those departures each year to tropical areas.³⁴ On a global basis, these numbers would be increased several fold.

Finally, the public health infrastructure required to deal with epidemic vector-borne infectious diseases has deteriorated during the past 30 years in most countries of the world. Limited financial and human resources, and competing priorities for those resources, have resulted in a "crisis mentality" among public health officials. The emphasis has thus been on implementing emergency control methods in response to epidemics rather than on developing programmes to prevent epidemic transmission.²² This approach has been particularly detrimental to dengue prevention and control because in most countries surveillance is very poor; the passive surveillance systems relied on to detect increased transmission are dependent upon reports by local physicians, who often have a low index of suspicion for dengue and do not consider it in their differential diagnosis of dengue-like illness. As a result, epidemics have often reached or passed peak transmission before they are detected, and emergency control measures are implemented, always too late to have any impact on the course of the epidemic.²²

Disease Prevention and Prospects for the Future

The prevention of epidemic DEN/DHF has become more urgent with the expanding geographic distribution and increased disease incidence in the past 20 years. Unfortunately, tools available to prevent dengue infec-

tion are very limited. There is no vaccine currently available (see below) and options for mosquito control are not good.

Effective vaccination to prevent DEN/DHF will likely require a tetravalent, live attenuated vaccine. Live, attenuated vaccine candidates for all four dengue virus serotypes have been developed, and have been evaluated in phase I and II trials in Thailand.³⁵ Moreover, promising progress has been made on developing second generation, recombinant dengue vaccines using cDNA infectious clone technology.³⁶ Development of new technology such as DNA vaccines is in its infancy. Despite the promising progress, however, it is unlikely that an effective, safe and economical dengue vaccine will be available for general use for at least 10 years. Prospects for reversing the trend of increased epidemic DEN/DHF in the near future, therefore, are not good. New dengue virus strains and serotypes will likely continue to move in infected air travellers between population centres where *Aedes aegypti* occurs, resulting in continued hyperendemicity, increased frequency of epidemic activity and increased incidence of DHF if effective prevention programmes are not implemented without delay. This will require changing the emergency response mentality of government officials, public health professionals and the public, to one of disease prevention.

Prevention and control of DEN/DHF currently depends on controlling the mosquito vector, *Aedes aegypti*, in and around the home, where most transmission occurs. As noted above, space sprays with insecticides to kill adult mosquitoes are not usually effective.^{22,32,33} The most effective way to control the mosquitoes that transmit dengue is larval source reduction, i.e. eliminating or cleaning water-holding containers that serve as the larval habitats for *Aedes aegypti* in the domestic environment.²²

There are two approaches to effective *Aedes aegypti* control that use the larval source-reduction approach. In the past, the most effective programmes have had a vertical, paramilitary organizational structure, with a large staff and budget. The successful American programmes in the 1950s and 1960s were also facilitated by the availability of residual insecticides such as DDT that contributed to ridding the mosquito from the domestic environment. Unfortunately, these vertical programmes have had poor sustainability because once the mosquito and the disease were controlled, limited health resources were moved to other competing programmes and the *Aedes aegypti* population usually rebounded to levels where epidemic transmission occurred. The most recent example of this lack of sustainability is Cuba, where *Aedes aegypti* had been effectively controlled and dengue transmission prevented since 1981. The vertically structured Cuban programme has recently failed because of

lack of support; the result was a major dengue epidemic in 1997.

In recent years emphasis has been placed on community-based, integrated approaches to larval source reduction to provide programme sustainability.²² The rationale is that sustainable *Aedes aegypti* control can only be accomplished by the people who live in the houses where transmission occurs, and who help create the mosquito larval habitats by their life-styles.²² Community participation and community ownership of prevention programmes require extensive social marketing of dengue prevention, with health education and community outreach. Unfortunately, this approach is a very slow process, and it will take years for effective disease control to be achieved through community participation alone. It has, therefore, been proposed that a combination top-down and bottom-up approach be used, the former to achieve immediate success and the latter to provide programme sustainability.²² The effectiveness of this approach, however, is not yet known.

In addition to community-based, integrated mosquito control, effective, sustainable prevention programmes for DEN/DHF must include several other components.³⁷ First, an active, laboratory-based surveillance system that can provide early warning for epidemic activity is essential. Health officials in dengue endemic areas must know at any point in time where dengue transmission is occurring, what serotypes are being transmitted and the severity of illness associated with dengue infection.^{37,38} Moreover, there must be effective use of surveillance data with information exchange and international cooperation. A second component of an effective prevention programme is a rapid response contingency mosquito control plan to prevent an incipient epidemic when the surveillance system predicts increased dengue transmission. Political and financial support to implement this rapid response in a timely manner is critical to preventing major epidemics of DHF. A third component of a sustainable prevention programme is education of the medical community on clinical diagnosis and management of DHF cases. Experience has shown that case fatality rates can be kept acceptably low if physicians and nurses understand the pathophysiologic changes that occur in DHF; early diagnosis and effective management are the keys to preventing fatalities in this disease.⁷

As noted above, sustainability of prevention programmes will depend on decreasing the reliance on government mosquito control agencies and the transfer of more responsibility for *Aedes aegypti* control to the occupants of houses in urban areas where most dengue transmission occurs. This will require community participation and community ownership of the programme, but does not absolve the government of its disease prevention responsibility; the government and commu-

nity should work in partnership to achieve effective disease prevention. There is a great need for research to develop more effective disease prevention strategies, including new mosquito control technology and dengue vaccines, and on the epidemiology and disease pathogenesis of DEN/DHF. Lastly, there is a desperate need to improve the public health infrastructure in disease endemic countries to support community-based, integrated prevention programmes. Only with these changes will we be able to reverse the trend of emergent epidemic DEN/DHF in the 21st century.

REFERENCES

- Plant A E. Infecting ourselves: How environmental and social disruptions trigger disease. Worldwatch paper No. 129. Washington DC: Worldwatch Institute, 1996.
- Knudsen A B, Sloof R. Vector-borne disease problems in rapid urbanization: New approaches to vector control. Bull WHO 1992; 70:1-6.
- Gubler D J. Dengue. In: Monath TP, editor. Epidemiology of Arthropod—Borne Viral Disease. Chapter 23. Vol. II. Boca Raton, Florida, USA: CRC Press Inc, 1988:223-60.
- Siler J F, Milton W H, Hitchens A I. Dengue. In: Its History, Epidemiology, Mechanism of Transmission, Etiology, Clinical Manifestations, Immunity, and Prevention. Manila, Philippines: Bureau of Printing, 1926:1-302.
- Gubler D J, Suharyono W, Lubis I, Eram S, Gunarso S. Epidemic dengue 3 in Central Java, associated with low viremia in man. Am J Trop Med Hyg 1981; 30:1094-9.
- Gubler D J, Suharyono W, Tan R, Abidin M, Sie A. Viraemia in patients with naturally acquired dengue infection. Bull WHO 1981; 59:623-30.
- Anonymous. Dengue haemorrhagic fever: diagnosis, treatment and control. Geneva: WHO, 1986.
- Halstead S B. Dengue hemorrhagic fever-public health problem and a field for research. Bull WHO 1980; 58:1-21.
- Rosen L. The Emperor's new clothes revisited, or reflections on the pathogenesis of dengue hemorrhagic fever. Am J Trop Med Hyg 1977; 26:337-43.
- Gubler D J, Trent D W. Emergence of epidemic dengue/dengue hemorrhagic fever as a public health problem in the Americas. Infect Agents Dis 1994; 2:383-93.
- Barnes W J S, Rosen L. Fatal hemorrhagic disease and shock associated with primary dengue infection on a pacific island. Am J Trop Med Hyg 1974; 23:495-506.
- Gubler D J. Dengue and dengue hemorrhagic fever in the Americas. Puerto Rico Health Sci J 1987; 6:107-11.
- Gubler D J. Dengue and dengue hemorrhagic fever in the Americas. In: Thoncharoen P, editor. Dengue Hemorrhagic Fever. Reg Pub No 22. New Delhi, India: WHO Monograph, SEARO, 1993:9-22.
- Meltzer M I, Rigau-Perez J G, Clark G G, Reiter I, Gubler D J. Using DALYs to assess the economic impact of dengue in Puerto Rico: 1984-1994. Am J Trop Med Hyg 1998 (In press).
- Rosen L. Dengue-An overview. In: Mackenzie J S, editor. Viral Diseases in Southeast Asia and the Western Pacific. Sydney, Australia: Academic Press, 1982:484-93.
16. Gubler D J, Clark G G. Dengue/dengue hemorrhagic fever: The emergence of a global health problem. Emerg Infect Dis 1995; 1:55-7.
17. Monath T F. Dengue: The risk to developed and developing countries. Proc Natl Acad Sci USA 1994; 91:2395-400.
18. Halstead S B. The XXth Century dengue pandemic: need for surveillance and research. World Health Stat Q 1992; 45:292-8.
19. Soper FL, Wilson D B, Lima S, Antunes W S. The organization of permanent nationwide anti-Aedes aegypti measure in Brazil. New York: The Rockefeller Foundation, 1943.
20. Schliessman D J, Calheiros L B. A review of the status of yellow fever and Aedes aegypti eradication programs in the Americas. Mosquito News 1974; 34:1-9.
21. PAHO (Pan American Health Organization). Dengue in the Caribbean, 1977. Proceedings of a Workshop Held in Montego Bay; Jamaica, 8-11 May, 1978. Washington DC: PAHO Sci Publ, 1979:375.
22. Gubler D J. Aedes aegypti and Aedes aegypti-borne disease control in the 1990s: top down or bottom up. Am J Trop Med Hyg 1989; 40:571-8.
23. Ehrenkranz N J, Ventura A K, Cuadrado R R, Pond W L, Porter J E. Pandemic dengue in Caribbean countries and the southern United States—past, present and potential problems. N Engl J Med 1971; 285:1460-9.
24. Rosen L. Dengue type 3 infection in Panama. Am J Trop Med Hyg 1974; 23:1205-6.
25. Gubler D J. Dengue and dengue hemorrhagic fever: Its history and resurgence as a global public health problem. In: Gubler D J, Kuno G, editors. Dengue and Dengue Hemorrhagic Fever. London, UK: CAB International Press, 1997:1-22.
26. Kouri G I, Guzman M G, Bravo J R, Triana C. Dengue haemorrhagic fever / dengue shock syndrome: Lessons from the Cuban epidemic, 1981. Bull WHO 1989; 67:375-80.
27. Lewis J A, Chang G J, Lanciotti R S, Kinney R M, Mayer L W, Trent D W. Phylogenetic relationships of dengue-2 viruses. Virology 1993; 197:216-24.
28. Rico-Hesse R. Molecular evolution and distribution of dengue viruses type 1 and 2 in Nature. Virology 1990; 174:479-93.
29. PAHO (Pan American Health Organization). Dengue hemorrhagic fever in Venezuela. Epidemiol Bull 1990; 11:7-9.
30. CDC (Centers for Disease Control). Imported dengue-United States, 1993-1994. MMWR Morb Mortal Wkly Rep 1995; 44:353-6.
31. Lanciotti R S, Lewis J G, Gubler D J, Trent D W. Molecular evolution and epidemiology of dengue-3 viruses. J Gen Virology 1994; 75:65-75.
32. Newton E A C, Reiter I. A model of the transmission of dengue fever with an evaluation of the impact of ultra-low volume (ULV) insecticide applications on dengue epidemics. Am J Trop Med Hyg 1992; 47:709-20.
33. Reiter P, Gubler D J. Surveillance and control of urban dengue vectors. In: Gubler D J, Kuno G, editors. Dengue and Dengue Hemorrhagic Fever. Chapter 20. London, UK: CAB International Press, 1997:425-62.
34. Gubler D J. Arboviruses as imported disease agents: The need for increased awareness. Arch Virol 1996; 11:21-32.
35. Bhamarapravati N, Yoksan S. Live attenuated tetravalent dengue vaccine. In: Gubler D J, Kuno G, editors. Dengue and Dengue Hemorrhagic Fever. Chapter 17. London, UK: CAB International Press, 1997:367-77.
36. Kinney R M, Butrapet S, Chang G-J, Tsuchiya K R, Roehrig J T, Bhamarapravati N, et al. Construction of infectious cDNA clones for dengue 2 virus: strain 16681 and its attenuated vaccine derivative, strain PDK-53. Virology 1997; 230:300-8.
37. Gubler D J, Casta-Valez A. A program for prevention and control of epidemic dengue and dengue hemorrhagic fever in Puerto Rico and the US Virgin Islands. Bull PAHO 1991; 25:237-47.
38. Rigau J G, Gubler D J. Surveillance for dengue and dengue hemorrhagic fever. In: Gubler D J, Kuno G, editors. Dengue and Dengue Hemorrhagic Fever. Chapter 19. London, UK: CAB International Press, 1997:405-23.