

# Dengue in the Americas and Southeast Asia: Do they differ?

Scott B. Halstead<sup>1</sup>

**Suggested citation** Halstead SB. Dengue in the Americas and Southeast Asia: Do they differ? *Rev Panam Salud Publica*. 2006;(6):407–15.

## ABSTRACT

*The populations of Southeast Asia (SE Asia) and tropical America are similar, and all four dengue viruses of Asian origin are endemic in both regions. Yet, during comparable 5-year periods, SE Asia experienced 1.16 million cases of dengue hemorrhagic fever (DHF), principally in children, whereas in the Americas there were 2.8 million dengue fever (DF) cases, principally in adults, and only 65 000 DHF cases. This review aims to explain these regional differences. In SE Asia, World War II amplified *Aedes aegypti* populations and the spread of dengue viruses. In the Americas, efforts to eradicate *A. aegypti* in the 1940s and 1950s contained dengue epidemics mainly to the Caribbean Basin. Cuba escaped infections with the American genotype dengue-2 and an Asian dengue-3 endemic in the 1960s and 1970s. Successive infections with dengue-1 and an Asian genotype dengue-2 resulted in the 1981 DHF epidemic. When this dengue-2 virus was introduced in other Caribbean countries, it encountered populations highly immune to the American genotype dengue-2. During the 1980s and 1990s, rapidly expanding populations of *A. aegypti* in Brazil permitted successive epidemics of dengue-1, -2, and -3. These exposures, however, resulted mainly in DF, with surprisingly few cases of DHF. The absence of high rates of severe dengue disease in Brazil, as elsewhere in the Americas, may be partly explained by the widespread prevalence of human dengue resistance genes. Understanding the nature and distribution of these genes holds promise for containing severe dengue. Future research on dengue infections should emphasize population-based designs.*

## Key words

Arboviruses; dengue, dengue fever; dengue hemorrhagic fever; genetics; Americas; Asia, Southeastern.

In some respects the epidemiology of dengue viruses in the Americas re-

sembles that in geographic Southeast Asia (SE Asia, i.e., Myanmar, Thailand, Laos, Cambodia, Viet Nam, the Philippines, Malaysia, Singapore, and Indonesia). Four dengue viruses (DENV) of Asian origin are endemically transmitted in the urban cycle by *Aedes aegypti*. But, after decades of hyperendemicity in both regions, human

disease patterns (Table 1) (1–3) are markedly different. The predominant clinical expression in the Americas is dengue fever (DF) in adults, whereas in SE Asia, severe dengue illness has been seen largely in infants and children. Numerous large series of cases from SE Asian countries have described the clinical syndromes that

<sup>1</sup> Pediatric Dengue Vaccine Initiative-Research, 5824 Edson Lane, Rockville, Maryland 20852, United States of America. Send correspondence and reprint requests to: Scott B. Halstead, Pediatric Dengue Vaccine Initiative-Research, 5824 Edson Lane, Rockville, MD 20852, United States of America; telephone: (301) 984 8704; fax: (301) 984 4423; e-mail: halsteads@erols.com

**TABLE 1. Numbers of dengue cases in Southeast Asia and the tropical Americas reported to World Health Organization (WHO) regional offices during 5-year periods of high endemicity, 1996–2005<sup>a</sup>**

Years	Regions	Population × 1000	Dengue fever	Dengue hemorrhagic fever	Deaths	Case fatality rate
2001–2005	Americas <sup>b</sup>	499 800	2 814 691	65 235	789	1.21% <sup>c</sup>
1996–2000	Southeast Asia	510 700		1 155 165 <sup>d</sup>	8 558	0.74% <sup>e</sup>

<sup>a</sup> Cases from the Americas are from the Pan American Health Organization (1). Cases from Indonesia, Myanmar, and Thailand are from the WHO Southeast Asia Regional Office (2). Cases from the Philippines, Viet Nam, Cambodia, Laos, Malaysia, and Singapore are a personal communication from the Dr. Kevin Palmer, Communicable Diseases Officer, Western Pacific Regional Office, WHO, Manila, the Philippines. Population data for 2000 are from the World Fact Book (3).

<sup>b</sup> Excludes the United States of America and Canada.

<sup>c</sup> Case fatality rates were: Brazil, 5.6%; Venezuela, 0.2%; Colombia, 0.6%; Nicaragua, 0.6%.

<sup>d</sup> Dengue fever and dengue hemorrhagic fever are not reported separately. Data from largest countries are hospital-based.

<sup>e</sup> Case fatality rates were: Cambodia, 3.1%; Indonesia, 2.4%; Myanmar, 1.6%; Philippines, 1.3%; Thailand, 0.28%; Viet Nam, 0.19%.

have been reported to the World Health Organization (WHO) for many years (4–7). Hospitalized cases and deaths attributed to dengue and reported to WHO regional offices have been published and updated since the 1980s (8–11). In populations of roughly equal size, dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) attack rates are 18-fold greater in SE Asia than in the Americas. Yet, outbreaks of classical DHF/DSS have occurred in the Americas, most notably in Cuba, after the introduction of DENV-2 in 1981 following the widespread DENV-1 epidemic of 1977, which occurred in a largely susceptible population (12). By contrast, in Brazil, which accounts for as much as 80% of contemporary dengue cases in the Americas, the sequential introduction of DENV-1, -2, and -3 was accompanied not by DHF but, predominantly, by DF in adults (13, 14).

These contrasting profiles raise two important questions: Why is the epidemiology of dengue diseases in the Americas so heterogeneous, and why does the predominant clinical expression of the disease in the Americas differ from that in SE Asia? This paper seeks answers to these two questions by examining the specific history of dengue infections in the two regions, and in light of what is known about the

virus- and host-related mechanisms that control the severity and clinical expression of dengue infections.

## MATERIAL AND METHODS

For more than 30 years, the author has systematically collected and published reports submitted to the WHO summarizing global hospitalizations and deaths due to dengue (8, 10, 11). As a member of the Faculty of 1000, director of a major dengue research program, referee for 15 high-impact scientific journals, and textbook author, he continuously reviews the dengue literature. This paper is not a comprehensive summary of dengue reports from two regions, but a perspective on current epidemiological research efforts that incorporates lessons learned from the author's research experience.

## HISTORY

### The Americas

During the 19th century, dengue outbreaks were common in port cities of the Caribbean, and in North, Central, and South America. The etiology of these outbreaks is unknown. The public health history of the 20th cen-

ture is one of mounting pressure against *A. aegypti*, beginning with the campaigns in Cuba during the Spanish-American war, in Panama during construction of the Canal, in Brazil with the work of Oswaldo Cruz, and the key city strategy of the Rockefeller Foundation. These efforts culminated in the 1950s with eradication campaigns mounted by the Pan American Health Organization (PAHO) (15). Possibly as a result of these efforts, only a single dengue virus seems to have remained in circulation by the middle of the 20th century. This virus, American genotype DENV-2 (genotype V), was recovered in 1953 in Trinidad and Tobago from a patient with DF (16). Despite the absence of a DF outbreak at the time, DENV-2-neutralizing antibodies were highly prevalent in sera obtained from residents born before World War II (16, 17). DENV-2-neutralizing antibodies have also been found in this same age group in residents of Cuba and Panama (18, 19). This widespread prevalence of DENV-2 antibodies correlates with the large number of DF outbreaks reported to PAHO early in the 20th century (20).

In spring 1963, with the relaxation of intensive vector control, the Western Hemisphere experienced its first dengue importation, in Jamaica. This epidemic was caused by DENV-3 genotype V, a virus of Asian origin. By August 1963, cases were observed in Puerto Rico, and over the subsequent six months the disease spread throughout the Caribbean islands and to Venezuela (21). Both DENV-2 and -3 were transmitted in much of that area for at least the following 15 years. For example, there was a sharp outbreak of classical DF due to DENV-2 in Puerto Rico in 1969. Many cases were accompanied by a secondary-type dengue antibody response (20). There was endemic DENV-2 transmission in Puerto Rico from 1970 to 1977 (22), and the same virus produced large outbreaks of DF in Colombia in 1968–1969 and 1975–1976, and in Venezuela in 1969, all producing disease in adults (23, 24). In all these countries during this period, infections must have occurred in

the sequence of American genotype DENV-2 followed by DENV-3, and vice versa. These phenomena remained virtually unstudied.

In 1977, an Asian DENV-1 (genotype III) was introduced. It produced massive epidemics in Cuba, Jamaica, Puerto Rico, and Venezuela, and quickly spread throughout the Caribbean islands, Mexico, Texas, Central America, and northern South America (25). During the 1977 epidemic in Puerto Rico, in addition to DENV-1, many strains of DENV-2 and -3 were isolated. Secondary infections in the sequence DENV-2–DENV-1 or DENV-3–DENV-1 must have occurred in great number, but the only syndrome observed continued to be DF in adults. Although secondary infection with DENV-1 does cause DHF/DSS in SE Asia, the exact sequence that produces severe disease is not known (6).

In 1981, both DENV-4 genotype I and DENV-2 genotype III were introduced into the Caribbean. DENV-4 spread rapidly westward to other Caribbean islands, then to Mexico, Central America, and northern South America (Caribbean Basin) (26). DENV-2 was introduced into Cuba from SE Asia, possibly from Viet Nam, and from there to the Caribbean basin and throughout tropical America (22).

In Brazil, the decade of the 1970s witnessed the reinvasion of *A. aegypti*. This permitted the intrusion in 1981 of DENV-1 and DENV-4 into Roraima state, in the North (13, 14). By 1986, DENV-1 caused a sharp outbreak of DF in Rio de Janeiro, then spread towards the Northeast and Midwest regions, where it remains endemic (27). In 1990, DENV-2 genotype III was reported in Rio de Janeiro, from whence it spread across the country, becoming endemic in some areas (13, 28). In 2002, DENV-3 produced a major epidemic, initially in Rio de Janeiro and later throughout the country (1, 29). In Rio de Janeiro, 62 deaths and many cases of DHF were reported. However, the predominant clinical expression throughout Brazil was still DF in adults (13). Remarkably, DENV-4 has not yet penetrated most of Brazil.

In 1994, DENV-3 genotype III was first detected in Central America, from whence it spread to other areas in the Caribbean Basin and beyond (26). After dropping from sight for nearly 20 years, American genotype DENV-2 virus reemerged in Iquitos, Peru, in 1995 (30). While not a dominant feature, DHF/DSS in children is a growing problem in several Central American and northern South American countries (31–34).

### Southeast Asia

Multiple dengue viruses have been endemic in SE Asia for a long time. It is known, for example, that in the 1920s, types 1 and type 4 dengue viruses were given to human volunteers in the Philippines (35–37). In contrast to developments in the Americas, no specific large-scale campaign was waged against *A. aegypti*. However, mosquito populations were controlled in some areas of Asia during the colonial era (e.g., in cantonment areas of British India) through the adoption of effective antimosquito hygienic practices (38).

An ecological catastrophe—World War II—altered the epidemiology of dengue in SE Asia permanently. The war spread dengue viruses among combatants and civilians alike throughout Asia and the Pacific Basin. The destruction of cities, the need to house refugees, and the abandonment of the colonial system resulted in enormously increased populations of *A. aegypti*. Population growth in cities resulted in increased numbers of human hosts for dengue infection, with the outcome that all four dengue viruses became endemic (26). The onset of the modern pandemic of DHF/DSS was documented as early as 1950 in Bangkok, Thailand (39), but was first reported in print in the Philippines in 1954 (40). The authors of this first report were impressed by the severity of gastrointestinal hemorrhages and the resemblance of the disease to cases of a hemorrhagic fever among United Nations troops in the Korean War, and named this new disease “epidemic he-

morrhagic fever.” Soon the terms “Philippine” and “Thai hemorrhagic fever” were in use. By 1958, dengue viruses were established as the etiology of this severe disease (41).

In the 1960s in Thailand, the modal age of children with DHF admitted to the hospital was 5 years, and cases in adults were unknown (1). At that time, the average annual dengue infection rate was estimated at 15% per year, with 50% of children experiencing one or more dengue infections by age 5 years, while nearly all 20-year-olds had antibodies to all four dengue viruses (42–44).

More recently, strong economic growth in many countries coupled with improved housing standards and vector control programs have reduced *A. aegypti* populations, thus decreasing annual dengue infection rates (45, 46). During the same period the modal age at which children in Thailand are hospitalized with DHF/DSS has increased (Figure 1) (10, 47). Reduced annual dengue infection rates also resulted in adults who were susceptible to primary or secondary dengue infections, and the “emergence” of dengue disease in adults (11, 48).

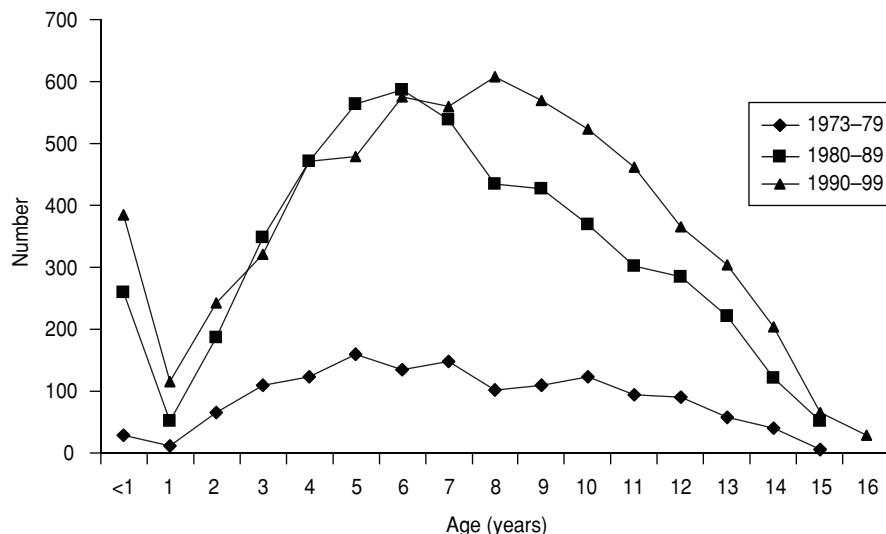
### FACTORS INFLUENCING THE EXPRESSION OF DENGUE DISEASE

One of the key mysteries of the biology of dengue viruses is why some humans are sickened by a dengue infection whereas others are not. An even more pressing question is why a few people develop severe, potentially fatal disease whereas most persons infected with dengue do not. Some of the more important observations on the factors correlated with dengue disease outcomes are described briefly below.

#### The role of age during primary infection

In children, initial infection with any dengue virus varies in expression from inapparent to mild disease,

**FIGURE 1. Distribution of age at hospitalization of patients admitted with serologically confirmed dengue hemorrhagic fever or dengue shock syndrome to the Queen Sirikit National Institute of Child Health, Bangkok, Thailand, for the periods 1973–79, 1980–89, and 1990–99<sup>a</sup>**



<sup>a</sup> Information supplied by Dr. Ananda Nisalak, Armed Forces Research Institute of the Medical Sciences, Bangkok, Thailand; personal communication, 2002.

whereas in adults the disease is often overt, and is most often classical DF. Clinic-based studies provide evidence that in SE Asia, primary DENV-2 or DENV-4 infections in children are usually silent (49, 50). However, the older the child, the more DF-like the dengue illness is (31). In experimental infections of susceptible adults, dengue types 1, 2, and 4 resulted in more than 80% overt DF cases (35, 36, 51). In a small series, DENV-3 consistently produced DF in susceptible volunteers (Dr. W Sun, Director, San Juan Laboratory, Centers for Disease Control, Puerto Rico; personal communication). There are good records of large DENV-1 DF outbreaks in susceptible Americans and Japanese during World War II in the Pacific, and more recently, in residents of Brazil, Cuba, Peru, and Hawaii (25, 30, 51–53). Some dengue strains do not consistently produce overt disease in adults. Infections caused by DENV-2 genotype III in susceptible Cuban children and adults were predominantly silent (54). After World War II, dengue infection rates steadily increased in SE Asia, resulting in solidly immune adults and scant records of DF outbreaks (44).

### The role of age during secondary infections

In humans who have a second dengue infection, age is an intrinsic risk factor for vascular permeability. Documentation of age susceptibility was made possible in the 1981 Cuban DENV-2 outbreak, because children aged 3 years and older, as well as adults through the age of 40 years, were all equally exposed to DENV-1 followed by DENV-2 infection 4 years later (18). Among those infected both times, the youngest children were at the greatest risk of increased vascular permeability (55). It is important to emphasize that adults who experienced secondary DENV-2 infections developed a mix of mild and severe disease. In 1997, for example, 5 208 adults infected with DENV-1 followed by DENV-2 at an interval of 20 years developed 24 DF cases for each single case of DHF/DSS (5 003 cases of DF versus 205 cases of DHF/DSS) (54).

When two or more dengue viruses are endemic, the overall dengue infection rate determines the age at which individuals develop severe dengue disease. This phenomenon was ex-

plored in a mathematical model, which showed that the rate of second dengue infections correlates with the modal age at hospitalization for DHF/DSS. When infection rates are low, the modal age at which children are admitted to hospital is high, and vice versa (43). Recently, the modal age at hospital admission for DHF in Bangkok has increased (Figure 1). This increase is consistent with observations that community-wide dengue infection rates are decreasing (47, 56). In Thailand, overt DF cases and a few DHF/DSS cases have begun to appear in adults (6).

### Sequence of secondary infections

Each of the four dengue viruses has been shown to cause DHF/DSS during a secondary dengue infection (3). In theory, a second dengue infection may occur in any of 12 possible sequences (1–2, 1–3, 1–4, etc.). Unfortunately, the precise sequence that causes severe illness is rarely known. Several population-based studies have demonstrated that between 2% and 4% of children who have a secondary dengue infection have severe illnesses requiring hospitalization (57). For each person hospitalized there are three to five additional children with milder illnesses (58). The only established pathogenic sequences are those observed in epidemics in isolated settings, or infections monitored longitudinally in a cohort population. Classical DHF/DSS has occurred with infections in the sequence DENV-1 followed by DENV-2 (18), DENV-3–DENV-2, or DENV-4–DENV-2 (59), and DENV-1–DENV-3 (60, 61). The introduction in 2001–2002 of DENV-3 genotype III in Havana, Cuba, resulted in dengue infections in the sequence DENV-1–DENV-3 or DENV-2–DENV-3. Infections caused by the sequence DENV-1–DENV-3 were accompanied by DHF/DSS cases, whereas DENV-2–DENV-3 infections produced DF in a few patients (61). Secondary infections with DENV-1 and -4 were accompanied by DHF/DSS (6), but the specific initial infection is not known.

Some infection sequences have not resulted in DHF/DSS. After 1977, DENV-1 was transmitted among persons immune to DENV-2 and -3 without producing DHF/DSS. In another instance, in the Americas from 1963 to 1977, many persons must have been infected in the sequence DENV-2–DENV-3 genotype V, but without developing DHF/DSS.

### Dengue virus virulence

Different strains of the same virus appear to vary in their ability to cause either DF or inapparent infections. To describe the association of disease during infection with a microorganism, the term “pathogenicity” is often used. Differences in viral pathogenicity are illustrated by responses to DENV-2 infections in susceptible adults. For example, Sabin and Schlesinger observed overt DF in susceptible volunteers infected with DENV-2 New Guinea C virus, as did physicians in Singapore during an outbreak of a DENV-2 cosmopolitan genotype (51, 62, 63). In contrast, no disease accompanied primary infections with DENV-2 genotype III strains in the 1997 Cuban outbreak (54). This latter strain might be referred to as non-pathogenic.

An explanation frequently given for the occurrence of DHF/DSS is that the infecting virus is “virulent” whereas viruses that cause only DF are “non-virulent.” Virulence is best understood as a quantitative outcome of infection, an expression of the ratio of disease to total infections. For example, rabies is a classical virulent virus: nearly all infections result in death. The closer this ratio is to 1, the more virulent the virus. The American genotype DENV-2 is said to be “non-virulent” (64), on the basis of laboratory observations that the ability of this virus to grow in cell cultures and mosquitoes was reduced. From these observations it has been predicted that in nature, this virus will be poorly transmitted by mosquitoes, and the disease in humans will be mild (65–67). However, these predictions

are not consistent with epidemiological observations. In 1995, a large epidemic of American genotype DENV-2 occurred in the Amazonian city of Iquitos, Peru (30). This virus was very likely transported up the Amazon River to Peru, a process probably accompanied by silent infections. This implies efficient transmission of this virus between humans and mosquitoes, and efficient transmission by geographically dispersed and genetically distinct populations of *A. aegypti*.

There are no ground rules for defining virulence in the two-infection context, because host susceptibility may be modified by a previous dengue infection. An alternative explanation for the failure of the American genotype DENV-2 to cause DHF is the observed cross-neutralization of this virus by DENV-1 antibodies. A very large proportion of human anti-DENV-1 sera from Iquitos residents significantly neutralized American genotype DENV-2 viruses (30, 68). It is possible that these cross-neutralizing antibodies, although not able to prevent DENV-2 infection, may decrease the severity of secondary infections and thus prevent DHF/DSS (see below).

### The protective effect of heterotypic dengue immunity

Sabin was the first to demonstrate in human volunteers that heterotypic immunity can prevent disease by a different dengue virus. This was observed when DENV-2 was given at an interval of less than 3 months after DENV-1 (51). Heterotypic neutralizing antibodies raised after a first dengue infection correlated with reduced disease severity during a second DENV-2 infection (69). In fact, high levels of heterotypic neutralizing antibodies rendered secondary DENV-2 infections largely inapparent. In 1990, DENV-1 became endemic in Iquitos, Peru. In 1995, a large proportion of the population was infected by American genotype DENV-2; most infections were silent. In a sizable study, sera from individuals infected only

with DENV-1 significantly neutralized American genotype DENV-2 viruses but not SE Asia genotypes (68). Additional evidence of the same phenomenon was observed in DENV-1-immune *Aotus* monkeys, which were protected from viremia with American genotype DENV-2 but not with an Asian genotype III DENV-2 virus (70).

### Disease enhancement by passively-acquired dengue antibodies

A unique observation in human medicine is that infants born to dengue-immune mothers in SE Asia regularly develop classical DHF/DSS during their very first dengue infection (71, 72). It is known that the mothers of these infants had multiple previous dengue infections, and that IgG<sub>1</sub> dengue antibodies are transferred via the placenta to the infant (73). This is an extremely important observation because it provides a unitary explanation for severe dengue disease, i.e., enhanced dengue viral infections of mononuclear phagocytes by exposure to infectious dengue virus-antibody complexes. This phenomenon is regularly demonstrated in vitro, and has been reproduced in rhesus monkeys (macaques) during second dengue infections, and in animals infected after receiving dengue antibodies passively, in vivo (74, 75). Hospital series in all large countries of SE Asia document 5% of total DHF/DSS cases to occur in infants with primary dengue infections (56). The clinical course, cytokine profile, and treatment requirements of DHF/DSS in infants are identical to those in children who acquire the disease during second dengue infections (76–78).

This clinical phenomenon has also been reported in Nicaragua, where typical cases in infants were observed with the same epidemiological profile as in SE Asia (32). The endemicity of multiple dengue viruses in many countries implies that this clinical group should be observed frequently, but in fact, infant DHF/DSS is not widely recognized in the Americas.

## Ethnicity and severe secondary dengue infections

Observations on dengue epidemiology in the Americas and in Africa suggest the possibility that the outcome of dengue infection is under host genetic control. During the DHF/DSS epidemics of 1981, 1997, and 2001–2 in Cuba, the hospitalization rates for blacks was consistently lower than those for whites (18, 54, 79). However, dengue infection rates of whites and blacks were the same (18). In Haiti, a country in which all four dengue viruses of the Asian genotypes are transmitted at high rates, DHF/DSS in children was predicted to occur but was not observed (80). The major DF outbreaks reported throughout the Caribbean islands over the past several decades have not been reported from Haiti, while during the same period DF was documented in visitors (81). These observations support the existence of one or more dengue resistance genes in black populations.

## DISCUSSION

### Why is the epidemiology of dengue in the Americas so heterogeneous?

The most glaring heterogeneities in the Americas are seen between the DHF/DSS epidemics in Cuba in 1981, 1997, and 2001–2. Each seems to be based upon the same historical accident in 1977, when DENV-1 infected a largely susceptible population in Cuba. The population was susceptible because DENV-2 genotype V and DENV-3 genotype V viruses failed to enter Cuba during the decades of the 1950s to the 1970s. Outside Cuba, in other Caribbean islands, and in Central America and northern South America, the prevalence of antibodies to DENV-2 and -3 viruses was probably quite high. Evidence of this was demonstrated by the lower number of mutations accumulated by DENV-2 compared to DENV-4 viruses, both introduced in 1981 (82). This observation suggests that DENV-4 was transmitted at a significantly higher rate

than DENV-2, the spread of which was retarded by high levels of pre-existing immunity to DENV-2. A possible explanation for why DHF/DSS did not immediately occur when DENV-2 infections spread outside Cuba is that only a small fraction of Caribbean Basin residents were monotypically immune to DENV-1. Infection with two or more dengue viruses greatly reduces the risk of DHF (57). Unfortunately, the seroepidemiological studies that might have documented this phenomenon were never conducted. Undoubtedly, infections in sequences such as DENV-1–DENV-2 have occurred since the 1970s in the Americas, as evidenced by the hospitalization of children for DHF/DSS in urban areas of Central America, Venezuela, and Colombia. Severe disease accompanies secondary DENV-4 infections in SE Asia, but the precise sequences involved are not known. The relative absence of severe secondary DENV-4 disease in the Americas remains unexplained.

### Why does the predominant clinical disease expression in the Americas differ from that in Southeast Asia?

One reason for the lower rates of DHF/DSS in the Americas compared to SE Asia may be the failure of clinicians in the Americas to collect sufficient data to fulfill the requirements for the WHO case definition (83). It has been noted that patients with dengue infections may not have platelet counts below 100 000/mm<sup>3</sup>, and acute-phase hematocrit values do not always demonstrate 20% hypovolemia. A frequent problem is that convalescent hematocrit values required to estimate the degree of hemoconcentration are often not available to compare with acute-phase values. Differences in laboratory test methods and the frequency of test performance may account for many of the reported difficulties.

It is also possible that children in Central America, Venezuela, and Colombia may not experience as severe vascular permeability during sec-

ondary dengue infections as children in SE Asia. Evidence suggesting this possibility can be found in the consistently low case fatality rates in American countries reporting DHF (Table 1) (31, 33). Because severe dengue is relatively new to parents and physicians in the Americas, high case fatality rates might have been expected based upon experiences in SE Asia.

Patients who are in dengue shock are in danger of dying if critical care is delayed. Resuscitation is often delayed if patients must be transported long distances to a hospital, or if the signs and symptoms of pre-shock are not recognized early by family members or physicians (84). In the 1960s, case fatality rates in Thailand and Viet Nam were 10% or higher. Both countries mounted intensive national programs to educate parents to seek early medical attention for their febrile children, and to make health system improvements in triage, implementation of vigorous early care, and avoidance of overhydration of patients with DHF/DSS (85). In Asia, improved case management is due at least in part to the stationing of hematocrit centrifuges on critical care wards so that intravenous infusion rates can be regulated by ward nurses on the basis of serial microhematocrit determinations (86). Due to system-wide changes in many SE Asian countries, case fatality rates have fallen steadily since the 1980s (11, 85).

There are no viral or immunological mechanisms that can be invoked to satisfactorily explain the absence of major outbreaks of DHF/DSS in Brazil. Such an outbreak should have occurred when DENV-2 genotype III viruses were introduced in 1990, four years after a large DENV-1 epidemic. Large DHF/DSS outbreaks should have occurred again when DENV-3 was introduced into a population in which persons with monotypic DENV-1 immunity might still have been found. Infection with DENV-1 followed by DENV-2 viruses, known to have circulated in Brazil at a four-year interval, exactly reproduced the conditions that led to DHF/DSS in Cuba. The absence of major epidemics

of DHF/DSS seems likely to be related to a high prevalence of dengue resistance genes in Brazil. The possibility of dengue resistance genes occurring in black populations has been predicted based upon observations made in Cuba and Haiti (54, 80). Human genetic resistance to severe dengue may operate to reduce the severity of disease arising from second dengue infections elsewhere in the Caribbean and along the northern coast of South America. Black populations are not conspicuously large in urban areas of Central America, or in central Colombia and Venezuela, where DHF/DSS is reported.

Virtually nothing is known about dengue resistance gene(s) in Africans. Is the gene dominant or recessive? Is it equally distributed in different African genetic groupings? Are the manifestations of DF suppressed by this gene, or does the gene selectively dampen dengue vasculopathy? The latter notion is an interesting possibility, because the origin of this gene may be resistance to yellow fever. The yellow fever virus is enzootic in Africa, and is transmitted to humans from infected subhuman primates (several members of the genus *Stegomyia*), and between humans after the virus has entered the urban *A. aegypti* cycle. Pri-

mary infection with yellow fever virus results in a disease that is remarkably similar to DHF/DSS, although with greater involvement of the liver (87). Yellow fever severity is not enhanced by previous heterotypic flavivirus infection.

To answer some of the questions raised in this paper there is an urgent need for accelerated research in dengue, particularly to understand infections in open populations. Prospective cohort studies and seroepidemiological methods are likely to shed light on the heterogeneity of dengue in populations living in the Western and Eastern hemispheres.

## REFERENCES

- Pan American Health Organization. Number of reported cases of dengue and dengue hemorrhagic fever, region of the Americas. Washington, D.C.: PAHO; 2001–2005. Available from: <http://www.paho.org/english/ad/dpc/cd/dengue-cases>. Accessed 10 December 2006.
- World Health Organization, Southeast Asia Regional Office. Number of reported dengue cases of DF/DHF in SEAR countries, 1985–2005. New Delhi: SEARO; 1996–2000. Available from: [http://www.searo.who.int/linkfile/dengue\\_Tb/1\\_SEARO\\_Countrywise\\_dengue\\_cases](http://www.searo.who.int/linkfile/dengue_Tb/1_SEARO_Countrywise_dengue_cases). Accessed 10 December 2006
- United States of America, Central Intelligence Agency. World fact book. Available from: <http://www.cia.gov/cia/publications/factbook>. Accessed 18 October 2006.
- Nimmannitya S, Halstead SB, Cohen S, Margiotta MR. Dengue and chikungunya virus infection in man in Thailand, 1962–1964. I. Observations on hospitalized patients with hemorrhagic fever. *Am J Trop Med Hyg.* 1969;18(6):954–71.
- Cohen SN, Halstead SB. Shock associated with dengue infection. I. Clinical and physiologic manifestations of dengue hemorrhagic fever in Thailand, 1964. *J Pediatr.* 1966;68:448–56.
- Nisalak A, Endy TP, Nimmannitya S, Kalayanaroj K, Thisyakorn U, Scott RM, et al. Serotype-specific dengue virus circulation and dengue disease in Bangkok, Thailand from 1973 to 1999. *Am J Trop Med Hyg.* 2003;68:191–202.
- Wills BA, Dung NM, Loan HT, Tam DTH, Thuy TTN, Minh LTT, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *New Eng J Med.* 2005;353:877–89.
- Halstead SB. Dengue haemorrhagic fever—a public health problem and a field for research. *Bull World Health Organ.* 1980;58(1):1–21.
- Halstead SB. Global epidemiology of dengue hemorrhagic fever. *Southeast Asian J Trop Med Public Health.* 1990;21:636–41.
- Halstead SB. Global epidemiology of dengue: Health systems in disarray. *Trop Med.* 1993;35:137–46.
- Halstead SB. Epidemiology of dengue and dengue hemorrhagic fever. In: Gubler DJ, Kuno G, eds. *Dengue and dengue hemorrhagic fever*. Wallingford: CAB; 1997. Pp. 23–44.
- Kouri G, Guzman MG, Bravo J. Hemorrhagic dengue in Cuba: history of an epidemic. *Bull Pan Am Health Organ.* 1986;20:24–30.
- Siqueira JBJ, Turchi Martelli CM, Evalim Coelho G, da Rocha Simplicio AC, Hatch DL. Dengue and dengue hemorrhagic fever, Brazil, 1981–2002. *Emerg Infect Dis.* 2005;11:48–53.
- Neto RJP, Lima DM, de Paula SO, Lima CM, Rocco IM, Fonseca BAL. Molecular epidemiology of type 1 and 2 dengue viruses in Brazil from 1988 to 2001. *Braz J Med Biol Res.* 2005;38:843–52.
- Strode GK, ed. *Yellow fever*. New York: McGraw-Hill Book Company; 1951.
- Anderson CR, Downs WG. Isolation of dengue virus from a human being in Trinidad. *Science.* 1956;124:224–5.
- Theiler M, Downs WG. *The arthropod-borne viruses of vertebrates*. New Haven, London: Yale University Press; 1973.
- Guzman MG, Kouri GP, Bravo J, Soler M, Vazquez S, Morier L. Dengue hemorrhagic fever in Cuba, 1981: a retrospective seroepidemiologic study. *Am J Trop Med Hyg.* 1990;42:179–84.
- Rosen L. Observations on the epidemiology of dengue in Panama. *Am J Hyg.* 1958;68:45–58.
- Likosky WH, Calisher CH, Michelson AL, Correa-Coronas R, Henderson BE, Feldman RA. An epidemiologic study of dengue type 2 in Puerto Rico, 1969. *Am J Epidemiol.* 1973;97(4):264–75.
- Neff JM, Morris L, Gonzalez-Alcover R, Coleman PH, Lyss SB, Negron H. Dengue fever in a Puerto Rican community. *Am J Epidemiol.* 1967;86:162–84.
- Lopez-Correa RH, Moore CG, Sather GE, Morens DM, Chiriboga J, Banegura F, et al. The 1977 dengue epidemic in Puerto Rico: epidemiological and clinical observations. In: Pan American Health Organization. *Dengue in the Caribbean*. Washington, D.C.: PAHO, 1979. Pp. 60–7.
- Groot H, Morales A, Romero M, Vidales H, Donaldson CL, Marquez G, et al. Recent outbreaks of dengue in Colombia. In: PAHO, ed. *Dengue in the Caribbean, 1977*. Washington D.C.: Pan American Health Organization, 1979. Pp. 31–9.
- Llopis A, Travieso R, Addimandi V. Dengue in Venezuela. In: Pan American Health Organization. *Dengue in the Caribbean, 1977*. Washington, D.C.: PAHO, 1979. Pp. 83–6.
- Pan American Health Organization. *Dengue in the Caribbean, 1977*. Washington, D.C.: PAHO; 1978.
- Gubler DJ. Dengue and dengue hemorrhagic fever: its history and resurgence as a global public health problem. In: Gubler DJ, Kuno G, eds. *Dengue and dengue hemorrhagic fever*. New York: CAB International; 1997. Pp. 1–22.
- Nogueira RM, Schatzmayr HG, Miagostovich MP, Farias MF, Farias Filho JD. Virological study of a dengue type 1 epidemic at Rio de

- Janeiro. Mem Inst Oswaldo Cruz. 1989;83:219-25.
28. Nogueira RM, Miagostovich MP, Schatzmayr HG, Moraes GC, Cardoso MA, Ferreira J, et al. Dengue type 2 outbreak in the south of the state of Bahia, Brazil: laboratorial and epidemiological studies. Rev Inst Med Trop Sao Paulo. 1995;37(6):507-10.
  29. Nogueira RM, Schatzmayr HG, de Filippis AM, dos Santos FB, da Cunha RV, Coelho JO, et al. Dengue virus type 3 in Brazil, 2002. Emerg Infect Dis. 2005;11:1376-81.
  30. Watts DM, Porter KR, Putvatana P, Vasquez B, Calampa C, Hayes CG, et al. Failure of secondary infection with American genotype dengue 2 to cause dengue haemorrhagic fever. Lancet. 1999;354(9188):1431-4.
  31. Mendez A, Gonzalez G. [Dengue haemorrhagic fever in children: ten years of clinical experience]. Biomedica. 2003;23:180-93.
  32. Hammond SN, Balmaseda A, Perez L, Tellez Y, Saborio SI, Mercado JC, et al. Differences in dengue severity in infants, children, and adults in a 3-year hospital-based study in Nicaragua. Am J Trop Med Hyg. 2005;73:1063-70.
  33. Balmaseda A, Hammond SN, Perez L, Tellez Y, Saborio SI, Mercado C, et al. Serotype-specific differences in clinical manifestations of dengue. Am J Trop Med Hyg. 2006;74:449-56.
  34. Larru Martinez B, Quiroz E, Bellon JM, Esquivel R, Nieto Guevara J, Saez-Llorens X. Dengue pediátrico en Panama. An Pediatr (Barc). 2006;64:517-22.
  35. Siler JF, Hall MW, Hitchens AP. Dengue: its history, epidemiology, mechanism of transmission, etiology, clinical manifestations, immunity, and prevention. Philipp J Sci. 1926;29:1-304.
  36. Simmons JS, St. John JH, Reynolds FHK. Experimental studies of dengue. Philipp J Sci. 1931;44(1-2):1-252.
  37. Halstead SB. Etiologies of the experimental dengues of Siler and Simmons. Am J Trop Med Hyg. 1974;23(5):974-82.
  38. Halstead SB. Dengue and hemorrhagic fevers of Southeast Asia. Yale J Biol Med. 1965;37:434-54.
  39. Halstead SB, Yamarat C. Recent epidemics of hemorrhagic fever in Thailand. Observations related to pathogenesis of a "new" dengue disease. J Am Pub Health Assoc. 1965;55(9):1386-95.
  40. Quintos FN, Lim LE, Juliano L, Reyes A, Lacson P. Hemorrhagic fever observed among children in the Philippines. Philippin J Pediatr. 1954;3:1-19.
  41. Hammon WM, Rudnick A, Sather GE. Viruses associated with epidemic hemorrhagic fevers of the Philippines and Thailand. Science. 1960;131:1102-3.
  42. Halstead SB, Scanlon J, Umpaivit P, Udomsakdi S. Dengue and chikungunya virus infection in man in Thailand, 1962-1964: IV. Epidemiologic studies in the Bangkok metropolitan area. Am J Trop Med Hyg. 1969;18(6):997-1021.
  43. Fischer DB, Halstead SB. Observations related to pathogenesis of dengue hemorrhagic fever. V. Examination of age specific sequential infection rates using a mathematical model. Yale J Biol Med. 1970;42:329-49.
  44. Halstead SB. Immunological parameters of Togavirus disease syndromes. In: Schlesinger RW, ed. The togaviruses, biology, structure, replication. New York: Academic Press; 1980. Pp. 107-73.
  45. Ooi EE, Hart TJ, Tan HC, Chan SH. Dengue seroepidemiology in Singapore. Lancet. 2001;357(9257):685-6.
  46. Ooi EE, Goh KT, Gubler DJ. Dengue prevention and 35 years of vector control in Singapore. Emerg Infect Dis. 2006;12:887-93.
  47. Halstead SB. Dengue in the health transition. Kaohsiung J Med Sci. 1994;10(Suppl):S2-14.
  48. Ooi EE, Goh KT, Chee Wang DN. Effect of increasing age on the trend of dengue and dengue hemorrhagic fever in Singapore. Int J Infect Dis. 2003;7:231-2.
  49. Vaughn DW, Green S, Kalayanarooj S, Innis BL, Nimmannitya S, Suntayakorn S, et al. Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. J Infect Dis. 2000;181(1):2-9.
  50. Buchy P, Vo VL, Trinh TX, Glaziou P, Le TT, Le VL, et al. Secondary dengue virus type 4 infections in Vietnam. Southeast Asian J Trop Med Public Health. 2005;36:178-85.
  51. Sabin AB. Research on dengue during World War II. Am J Trop Med Hyg. 1952;1:30-50.
  52. Hotta S. Dengue epidemics in Japan, 1942-1945. J Trop Med Hyg. 1953;56:83-9.
  53. Schatzmayr HG. Dengue situation in Brazil by year 2000. Mem Inst Oswaldo Cruz. 2000;95(Suppl 1):179-81.
  54. Guzman MG, Kouri G, Valdes L, Bravo J, Alvarez M, Vazquez S, et al. Epidemiologic studies on dengue in Santiago de Cuba, 1997. Am J Epidemiol. 2000;152(9):793-9.
  55. Guzman MG, Kouri G, Bravo J, Valdes L, Vazquez S, Halstead SB. Effect of age on outcome of secondary dengue 2 infections. Int J Infect Dis. 2002;6:118-24.
  56. Halstead SB, Lan NT, Myint TT, Shwe TN, Nisalak A, Soegijanto S, et al. Infant dengue hemorrhagic fever: research opportunities ignored. Emerg Infect Dis. 2002;12:1474-9.
  57. Halstead SB. Neutralization and antibody-dependent enhancement of dengue viruses. In: Chambers TJ, Monath TP, eds. The flaviviruses: pathogenesis and immunity. New York: Elsevier Academic Press; 2003. Pp. 422-67.
  58. Endy TP, Chunsittivat S, Nisalak A, Libraty D, Green S, Rothman A, et al. Epidemiology of inapparent and symptomatic acute dengue virus infection: a prospective study of primary school children in Kamphaeng Phet, Thailand. Am J Epidemiol. 2002;156:40-51.
  59. Sangkawibha N, Rojanasuphot S, Ahandrik S, Viriyapongse S, Jatanasen S, Salitul V, et al. Risk factors in dengue shock syndrome: a prospective epidemiologic study in Rayong, Thailand. I. The 1980 outbreak. Am J Epidemiol. 1984;120:653-69.
  60. Endy TP, Nisalak A, Chunsittivat S, Vaughn DW, Green S, Ennis FA, et al. The relationship of pre-existing dengue virus neutralizing antibody levels to viremia and disease severity in a prospective cohort study of dengue in Thailand. J Infect Dis. 2004;189:990-1000.
  61. Alvarez M, Rodriguez-Roche R, Bernardo L, Vasquez S, Morier L, Gonzalez D, et al. Dengue hemorrhagic fever caused by sequential dengue 1-3 infections at a long interval: Havana epidemic, 2001-2002. Am J Trop Med Hyg. 2006;75:1113-7.
  62. Schlesinger RW, Gordon I, Frankel JW, Winter JW, Patterson PR, Dorrance WR. Clinical and serologic response of man to immunization with attenuated dengue and yellow fever viruses. J Immunol. 1956;77(5):352-64.
  63. Seet RCS, Ooi E, Wong HB, Paton NI. An outbreak of primary dengue infection among migrant Chinese workers in Singapore characterized by prominent gastrointestinal symptoms and a high proportion of symptomatic cases. J Clin Virol. 2005;33:336-40.
  64. Rico-Hesse R, Harrison LM, Salas RA, Tovar D, Nisalak A, Ramos C, et al. Origins of dengue type 2 viruses associated with increased pathogenicity in the Americas. Virology. 1997;230:244-51.
  65. Pryor MJ, Carr JM, Hocking H, Davidson AD, Li PX, Wright PJ. Replication of dengue virus type 2 in human monocyte-derived macrophages: comparisons of isolates and recombinant viruses with substitutions at amino acid 390 in the envelope glycoprotein. Am J Trop Med Hyg. 2001;65:427-34.
  66. Cologna R, Rico-Hesse R. American genotype structures decrease dengue virus output from human monocytes and dendritic cells. J Virol. 2003;77:3929-38.
  67. Cologna R, Armstrong PM, Rico-Hesse R. Selection for virulent dengue viruses occurs in humans and mosquitoes. J Virol. 2005;79:853-9.
  68. Kochel TJ, Watts DM, Halstead SB, Hayes CG, Espinosa A, Felices V, et al. Effect of dengue-1 antibodies on American dengue-2 viral infection and dengue haemorrhagic fever. Lancet. 2002;360:310-2.
  69. Kliks SC, Nisalak A, Brandt WE, Wahl L, Burke DS. Antibody-dependent enhancement of dengue virus growth in human monocytes as a risk factor for dengue hemorrhagic fever. Am J Trop Med Hyg. 1989;40(4):444-51.
  70. Kochel TJ, Watts DM, Gozalo AS, Ewing DF, Porter KH, Russell KL. Cross-serotype neutralization of dengue virus in *Aotus nancymae* monkeys. J Infect Dis. 2005;191:1000-4.
  71. Halstead SB. Observations related to pathogenesis of dengue hemorrhagic fever. VI. Hypotheses and discussion. Yale J Biol Med. 1970;42:350-62.
  72. Halstead SB, Nimmannitya S, Cohen SN. Observations related to pathogenesis of dengue hemorrhagic fever. IV. Relation of disease severity to antibody response and virus recovered. Yale J Biol Med. 1970;42:311-28.
  73. Kliks SC, Nimmannitya S, Nisalak A, Burke DS. Evidence that maternal dengue antibodies are important in the development of dengue hemorrhagic fever in infants. Am J Trop Med Hyg. 1988;38(2):411-9.
  74. Halstead SB, Chow J, Marchette NJ. Immunologic enhancement of dengue virus replication. Nature New Biol. 1973;243(122):24-6.
  75. Halstead SB. In vivo enhancement of dengue virus infection in Rhesus monkeys by passively transferred antibody. J Infect Dis. 1979;140(4):527-33.
  76. Hung NT, Lei HY, Lan NT, Lin YS, Huang KJ, Lien LB, et al. Dengue hemorrhagic fever in



- infants: a study of clinical and cytokine profiles. *J Infect Dis.* 2004;189:221–32.
77. Hung NT, Lan NT, Lei HY, Lien LB, Huang KJ, Lin CF, et al. Association between sex, nutritional status, severity of dengue hemorrhagic fever and immune status in infants with dengue hemorrhagic fever. *Am J Trop Med Hyg.* 2005;72:370–74.
78. Nguyen TH, Nguyen TL, Lei HY, Lin YS, Lien LB, Huang KJ, et al. Volume replacement in infants with dengue hemorrhagic fever/dengue shock syndrome. *Am J Trop Med Hyg.* 2006;74(5):684–91.
79. Rodriguez-Roche R, Alvarez M, Holmes EC, Bernardo L, Kouri G, Gould EA, et al. Dengue virus type 3, Cuba, 2000–2002. *Emerg Infect Dis.* 2005;11:773–4.
80. Halstead SB, Streit TG, Lafontant JG, Putvatana R, Russell K, Sun W, et al. Haiti: absence of dengue hemorrhagic fever despite hyperendemic dengue virus transmission. *Am J Trop Med Hyg.* 2001;65:180–3.
81. Ehrenkranz NJ, Ventura AK, Cuadrado RR, Pond WL, Porter JE. Pandemic dengue in Caribbean countries and the Southern United States—past, present and potential problems. *N Engl J Med.* 1971;285(26):1460–9.
82. Carrington CV, Foster JE, Pybus OG, Bennett SN, Holmes EC. The invasion and maintenance of dengue virus type 2 and type 4 in the Americas. *J Virol.* 2005;79:14680–7.
83. Hayes JM, Rigau-Perez JG, Reiter P, Effler PV, Pang L, Vorndam V, et al. Risk factors for infection during a dengue-1 outbreak in Maui, Hawaii, 2001. *Trans R Soc Trop Med Hyg.* 2006;199:559–66.
84. Nimmannitya S. Dengue hemorrhagic fever: diagnosis and management. In: Gubler DJ, Kuno G, eds. *Dengue and dengue hemorrhagic fever.* Cambridge: CAB International; 1997. Pp. 133–45.
85. Nguyen TN, Tran TT. Vietnam: orientation appropriée d'un hôpital pédiatrique dans un contexte de ressources limitées. *Med Trop (Mars).* 1995;55:275–80.
86. Nimmannitya S. Clinical spectrum and management of dengue haemorrhagic fever. *Southeast Asian J Trop Med Public Health.* 1987;18(3):392–7.
87. Rosen L, Khin MM, U T. Recovery of virus from the liver of children with fatal dengue: reflections on the pathogenesis of the disease and its possible analogy with that of yellow fever. *Res Virol.* 1989;140:351–60.

Manuscript received 13 June 2006. Revised version accepted for publication 1 December 2006.

## RESUMEN

### El dengue en las Américas y el sudeste asiático: ¿son diferentes?

Las poblaciones de Asia suroriental y de la América tropical son similares y los cuatro tipos de virus del dengue de origen asiático son endémicos en ambas regiones. Aun así, durante periodos quinquenales comparables ocurrieron 1,16 millones de casos de dengue hemorrágico (DH) en Asia suroriental, principalmente en niños, mientras que en las Américas ocurrieron 2,8 millones de casos de dengue, principalmente en adultos, y solo 65 000 casos de DH. El objetivo de esta revisión es explicar estas diferencias regionales. En el sudeste asiático, con la Segunda Guerra Mundial se extendieron las poblaciones del mosquito *Aedes aegypti* y se diseminó el virus del dengue. En las Américas, los esfuerzos para erradicar el *A. aegypti* en las décadas de 1940 y 1950 restringieron las epidemias de dengue principalmente a la cuenca del Caribe. Cuba escapó a las infecciones por el genotipo americano del dengue-2 y un endémico asiático del dengue-3 en las décadas de 1960 y 1970. Infecciones sucesivas con el virus del dengue-1 y un genotipo asiático del dengue-2 dio como resultado una epidemia de DH en 1981. Cuando este virus del dengue-2 se introdujo en otros países caribeños encontró poblaciones con un alto grado de inmunidad al genotipo americano del dengue-2. Durante las décadas de 1980 y 1990, la rápida expansión de las poblaciones de *A. aegypti* en Brasil favorecieron la aparición de epidemias sucesivas de dengue-1, dengue-2 y dengue-3. Estas, no obstante, provocaron principalmente casos de dengue con sorpresivamente pocos casos de DH. La ausencia de altas tasas de formas graves de dengue en Brasil y otros países de la Región puede explicarse en parte por la amplia presencia de genes humanos de resistencia al dengue. La comprensión de la naturaleza y de la distribución de estos genes crea grandes expectativas para frenar las formas graves de dengue. Las investigaciones futuras sobre la infección por los virus del dengue deben poner énfasis en diseños basados en la población.

## Palabras clave

Arbovirus, dengue, fiebre dengue hemorrágica, genética, las Américas, Asia sudoriental.