

Re-Emergence of Dengue and Emergence of Dengue Haemorrhagic Fever in the Americas

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Abstract

Dengue has been known in the Americas since the 18th century. During the 1960s and 1970s dengue pandemics occurred in the Caribbean, northern South America and Central America, and, during the 1980s and 1990s, virtually every country in the Americas experienced dengue epidemics. Dengue serotypes 1, 2 and 4 circulate widely and, since 1994, DEN-3 has circulated in Central America and Mexico.

The first epidemic of dengue haemorrhagic fever in the Americas occurred in Cuba in 1981 with the introduction of DEN-2 four years after an epidemic of DEN-1, resulting in 344 203 cases, of which 10 312 were severe cases with 158 deaths. Subsequently, occasional cases of DHF occurred in the Americas until 1989-1990 when an epidemic occurred in Venezuela with 3 108 DHF cases and 73 deaths. Between 1981 and 1996 a total of 42 246 cases of DHF and 582 deaths were reported by 25 countries. Countries which reported more than 1000 cases each were Venezuela, Cuba, Colombia, Nicaragua and Mexico.

Aedes aegypti, the vector of dengue in the Americas, was eradicated from 21 countries in the region during 1948-1972, but due to inadequate surveillance against re-infestation, these countries got infested again and suffered dengue epidemics. As of October 1997, all countries in the Americas, except Bermuda, Canada and Chile, are infested. *Aedes albopictus*, a vector of dengue in Asia, was first found in the Americas in 1985 and is now present in eight countries. Until now this mosquito has not been incriminated as a vector of any virus in the Americas.

In 1997 the Directing Council of the Pan American Health Organization (PAHO) called on the Member countries to follow the hemispheric plan to expand and intensify efforts to combat *Aedes aegypti* with a view to its eventual eradication in the Americas.

Historical overview

The first description of a dengue-like disease in the Americas relates to an outbreak that occurred in Philadelphia, U.S.A., in 1780⁽¹⁾. In the following century four large epidemics, which occurred during 1827-28, 1850-51, 1879-80 and 1897-99, affected Caribbean countries and the southern United States⁽²⁾. Interestingly, small-joint arthritis, including swelling, which are commonly found in infections associated with the arboviruses Chikun-gunya and Mayaro, were among the clinical manifestations observed during the dengue outbreaks between 1827-1880 but not during the ones which occurred after this period. In the first half of this century, four epidemics were reported in the same countries, the last one occurring during 1941-1946, which affected cities in the Texas Gulf, several Caribbean islands including Cuba, Puerto Rico and Bermuda, Mexico, Panama and Venezuela⁽²⁾. In Brazil, epidemics of dengue were recorded during 1846-1848 and 1851-1853. Since then, until 1982, only two outbreaks were reported in 1916 and 1923^(3,4). Peru reported cases of dengue during the 1950s but not in the following three decades⁽⁵⁾. In 1953, dengue virus, which was identified as DEN-2, was isolated for the first time in the Americas in the island of Trinidad. Several isolates of DEN-2 were obtained from persons in the same island during 1953-1954 but, interestingly, no outbreaks were reported in this period in Trinidad nor in any other Caribbean island⁽⁶⁾.

Re-emergence of dengue

During the 1960s two extensive pandemics of dengue affected the Caribbean and Venezuela. The first one which broke out in 1963 was due to DEN-3 and swept the Caribbean after almost 20 years of silence. Jamaica, Puerto Rico, islands of the Lesser Antilles and Venezuela were among the countries affected but, interestingly, Cuba, Hispaniola and Trinidad were spared in this outbreak. The second epidemic occurred in the Caribbean and Venezuela during 1968-1969, and although DEN-2 was pre-dominantly isolated, DEN-3 was also recovered from persons in some islands⁽²⁾. During the 1970s these two serotypes caused extensive epidemics in Colombia where dengue had not been recognized since 1952⁽⁷⁾. The first epidemic occurred during 1971-1972 and was due to DEN-2 whereas the 1975-1977 epidemic was associated with DEN-3. It was estimated that more than a half million persons became infected; however, both the outbreaks occurred 'silently' for the most part or were confused with other illnesses and did not attract much attention of the health authorities.

A milestone in the re-emergence of dengue in the Americas was the introduction of DEN-1 in 1977. This was followed by a devastating pandemic that lasted until 1980⁽⁸⁾. The virus was initially detected in Jamaica, possibly having been imported from Africa, and from there the epidemic spread to virtually every island of the Caribbean. The epidemic in South America began in 1978, affecting

Venezuela, Colombia, Guyana, Suriname and French Guiana. The epidemic in Central America was also detected in 1978 which affected Honduras initially and subsequently El Salvador, Guatemala and Belize. Spreading to the north the epidemic reached Mexico at the end of 1978 and during 1979-1980 continued to affect other Mexican states, and arrived in the state of Texas in the second half of 1980. About 702 000 cases were reported to the Pan American Health Organization (PAHO) for the period 1977-1980, but the incidence was much higher since estimates from Colombia, Cuba and Venezuela alone indicated that over five million persons were infected. In 1981, a DEN-4 strain, probably imported from Pacific islands, emerged in the Americas causing a series of outbreaks in the Caribbean, northern South America, Central America and Mexico. With some exceptions DEN-4 infection has generally been associated with mild disease⁽⁸⁾.

During the 1980s five countries in South America, namely, Brazil, Bolivia, Paraguay, Ecuador and Peru, that had not experienced dengue before or had been free of the disease for several decades were affected by explosive epidemics caused by DEN-1⁽⁸⁾; in the epidemic in Peru, DEN-4 was also isolated⁽⁹⁾. The first epidemic which occurred in the state of Roraima in northern Brazil in 1982 was associated with DEN-s 1 and 4⁽¹⁰⁾; vector control measures were implemented and, since then, no dengue activity was reported in this area until 1996. In 1986, DEN-1 was introduced in Rio de Janeiro, Brazil, causing major outbreaks⁽¹¹⁾. It was

subsequently disseminated to most states in Brazil. Following its introduction in those countries, DEN-1 virus has continued to cause major epidemics in Brazil, Ecuador and Peru in subsequent years.

During 1993 the last two tropical Latin American countries which had been free of dengue for several decades, namely, Costa Rica and Panama, reported indigenous transmission of dengue; the agent was DEN-1 and its introduction in Costa Rica was associated with severe outbreaks in this and subsequent years⁽¹²⁾. In 1994, DEN-3 was reintroduced in the Americas after an absence of 16 years when it was last isolated in Puerto Rico in 1978⁽¹³⁾. This serotype was initially detected in Panama and Nicaragua and, in the following year, it spread to other Central American countries and to Mexico, causing numerous epidemics of dengue. In Nicaragua, in 1994, the introduction of DEN-3 was associated with a countrywide epidemic of dengue/DHF but DEN-1 was also present. The introduction of DEN-3 in Mexico in 1995 coincided with an increased number of DHF cases; however, only DEN-1 and particularly DEN-2 were associated with DHF⁽¹⁴⁾. It should be noted that this DEN-3 virus belonged to the genotype that caused major epidemics of DHF in Sri Lanka and India in 1996. Since October 1997, DEN-3 has not been isolated outside Central America and Mexico.

The number of dengue and DHF cases reported annually in the Americas during the period 1980-1996 varied from 39 307 cases in 1984 to 388 591 cases in 1991.

An increase in the number of reports has been observed since 1994, especially in 1995 when over 315 000 cases were notified. In 1997 (as of October), over 270 000 cases had been reported.

The emergence of DHF

In 1981, Cuba reported the first major outbreak of DHF in the Americas⁽⁸⁾. Prior to this, suspected cases of DHF or fatal dengue cases had been reported by five countries or territories, namely, Venezuela, Jamaica, Honduras, Curacao and Puerto Rico, but only a few of them fulfilled the WHO criteria for the diagnosis of dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) and most were not laboratory-confirmed⁽⁸⁾. During the Cuban epidemic a total of 344 203 cases of dengue were notified, of which 10 312 were classified as severe cases (WHO grades II-IV) and 158 were fatal; a total of 116 143 patients were hospitalized, the majority of them during a three-month period⁽⁸⁾. The Cuban DHF epidemic was associated with a strain of DEN-2 virus and it occurred four years after DEN-1 had been introduced in the island causing epidemics of dengue fever and infecting almost half of the country's population.

The epidemic was rapidly brought under control and the last cases were reported in October 1981. *Aedes aegypti* was nearly eradicated from the island which became free of dengue virus circulation until 1997 when an outbreak broke out in the Santiago province, eastern Cuba. As of August 1997, 2 946 cases were reported, of which 205 were

DHF cases with 12 deaths, all of whom were adults (Cuban Ministry of Health, August 1997).

The outbreak of DHF/DSS in Cuba is the most important event in the history of dengue in the Americas. Subsequent to it, in every year except 1983, confirmed or suspected cases of DHF have been reported in the American region. A marked increase in the annual incidence occurred in 1989 which was due to a countrywide epidemic in Venezuela. This was the second major DHF epidemic in the Americas with 3 108 DHF cases and 73 deaths being reported between December 1989 and April 1990 when it was declared to be over. DEN-2 was the predominant serotype isolated from cases but DEN-s 1 and 4 were also recovered from patients; although no isolates were obtained from fatal cases, immunohistochemical analysis performed with formalin-fixed paraffin-embedded tissues of the fatal cases revealed the presence of DEN-2 antigen in the liver of four of them⁽¹⁵⁾. The epidemic recurred in the second half of 1990 and since then Venezuela has suffered epidemics of DHF every year.

Between 1981 and 1996 a total of 42 246 cases of DHF and 582 deaths were reported by 25 countries in the Americas. The figure below shows the distribution of cases by country where it can be observed that 22 170 (53%) of the reports originated from Venezuela. It can also be seen that, excluding Cuba and Venezuela, the number of cases by country varies from 1 to 3 929 cases. Colombia, Nicaragua and Mexico have each reported over 1 000 cases, most of

Figure. Number of Reported Cases and deaths of Dengue Haemorrhagic Fever in the Americas by country, 1981-1996*

them during the period 1992-1996. In Brazil, four fatal cases which exhibited fever, haemorrhages and shock, occurred during 1986-1987 and were associated with DEN-1 virus; confirmation was obtained by virus isolation or by antigen detection⁽¹⁶⁾. In 1990-1991 an outbreak of DHF was recorded in Rio de Janeiro, Brazil⁽¹⁷⁾, and 24 cases with 11 deaths occurred in the Brazilian state of Ceara⁽¹⁸⁾.

The age distribution of DHF cases in the Americas is different from that observed in Asia. In the outbreaks in Cuba and Venezuela, the disease occurred in all age groups, although children under 15 years of age comprised about two-thirds of the fatalities. Studies of DHF cases in Brazil that fulfilled WHO criteria⁽¹⁹⁾ showed a modal age range of 31-45 years. Obser-

vations made in Puerto Rico showed distinct age distribution patterns of cases that fulfilled WHO criteria: in 1986, two-thirds of the cases were under 15 years of age but during 1990-91 the mean age of patients was 38 years^(20,21). This age distribution pattern is different from that found in south-east Asia where predominantly young children are affected. It should be noted, however, that a marked increase in the number of DHF cases in persons over 15 years has been observed in the Philippines and Malaysia during recent years⁽²²⁾. Regarding the sex distribution, Cuba reported no significant female predominance - a finding that is in contrast with observations from Asia.

The epidemics of DHF in Cuba and Brazil were clearly associated with DEN-2 virus. In both countries DEN-1 had been introduced four years earlier, after a period of several decades of absence of dengue virus circulation. However, Cuba suffered a major epidemic of DHF while only relatively small outbreaks have been observed in Brazil. Other countries such as Peru and Ecuador have experienced a similar sequence of dengue infections with these serotypes but no DHF epidemics were recorded. A distinct epidemiological pattern was observed in Venezuela and in French Guiana where dengue was endemic for over 20 years before the emergence of their first epidemics of DHF in 1989-1990 and 1990-1991 respectively: DEN-2 was predominant in Venezuela⁽¹⁵⁾ and in French Guiana⁽²³⁾ and the only serotype found in the tissues of fatal cases in Venezuela⁽¹⁵⁾. Interestingly, in French Guiana, the DEN-2 strains isolated during the DHF outbreak and during an outbreak of dengue fever that occurred in 1986 were genetically similar and belonged to the Jamaican genotype which, in turn, has a genome sequence very close to DEN-2 strains from Viet Nam where DHF is highly endemic⁽²³⁾. These findings illustrate the complexity of the factors responsible for triggering DHF. Studies in Cuba suggested that individual risk factors for DHF include chronic diseases such as bronchial asthma, diabetes mellitus and sickle cell anaemia, and that race seems also to be important since DHF/DSS was more prevalent in white than in black persons⁽²⁴⁾.

Overall, the case fatality rate (CFR) of DHF in the Americas is 1.4% (Figure). However, a marked variation has been observed among countries. In 1995, the CFR ranged from 8.3% in Puerto Rico to 0.8% in Venezuela. This variation could be due to several factors such as reporting criteria, viral strain, case management, host genetic factors and possibly other causes.

Causes of the emergence/re-emergence

Factors contributing to the emergence/re-emergence of dengue/DHF include the rapid growth and urbanization of populations in Latin America and the Caribbean, increased travel of people which facilitates dissemination of dengue viruses, the circulation of all four dengue serotypes in the Americas thus increasing the risk of DHF in the Region, and the inadequacy of the vector control programmes.

Vector control

In 1947, PAHO was entrusted by its Directing Council to organize a hemispheric campaign to eradicate the mosquito *Aedes aegypti*. With the establishment of highly organized, centralized, vertical programmes with excellent supervision and adequate funding, 18 continental countries and several Caribbean island states had, by 1962, successfully achieved eradication. Unfortunately, after 1962, only three new countries eliminated the vector. Even more serious, however, was the fact that the countries that had achieved eradication became reinfested

with the vector in the 1960s and in subsequent decades. Countries still infested (the United States, Venezuela, Cuba and some other Caribbean islands) became sources of reinfestation for those that had eradicated the vector. When the reinfestations occurred, most countries had reduced their surveillance activities to a minimum, did not discover the new infestations until the vector was well established, and did not react with sufficient manpower and funding to eliminate the new infestations. Other reasons for the programme failure include reduced political support for the programmes, resulting in inadequate management and scarcity of trained technical personnel, resistance of *Ae. aegypti* to chlorinated insecticides, and high cost of materials, equipment and wages. There was a progressive dissemination of the vector so that, by 1997, with the exception of Canada, Chile and Bermuda, all countries in the Americas were infested. The practice of water storage in domestic settings due to the problem of water supply and the exponential growth of containers that can hold water (tyres, disposable containers) greatly contribute to the increase of vector densities favouring virus transmission.

Aedes albopictus, a secondary vector of dengue in Asia, was first found to be established in the Americas (in Texas, USA) in 1985. Subsequent infestations have been reported from Brazil (1986), Mexico (1993), Dominican Republic (1993), Guatemala (1995), Bolivia (1995, probably eliminated), Cuba (1995), El Salvador (1996) and the Cayman Islands (1997). Although this species is an efficient

laboratory vector of dengue, yellow fever and several other arboviruses, and has been found infected with Eastern Equine Encephalitis in Florida, it has not yet been implicated as a vector of any virus in the Americas. Thus, in Brazil where *Aedes albopictus* is now widespread, no specific efforts are made to combat it other than those in place against *Aedes aegypti*.

In 1985, PAHO approved a resolution which, for the first time, gave the countries the alternative of eradication, i.e. control of *Aedes aegypti*. During the next decade, this new control strategy of maintenance of vector populations at levels that did not present a significant public health threat, through the integration of chemical, biological and physical methods, education of the public and participation of the community, was developed and eventually set forth in 1994 in the document "Dengue and Dengue Hemorrhagic Fever in the Americas: Guidelines for Prevention and Control"⁽⁶⁾. However, as dengue and DHF continued to spread and increase, Brazil, in 1995, proposed that the strategy of hemispheric eradication be reconsidered, and the Directing Council of PAHO approved a resolution directing a task force to consider the feasibility, timeliness and appropriateness of drawing up a plan for eradication for the Americas. In 1996, this task force recommended that the plan be written, and the Directing Council directed the countries "to prepare national plans to expand and intensify efforts to combat *Aedes aegypti* with a view to its eventual eradication in the Americas" and that another task force prepare a hemispheric plan. This plan was formulated in 1997, and another resolution was passed

in September of that year directing the countries to carry out the Hemispheric Plan, with the following five steps:

- (1) Avoid epidemics of dengue, DHF and urban yellow fever;
- (2) Avoid outbreaks of dengue;
- (3) Interrupt transmission of dengue;
- (4) Eradicate *Aedes aegypti*, and
- (5) Establish sustainable surveillance against the re-infestation of areas free of *Aedes aegypti*.

The anti-*Aedes aegypti* programmes of the Americas have changed considerably since the days of the eradication campaigns. Most have become decentralized or are in the process of decentralizing, and have suffered much reduction in manpower and funding. In accordance with the Hemispheric Plan, each country will begin at the step that is appropriate to its own epidemiological and entomological situation and progress to the subsequent steps depending on its human and financial resources until eventually eradication is achieved and sustainable surveillance against reinfestation is maintained.

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