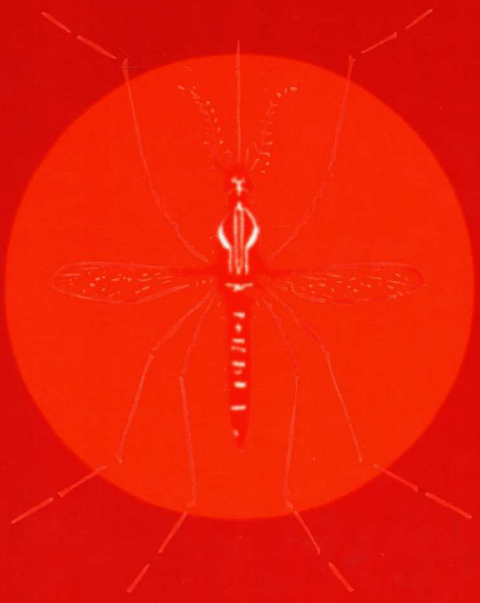

Dengue haemorrhagic fever

Diagnosis, treatment, prevention and control

2nd edition

World Health Organization
Geneva

Dengue haemorrhagic fever

Diagnosis, treatment, prevention and control

SECOND EDITION

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Preface

Dengue fever, and especially the more severe manifestation dengue haemorrhagic fever, ranks highly among new and newly emerging infectious diseases in public health significance and is considered to be the most important of the arthropod-borne viral diseases. Since the early 1970s, the World Health Organization (WHO) has been actively involved in developing and promoting strategies for the treatment and control of dengue. In 1986, WHO published a guide to the diagnosis, treatment and control of dengue haemorrhagic fever which has enjoyed popularity and been internationally recognized as an authoritative reference.

In resolution WHA46.31 the Forty-sixth World Health Assembly in 1993 confirmed that dengue prevention and control should be among the priorities of WHO. Global and regional strategies emphasizing the need for effective prevention, active surveillance and outbreak preparedness have since been developed. Three WHO Regional Offices have recently issued publications on dengue: in 1993, the Regional Office for South-East Asia (SEARO) published *Monograph on dengue/dengue haemorrhagic fever*; in 1994, the Regional Office for the Americas (PAHO) published *Dengue and dengue hemorrhagic fever in the Americas: guidelines for prevention and control*; and in 1995, the Regional Office for the Western Pacific (WPRO) published *Guidelines for dengue surveillance and mosquito control.*

This second edition of the 1986 book has been produced to make widely available to health practitioners, laboratory personnel, those involved in vector-control efforts and public health officials a concise publication of worldwide relevance containing practical information about dengue and dengue haemorrhagic fever. It offers in-depth, proven and easy-to-follow recommendations for the diagnosis and treatment of dengue and dengue haemorrhagic fever and provides a global perspective on the history, prevention, surveillance and control of dengue. While retaining key features of the original, the present edition furnishes some new information, particularly with respect to methods of laboratory diagnosis and vector surveillance and control.

Like the WHO regional publications, this book has benefited from the review of numerous experts within and outside WHO, as well as from the work of several international meetings addressing aspects of the global dengue problem. In particular, Dr Natth Bhamarapravati, Dr Duane Gubler, Dr Scott

Halstead, Dr Bruce Innis, Dr Suchitra Nimmanitya and Dr David Vaughn should be acknowledged for their kind assistance. It is hoped this publication will contribute to prevention and control of the morbidity and mortality due to dengue, and continue to serve as an authoritative reference for workers and researchers in the field.

Contents

CHAPTER 1

General considerations

Dengue fever (DF) is an acute febrile viral disease frequently presenting with headaches, bone or joint and muscular pains, rash and leukopenia as symptoms. Dengue haemorrhagic fever (DHF) is characterized by four major clinical manifestations: high fever, haemorrhagic phenomena, often with hepatomegaly and, in severe cases, signs of circulatory failure. Such patients may develop hypovolaemic shock resulting from plasma leakage. This is called dengue shock syndrome (DSS) and can be fatal.

Dengue[1] or dengue-like epidemics were reported throughout the nineteenth and early twentieth centuries in the Americas, southern Europe, North Africa, the eastern Mediterranean, Asia and Australia, and on various islands in the Indian Ocean, the south and central Pacific and the Caribbean. As discussed below, DF and DHF have steadily increased in both incidence and distribution over the past 40 years, and in 1996, 2500–3000 million people lived in areas potentially at risk for dengue virus transmission. Annually, it is estimated that there are 20 million cases of dengue infection, resulting in around 24 000 deaths. Annex 1 lists countries or territories by WHO Region in which DF or DHF is known to have occurred between 1975 and 1996. Figure 1.1 is a map illustrating the same information. Reported cases of DF and DHF for the period 1956–1995 are shown in Table 1.1.

Dengue in the South-East Asia and Western Pacific Regions of WHO

The disease now known as DHF was first recognized in the Philippines in 1953. The syndrome was etiologically related to dengue viruses when serotypes 2, 3 and 4 were isolated from patients in the Philippines in 1956; 2 years later dengue viruses of multiple types were isolated from patients during an epidemic in Bangkok, Thailand. During the next three decades, DHF/DSS was recognized in Cambodia, China, India, Indonesia, the Lao People's Democratic Republic, Malaysia, Maldives, Myanmar, Singapore, Sri Lanka, Viet Nam, and several Pacific Island groups.

[1] In this book "dengue" refers to the entire spectrum of dengue viral disease; abbreviations (i.e. DF, DHF, DSS) are used to refer to specific gradations of dengue.

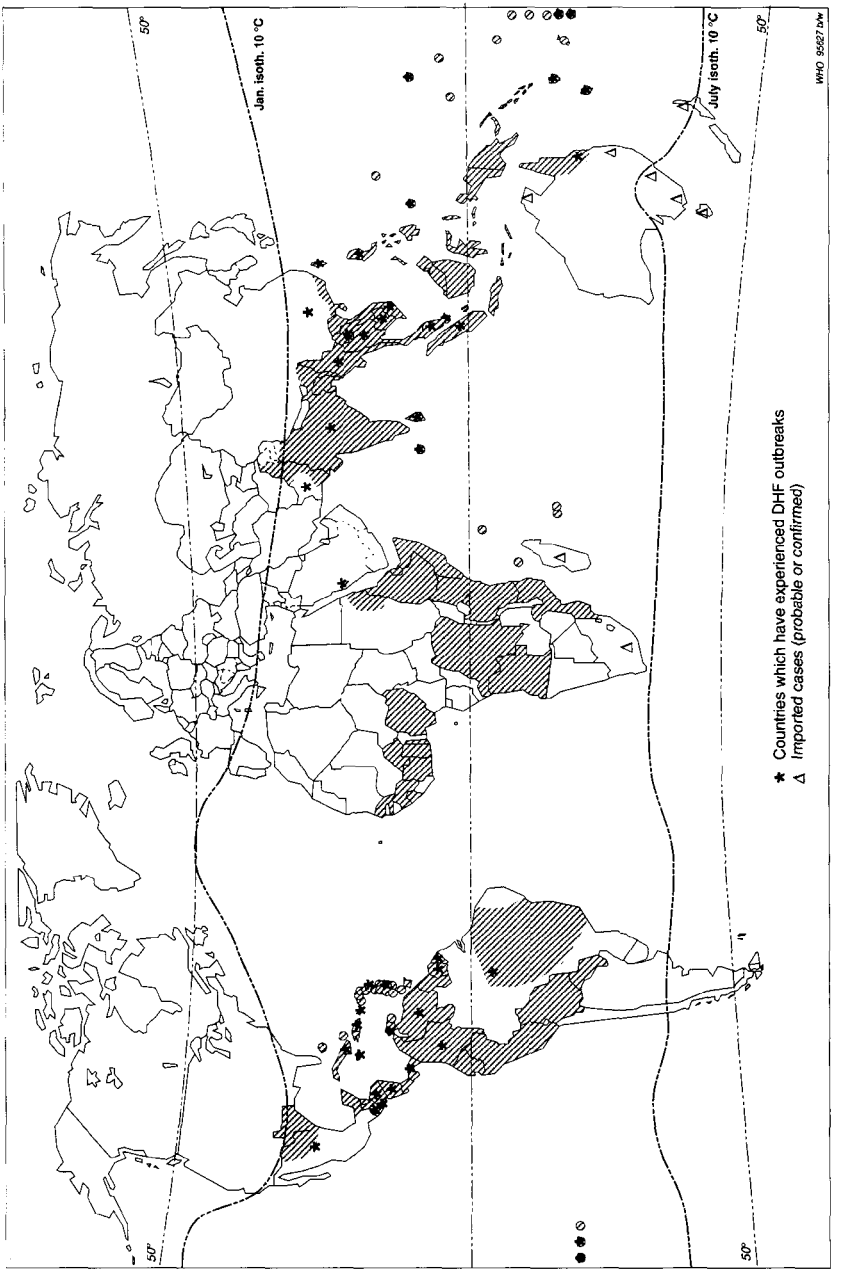


Fig. 1.1
The general distribution of dengue fever and/or dengue haemorrhagic fever, 1975–1996

Table 1.1
Global reports of dengue and dengue haemorrhagic fever, 1956–1995[a]

Time interval	No. years	No. cases	Mean no. cases per year
1956–1980	25	1547760	61910
1981–1985	5	1304305	260861
1986–1990	5	1776140	355228
1991–1995	5	1704050	340810

[a] Figures compiled from reports in WHO Regional Offices (AMRO, SEARO & WPRO).

During the 1960s and 1970s, DHF/DSS progressively increased as a health problem, spreading from its primary location in major cities to smaller cities and towns in endemic countries. It established seasonal and cyclical epidemic patterns, with large outbreaks occurring at 2–3 year intervals. During this period, 1070207 cases and 42808 deaths were reported, mostly in children. During most of the 1980s, in the endemic countries of China, Indonesia, Malaysia, Myanmar, Philippines, Thailand, and Viet Nam, DHF/DSS spread peripherally, affecting even rural villages. Exceptionally large outbreaks occurred in Viet Nam (354517 cases in 1987) and Thailand (174285 cases in 1987). The total number of people contracting and dying from DHF/DSS reported in all countries of the Western Pacific and South-East Asia Regions for the decade of the 1980s was 1946965 and 23793, respectively. Epidemiologically important new introductions of DHF/DSS were reported in China (1985), Maldives (1985), India (1988), New Caledonia (1988), Sri Lanka (1989) and Tahiti (1989). The experiences in India and Sri Lanka are particularly interesting, because virological surveillance documented the endemic transmission of all four dengue serotypes accompanied by DF cases, but not by DHF/DSS prior to the above-mentioned outbreaks.

In each country of these Regions where DHF has become endemic, the sequence has been more or less the same; frequent transmission of dengue virus, first associated with sporadic cases of DHF, followed by DHF epidemics which progressively become more frequent, until DHF cases are seen virtually every year, with major epidemics occurring at 3–5 year intervals. All four dengue serotypes are present in these two Regions, and increasing international travel serves to introduce new virus strains and serotypes rapidly into susceptible populations. In many countries, DF and DHF are primarily diseases of children, since they represent the largest segment of susceptible individuals within the population at risk. Increasingly, DF, and occasionally DHF, are also seen among travellers. DHF is now a significant public health problem in most of the countries in the tropical areas of the South-East Asia and Western Pacific Regions. The disease is among the ten leading causes of hospitalization and death in children in at least eight tropical Asian countries.

Dengue outbreaks in the Americas

Until 1981, only sporadic suspected cases of DHF had been reported in the Americas, although epidemics of classic DF occurred in the Caribbean and northern South America in 1963–64, 1968–69, 1972–75 and 1977–78. However, in 1981 an outbreak of DHF/DSS occurred in Cuba that marked the start of DHF in the Region of the Americas. During this epidemic, 344 203 cases of dengue were reported, including 10 312 patients classified as severely ill according to the WHO criteria (grades III and IV; see Chapter 2). During the same epidemic, 158 deaths, of which 101 were in children, were reported. In a 3-month period, 116 143 persons were hospitalized. The second largest outbreak of DHF/DSS in the Region occurred in Venezuela from October 1989 to April 1990. Moreover, the epidemic reappeared in the second half of 1990 and in each of the subsequent years up to and including 1993. A total of 11 260 cases of DHF and 136 deaths were reported in Venezuela during the period 1989–1993. Dengue virus serotypes 1, 2 and 4 were isolated during these outbreaks.

Cases of DHF or DHF-like disease have been reported in the Americas nearly every year since 1981. The countries or territories affected include Aruba, Barbados, Brazil, Colombia, the Dominican Republic, El Salvador, French Guiana, Guadeloupe, Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Panama, Puerto Rico, Saint Lucia, Suriname and Venezuela. Dengue has been recorded in virtually all Latin American countries, with the possible exceptions of Argentina, Chile and Uruguay, and it appears that DHF/DSS is gradually becoming endemic in several countries of the Americas, following the trend observed in Asia. The marked increase in DHF/DSS noted in several Asian countries during the past 30 years clearly illustrates what the Americas may face.

Dengue in the African and Eastern Mediterranean Regions

All countries with dengue virus transmission should be considered at risk for DHF outbreaks, and while there is comparatively little information on DF and DHF in the African and the Eastern Mediterranean Regions, it is nevertheless clear that they pose a growing threat there. Dengue disease has been prevalent in tropical Africa and has appeared episodically in the temperate regions of North Africa and the Mediterranean region of Europe. Since 1967, dengue virus has been reported in Angola, Burkina Faso, Comoros, Côte d'Ivoire, Democratic Republic of the Congo, Djibouti, Ethiopia, Ghana, Guinea, Kenya, Madagascar, Mauritius, Mozambique, Nigeria, Pakistan, Réunion, Saudi Arabia, Senegal, Seychelles, Sierra Leone, Somalia, Sudan and the United Republic of Tanzania. Some outbreaks have involved a large portion of the population, as for example the 1993 outbreak of serotype 1 in the Comoros, in which more than 60 000 people were estimated to have contracted dengue. The appearance of dengue in Pakistan in 1994 constituted the first epidemic of DHF in these Regions.

Economic impact of dengue

Few studies of the economic impact of DF and DHF/DSS have been conducted. Children most frequently suffer from DHF/DSS, with average hospital stays of 5–10 days for severe cases. Intensive care is required for severely ill patients, including intravenous fluids, blood or plasma transfusion and medicines, and adults can miss work in order to attend to their children's illness. Consequently, there are both direct and indirect costs for each dengue patient, ranging from inconvenience due to a sick child (or adult) with uncomplicated DF, to substantial costs for hospitalization and significant disruption of earning potential. In addition, there are costs to local municipalities for vector control activities, and often revenue lost through reduced tourism. The cost of the 1981 Cuban epidemic of DHF/DSS was estimated to be approximately US$ 103 million, which includes the cost of control measures (US$ 43 million) and medical services (US$ 41 million). As another example, DF and DHF/DSS epidemics in Puerto Rico since 1977 are estimated to have cost US$ 150–200 million. The direct costs that were estimated for the 1987 epidemic of DHF/DSS in Thailand, including hospitalization and mosquito control, were US$ 16 million. A 1995 report estimated that the annual economic burden due to DHF in Thailand ranges from US$ 19 million to US$ 51 million per year, depending on whether low or high levels of transmission occur. While the exact cost of each epidemic is difficult to calculate, it is clear that DF and DHF/DSS represent a significant economic burden on the societies affected.

Characteristics of dengue haemorrhagic fever outbreaks

Although the early outbreaks of DHF seem to have appeared suddenly in the Philippines and in Thailand, retrospective studies indicate that they were probably preceded by a decade or so in which cases occurred but were not recognized. In Thailand, outbreaks first occurred in Bangkok in a pattern with a 2-year cycle, then subsequently in irregular cycles as the disease spread throughout the country. DHF then became endemic in many large cities of Thailand, eventually spreading to smaller towns and villages during periods of epidemic transmission. A similar pattern was observed in Indonesia, Myanmar and Viet Nam.

During the 40 years' experience with dengue in the Western Pacific and South-East Asia Regions, two important epidemiological patterns have been recognized. First, DHF/DSS has appeared most frequently in areas where multiple dengue serotypes are endemic. The usual pattern is that of sporadic cases or small outbreaks in urban areas that steadily increase in size until there is an explosive outbreak that brings the disease to the attention of public health authorities. The disease then usually establishes a pattern of epidemic activity every 2–5 years. In addition, DHF/DSS is typically confined to children, with a modal age at hospitalization of 4–6 years. A second pattern is observed in areas of low endemicity. Multiple dengue serotypes may be transmitted at

relatively low rates of infection (below 5% of the population per year). In these areas, previously uninfected adults are susceptible to dengue infection, and children and young adults, with a modal age of 6–8 years, are also vulnerable.

A cyclical pattern of increased transmission coinciding with the rainy season has been observed in some countries. The interactions between temperature and rainfall are important determinants of dengue transmission, as cooler temperatures affect adult mosquito survival, thus influencing transmission rates. Furthermore, rainfall and temperature may affect patterns of mosquito feeding and reproduction, and hence the population density of vector mosquitos.

Although DHF may affect persons of all ages in dengue endemic areas, most DHF cases occur in children less than 15 years of age. Since 1964, the trend in Bangkok has been towards progressively lower attack rates (constant hospital admission rates despite an increasing population), with the modal age of hospitalized children being 6–7 years throughout Thailand. Surveillance data from some areas have suggested a slight excess of infected girls over boys, while other areas have shown an almost even distribution.

A retrospective evaluation of the impact of DHF during an outbreak in Bangkok/Thon Buri in May–November 1962 indicated that in a population of 870 000 children under 15 years of age, an estimated 150 000–200 000 minor febrile illnesses were caused by dengue and occasionally by chikungunya viruses; 4187 patients were hospitalized with DHF, and 4000 additional patients were treated in private clinics or at home. Moreover, shock occurred in about one-third of the hospitalized DHF patients. In the more recent large epidemic in Thailand in 1987, the attack rate of DHF/DSS was 320 cases per 100 000 population for all ages. In southern Viet Nam between 1975 and 1992, the attack rate of DHF/DSS ranged from 30 to 380 per 100 000 population, with mortality rates from 0.39 to 6.42 per 100 000 population, while the incidence of DHF in Indonesia for 1991 and 1992 was 11.56 and 9.45 per 100 000, respectively.

Transmission of dengue viruses

Dengue viruses are transmitted to humans through the bite of infected *Aedes* mosquitos, principally *Aedes aegypti*, and are therefore considered to be arboviruses (arthropod-borne viruses). Once infected, a mosquito remains infected for life, transmitting the virus to susceptible individuals during probing and feeding. Infected female mosquitos may also pass the virus to the next generation of mosquitos by transovarian transmission, but this occurs infrequently and probably does not contribute significantly to human transmission. Humans are the main amplifying host of the virus, although studies have shown that monkeys in some parts of the world may become infected and perhaps serve as a source of virus for feeding mosquitos. The virus circulates in the blood of infected humans at approximately the time that they have fever, and uninfected

mosquitos may acquire the virus if they feed on an individual when he or she is viraemic. The virus then develops in the mosquito for a period of 8–10 days before it can be transmitted to other humans during subsequent probing or feeding. The length of time required for this extrinsic incubation depends in part on environmental conditions, especially ambient temperature.

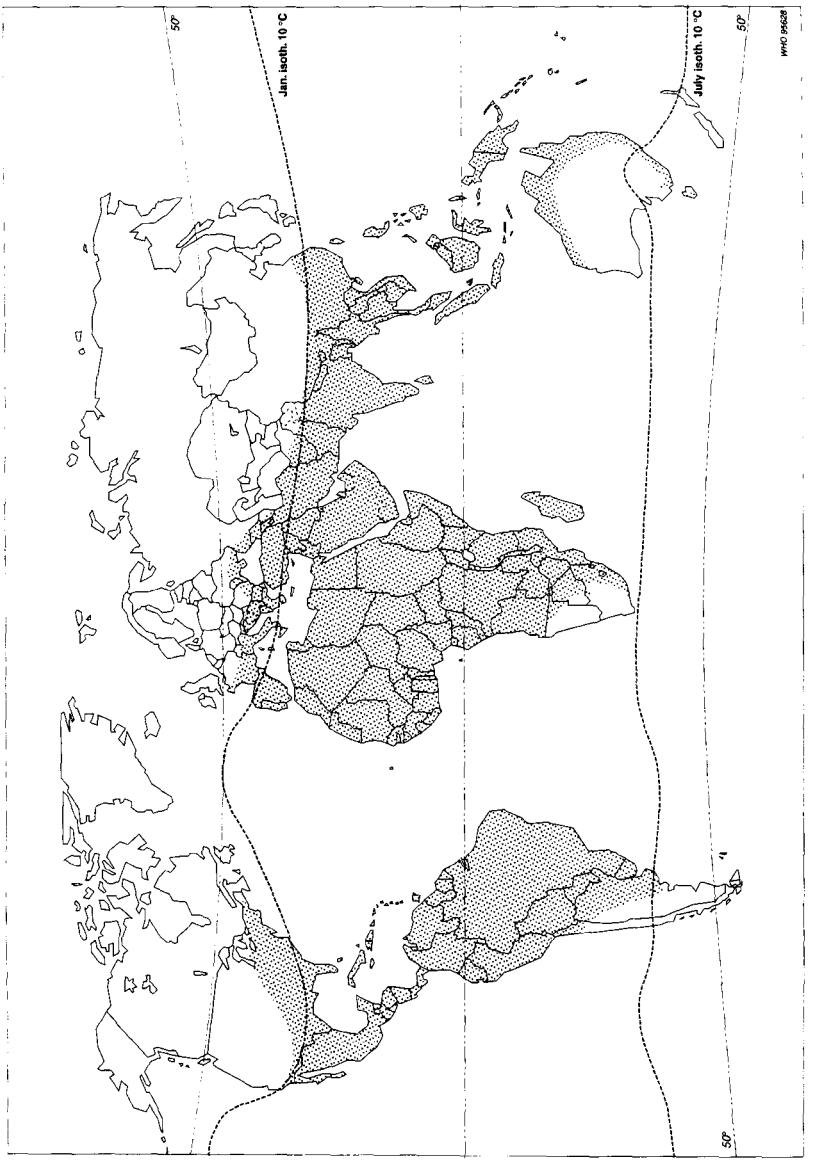
The virus

Dengue virus belongs to the family *Flaviviridae*. The four serotypes of dengue virus (designated DEN-1, DEN-2, etc.) can be distinguished by serological methods. Infection in humans by one serotype produces life-long immunity against reinfection by that same serotype, but only temporary and partial protection against the other serotypes. Dengue viruses share many characteristics with other flaviviruses, having a single-stranded RNA genome surrounded by an icosahedral nucleocapsid and covered by a lipid envelope. The virion is approximately 50 nm in diameter. The flavivirus genome is approximately 11 kb (kilobases) in length, and the complete genome sequence is known for isolates of all four serotypes of dengue virus. The genome is composed of three structural protein genes, encoding the nucleocapsid or core protein (C), a membrane-associated protein (M), an envelope protein (E) and seven non-structural (NS) protein genes. The domains responsible for neutralization, fusion and interactions with virus receptors are associated with the envelope protein. The order of proteins encoded is 5′-C-prM(M)-E-NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5-3′.

The vectors

Ae. aegypti is a tropical and subtropical species of mosquito found around the globe, usually between latitudes 35°N and 35°S, approximately corresponding to a winter isotherm of 10 °C as shown in Figure 1.2. Although *Ae. aegypti* has been found as far north as 45°N, such invasions have occurred during the warm season, and the mosquitos have not survived the winters. Distribution of *Ae. aegypti* is also limited by altitude. It is usually not found above 1000 m but has been reported at 2121 m in India, at 2200 m in Colombia, where the mean annual temperature is 17 °C, and at 2400 m in Eritrea. *Ae. aegypti* is one of the most efficient mosquito vectors for arboviruses, because it is highly anthropophilic and thrives in close proximity to humans and often lives indoors. Dengue outbreaks have also been attributed to *Ae. albopictus, Ae. polynesiensis*, and several species of the *Ae. scutellaris* complex. Each of these species has its own particular geographical distribution; however, they are less efficient epidemic vectors than *Ae. aegypti*. While vertical (possibly transovarian) transmission of dengue viruses has been demonstrated in both the laboratory and the field, the significance of this to maintenance of the virus has not been established. A factor complicating eradication of the vector is that *Ae. aegypti*

Fig. 1.2
Approximate actual and potential distribution of *Aedes aegypti*[a]



[a] The band between the 10 °C isotherms represents potential distribution.

eggs can withstand long periods of desiccation, sometimes for more than a year.

The host

In humans, each of the four dengue virus serotypes has been associated with DF and with DHF. Studies in Cuba and Thailand have shown a consistently high association between DEN-2 infection and DHF/DSS, but in the 1976–1978 Indonesia, 1980–1982 Malaysia, and 1989–90 Tahiti epidemics, and from 1983 onwards in Thailand, DEN-3 was the predominant serotype recovered from patients with severe disease. In the 1984 Mexico, the 1986 Puerto Rico, and the 1989 El Salvador outbreaks, DEN-4 was most often isolated from DHF patients. DSS occurs with higher frequency in two immunologically defined groups: children who have experienced a previous dengue infection, and infants with waning levels of maternal dengue antibody. The acute phase of infection, following an incubation of 3–14 days, lasts about 5–7 days and is followed by an immune response. The first infection produces life-long immunity to the infecting serotype but only temporary and partial protection against the other three serotypes, and secondary or sequential infections are possible after a short time. Transmission of dengue virus from infected humans to feeding mosquitos is determined by the magnitude and duration of viraemia in the human host; persons with high viraemia provide a higher infectious dose of virus to the feeding mosquito, normally leading to a greater percentage of feeding mosquitos becoming infected, although even very low levels of virus in blood may be infectious to some vector mosquitos.

Pathology

At autopsy, all patients who have died of DHF show some degree of haemorrhage; in order of frequency, haemorrhage is found in the skin and subcutaneous tissue, in the mucosa of the gastrointestinal tract, and in the heart and liver. Gastrointestinal haemorrhage may be severe, but subarachnoid or cerebral haemorrhage is rarely seen. Serous effusion with a high protein content (mostly albumin) is commonly present in the pleural and abdominal cavities, but is less common in the pericardial cavity.

Light microscopy of blood vessels shows no significant changes in vascular walls. Capillaries and venules in the affected organ systems may show extravascular bleeding by diapedesis and perivascular haemorrhage, with perivascular infiltration by lymphocytes and mononuclear cells. Morphological evidence of intravascular clot formation in small vessels has been recognized in patients with severe haemorrhage.

In most fatal cases, lymphocyte tissue shows an increased activity of the B-lymphocyte system, with active proliferation of plasma cells and lymphoblastoid cells, and active germinal centres. There is evidence indicating that