Chapter 10
Dengue Infections

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10.1 Introduction

The dengue viruses are among the most widespread geographically of the arboviruses and are found in tropical and subtropical areas where 2.5–3 billion people are at risk of infection [1]. Each year, an estimated 50–100 million dengue infections occur, with several hundred thousand cases of dengue hemorrhagic fever (DHF), and about 20,000 deaths [2]. Global deaths from DHF already rank with yellow fever in exceeding combined deaths from all other viral hemorrhagic fevers, including Ebola, Marburg, Lassa, and Crimean-Congo. The past two decades saw an unprecedented geographic expansion of dengue.

10.2 The Virus

Dengue viruses belong to the family of Flaviviridae (single-stranded, non-segmented RNA viruses); there are four serologically distinct dengue virus serotypes (DENV-1, DENV-2, DENV-3, DENV-4). Infection with one serotype confers long-term immunity to that serotype but not to the other types. Dengue virus infection of all four virus serotypes causes a spectrum of illness ranging from asymptomatic or mild febrile illness to classical dengue fever (DF) and to severe and fatal hemorrhagic disease.

The evolution of dengue viruses has had a major impact on their virulence for humans and on the epidemiology of dengue disease around the world [3]. The RNA genome of the virus is susceptible to random mutations due to the lack of proofreading

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capacity of the RNA-dependent RNA polymerase, which could thus give rise to more virulent strains following increased levels of infection in a population [4]. Although antigenic and genetic differences in virus strains have become evident, the lack of animal models for severe dengue has made it difficult to study variation in virulence among dengue viruses. However, phylogenetic studies of many different dengue virus samples have led to the association between specific subtypes (within serotypes) and the presentation of more or less severe disease [3]. Currently, dengue viruses can be classified as being of epidemiologically low, medium, or high impact [3]. Subtypes within the American genotype of DENV-2 and genotype IV of DENV-3, for example, are less virulent with a reduced ability to grow in cell cultures and mosquitoes compared to the Asian genotypes of DENV-2 and DENV-3. Phylogenetic and epidemiological analyses suggest that the genotypes and subtypes with greater epidemic potential are now displacing those that have lower epidemiological impact [1].

10.3 The Vector

Dengue viruses are transmitted by mosquitoes of the genus *Aedes*, subgenus *stegomyia (*such as *Aedes aegypti* and *albopictus*) [2]. *Aedes aegypti* is well established in much of the tropical and subtropical world. It is the principal vector and is an efficient epidemic vector for several reasons: it is highly susceptible to dengue virus, feeds preferentially on human blood, is a daytime feeder, has an almost imperceptible bite, and is capable of biting several people in a short period for one blood meal [2, 5]. As a peri-domicillary mosquito, it is well adapted to urban life as it typically breeds in clean stagnant water in a wide variety of man-made containers such as tires, tin cans, pots, and buckets that collect rainwater. The alternative dengue vector, *Aedes albopictus*, is continuing its geographic expansion into both tropical and temperate climates, but this has had little impact on epidemic dengue transmission [6].

Epidemic dengue was effectively controlled in most of tropical America in the 1950s and the 1960s as a side benefit of malaria and yellow fever control programs [2]. Disruption of vector control programs, be it for reasons of political and social unrest or scientific reservations about the safety of DDT, has contributed to the resurgence of dengue around the world. Lack of political will or complacency concerning vector-borne diseases is another factor. Few new and effective mosquito control methods have been developed in the past 30 years [7].

10.4 Epidemiology of Dengue

At the beginning of the twenty-first century, dengue is the most important arboviral disease of humans [8]. More than 100 tropical countries now have endemic dengue virus infections, and DHF has been documented in >60 of these countries [2]. Global reports of DHF have increased on average by fivefold in the past 20 years [2]

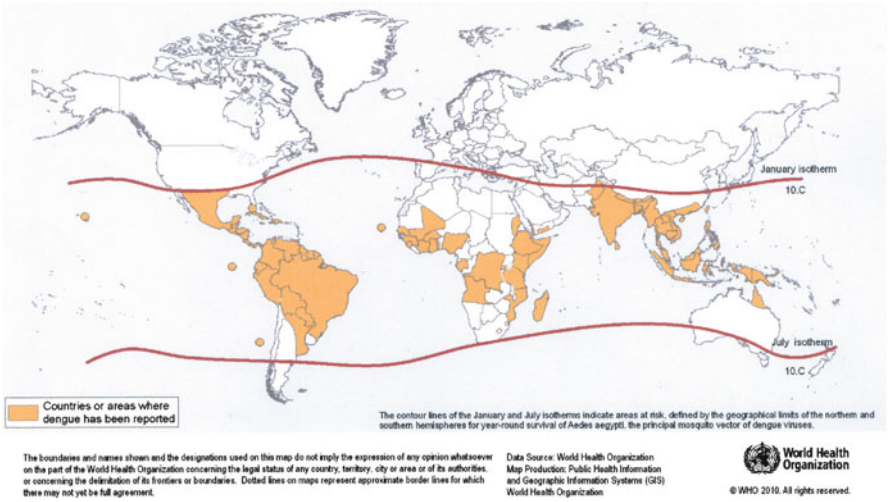

Fig. 10.1 Countries and areas at risk of dengue, 2010 (NB: Reproduced with the permission of the WHO)

(Fig 10.1). Dengue epidemics vary greatly in magnitude and severity. In 1998, the largest epidemics in history occurred throughout Asia and the Americas, with >1.2 million cases of DF/DHF reported to the WHO. The reasons for the resurgence of dengue are complex. It is impossible to determine the extent that single factors such as climate change, virus evolution, deteriorating vector control, and societal changes play in the expansion of dengue. Population growth associated with rapid uncontrolled urbanization is likely the main factor that has driven the rapid amplification of dengue in the past decades. But the main factors responsible for the geographic spread are movements of populations or individuals via travel [1, 9, 10].

The factors responsible for periodic epidemics in an area are not well understood. They are likely a combination of the increased movement of viruses in people among countries and regions, the level of herd immunity to specific virus serotypes in human population, and genetic changes in circulating or introduced viruses that give them greater epidemic potential [10].

The World Health Organization (WHO) states that the Southeast Asian and Western Pacific Regions bear nearly 75 % of the current global disease burden of dengue [11]. Dengue inflicts a significant health, economic, and social burden on the populations of endemic areas. Globally, the number of disability-adjusted life years (DALYs) per million population lost to dengue is estimated to be between 528 and 621 per million population [11]. Dengue imposes substantial costs on both the health sector and the overall economy.

The number of cases reported annually to WHO ranged from 0.4 to 1.3 million in the decade 1996–2005 [11]. The number of cases varies substantially from year to year, with epidemics occurring every 3–5 years. The underlying reason for this cyclical trend is poorly understood but is perhaps best explained by demographic,

immunologic, and environmental changes combined with globalization and ineffective public health measures [1, 12–14]. Climatic influences, such as the El Nino Southern Oscillation (ENSO) and global warming, have been suggested as other factors contributing to the cyclical pattern of dengue activity [7, 15]. Furthermore, dengue activity is seasonal within a year in most endemic countries [12, 16, 17]. The greatest burden of dengue in endemic countries is in children. However, there has been an increasing trend of adult infection in certain countries [18, 19]. Most travelers with dengue have been adults [9].

10.4.1 Risk for Travelers

The chance of contracting DF is determined by several factors including travel destination, length of exposure in endemic areas, the intensity of dengue transmission, and the season of travel. Risk is thought to be higher during periods of intense mosquito feeding activity 2–3 h after dawn and during the early evening.

The GeoSentinel [20] global network of travel and tropical medicine clinics reported on illness in returned travelers and determined that the regions at highest risk for dengue were SE Asia and the Caribbean [16]. The true incidence of dengue fever in travelers is probably underestimated because in many countries reporting is not obligatory, and, due to its nonspecific symptoms, it is probably underdiagnosed [9].

10.5 Pathogenesis, Clinical Manifestations, Diagnosis and Differential Diagnosis, and Clinical Management

Dengue fever is most often a self-limiting disease with a low case fatality rate. Often presenting as nonspecific febrile illness, its differential diagnosis is broad, thereby posing diagnostic challenges. In the absence of specific antiviral therapy, the clinical management of dengue is supportive.

10.5.1 Pathogenesis

After the bite of an infected mosquito, the virus replicates in regional lymph nodes and is disseminated via the lymph and blood to other tissues [21]. Replication in the reticuloendothelial system and skin produces a viremia [21]. The incubation period is 3–14 days. Dengue virus infection of all four virus serotypes causes a spectrum of illness ranging from asymptomatic or mild febrile illness to severe and fatal hemorrhagic disease, depending largely on age and immunologic condition [5]. Although the mechanisms for developing severe hemorrhagic disease are not fully understood, the majority view is that secondary infection is the main risk factor for

dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [22, 23]. Secondary infection with a different serotype may result in complexes between heterotypic antibodies and dengue viruses, a phenomenon that has been called antibody-dependent enhancement [24–26]. Severity of disease also depends on the strain and serotype of the infecting virus, age and genetic background of the patient [23, 27, 28], and the degree of viremia [29].

The primary pathophysiological abnormality in DHF and DSS is an acute increase in vascular permeability that leads to leakage of plasma into the extravascular compartment, resulting in hemoconcentration and decreased blood pressure [28]. Plasma volume studies have shown a reduction of more than 20 % in severe cases [30].

10.5.2 Clinical Manifestations

10.5.2.1 Asymptomatic Infections

The vast majority of dengue infection in endemic areas are asymptomatic or subclinical (mild febrile illness), particularly among young children [5, 31].

10.5.2.2 Classic Dengue Fever (DF)

Classic dengue fever is characterized by a sudden onset of fever, accompanied by a significant headache (usually frontal), retro-orbital pain and fatigue, and often associated with severe myalgia and arthralgia ("breakbone disease") and gastrointestinal and respiratory symptoms [32]. The conjunctivae may be injected and the pharynx inflamed. Lymphadenopathy is common. Rash is variable and may not occur in 50 % of patients [33–35]. Transient flushing (which can be differentiated from a sunburn in a traveler by its blanching) or erythematous mottling may be present during the first 24–48 h. Fever usually lasts 5–7 days. A second rash, varying from scarlatiniform to maculopapular, may appear at the time of defervescence, often lasts for 2–3 days and may be accompanied by scaling and pruritus [32]. Hemorrhagic manifestations in dengue fever patients may occur with skin hemorrhages being the most frequent (petechia and purpura) [21]. The tourniquet test (a simple bedside test that reflects capillary fragility) may be positive. Gum bleeding, epistaxis, menorrhagia, and gastrointestinal hemorrhage may also occur, but are less common. Very rare complications of dengue fever include myocarditis, hepatitis [36], and neurological abnormalities such as encephalopathy and neuropathies [32, 37]. Convalescence may be prolonged for weeks with asthenia and depression [38].

Laboratory findings commonly associated with dengue fever include thrombocytopenia, leucopenia with lymphopenia, mild to moderately elevated liver transaminases and lactate dehydrogenase, and hyponatremia [5, 33, 39].

10.5.2.3 Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS)

The hallmark of this syndrome is a capillary leakage syndrome, accompanied by hemorrhagic manifestations. Patients present in the first days similarly to DF, but then plasma leakage develops at the time of defervescence around 5–7 days after onset of symptoms. Abdominal pain and vomiting, restlessness, change in level of consciousness, and a sudden change from fever to hypothermia may be the first clinical warning signs, associated with a significant decrease in platelets [5].

The diagnosis of DHF is made based on the combination of hemorrhagic manifestations, platelet count <100,000/mm^3, and objective evidence of plasma leakage shown by either fluctuation of packed cell volume >20 % during the course of illness or clinical signs of plasma leakage such as pleural effusion, ascites, or hypoproteinemia. Hemorrhagic manifestations without capillary leakage do not constitute DHF. A positive tourniquet test differentiates poorly between DF and DHF and seems to be not very specific [40]. Mortality of DHF can be up to 10–20 %, but it is as low as 0.2 % in hospitals with staff experienced in the management of the disease [5, 28, 41]. The criteria for dengue shock syndrome are those for DHF plus either a narrowing pulse pressure <20 mmHg or hypotension (defined as systolic pressure <80 mmHg for those aged <5 years or <90 mmHg for those ≥5). DSS is associated with a mortality up to 40 % [5].

10.5.3 New Case Definition

The World Health Organization (WHO) has outlined in its new global dengue guidelines a revised classification into levels of severity: dengue fever with an intermediary group of "dengue fever with warning sings," and severe dengue [11]. The revised dengue classification has a high potential for facilitating dengue case management and surveillance [42].

10.5.4 Diagnosis and Differential Diagnosis of Dengue Fever

Nonspecific fever with or without a rash, in particular if associated with thrombocytopenia and leukopenia, should alert the clinician to the possibility of dengue fever and should initiate laboratory confirmation. Probable diagnosis of dengue infection is made based on a supportive serology on a single serum sample of a positive IgM antibody test or a titer ≥1,280 with the hemagglutination inhibition test [5]. Confirmed diagnosis of dengue requires at least one of the following: fourfold or greater rise in serum IgG titers (by hemagglutination inhibition test) specific to dengue virus between acute and convalescent serum; detection of dengue virus in

serum, tissue, or autopsy samples; and detection of dengue virus genomic sequences by reverse transcription-polymerase chain reaction (RT-PCR) [5].

During the first 5 days of illness, the most sensitive test is virus isolation (i.e., PCR), but these tests may not be available in many settings. The more commonly available IgM capture enzyme-linked immunosorbent assay is negative early in the illness and should only be done at least 5 days after onset of symptoms [43]. Cross-reactivity exists between Dengue ELISA IgG and other flaviviruses, such as Japanese encephalitis (JE), yellow fever (YF), and West Nile virus, but far less so for dengue IgM [21, 44, 45]. The ELISA IgG test is therefore of limited use in JE or YF vaccinated travelers to differentiate between primary and secondary dengue and to determine seroconversion rates [43].

As a diagnosis of dengue is often hard to make in a timely manner, the diagnosis of dengue is initially only clinical, based on the development of clinical manifestations and laboratory features over time, while excluding other potentially life-threatening diagnoses such as malaria.

The differential diagnosis of dengue is extensive and includes malaria, measles, rubella, influenza, typhoid, leptospirosis, Epstein-Barr virus infection, Chikungunya, viral hemorrhagic fevers and rickettsial diseases, and any other diseases that may present in the acute phase as an undifferentiated febrile syndrome.

10.5.5 Clinical Management

There is no specific antiviral drug yet developed against dengue. Treatment is therefore symptomatic and supportive, with the primary aim to prevent mortality from severe DHF/DSS. Classic dengue is treated with antipyretics (i.e., paracetamol), bed rest, and oral (rarely parenteral) fluid replacement, and most cases can be managed on an outpatient basis. Aspirin and nonsteroidal anti-inflammatory drugs are contraindicated as they may increase bleeding tendencies. Intramuscular injections are contraindicated as they may cause massive hematomas. Patients should be advised to repeat platelet and hematocrit determinations every 24 h [30]. Prompt and correct institution of fluid replacement is thought to reduce mortality due to DHF/DSS [46]. The critical period is usually on the day of defervescence, typically 4–7 days after onset of the illness. A decrease in the platelet count which usually precedes the rise in hematocrit is of diagnostic and prognostic value [30]. A rise in hematocrit of 20 % indicates significant plasma loss, and prompt institution of intravenous fluid replacement is indicated, with normal saline or lactated Ringer's solution [46, 47]. In continued shock, plasma or other colloid may be added [21, 46]. If there is evidence of bleeding or disseminated intravascular coagulation, fresh blood or fresh frozen plasma/platelets should be administered. Once the capillary leakage stops and resorption of extravasated fluid begins, care must be taken not to induce fluid overload and pulmonary edema [21].

10.6 Prevention and Control

Dengue control follows three main strategies: source reduction (location and destruction of mosquitoes, breeding sites), use of larvicides, and use of ultralow-volume aerosolised adulticides. The first two strategies have been used with varying success. However, the efficacy of current methods to control adult mosquitoes is controversial. *Aedes aegypti* had been highly susceptible to DDT, with DDT-based control strategies resulting in the eradication of *A. aegypti* from 22 countries in the Americas in 1962 and from all countries in the Mediterranean region in 1972 [48]. Since DDT was abandoned, the control of dengue has shifted to source reduction and use of larvicides and adulticides from other chemical classes. Biological control of larvae in the form of larvivorous fish and/or predatory copepods – small freshwater crustaceans – has proved effective in operational contexts in specific container habitats, but has not yet been used on a large scale. The willingness of local communities to accept the introduction of organisms into water containers is essential to make biological control agents such as mesocyclops successful. Vector control should be integrated and include a combined vertical and horizontal approach that depends on community participation [49].

Personal protection against dengue is difficult to implement on a long-term basis as it requires daily protective measures with insect repellents, applied throughout the day as Aedes mosquitoes are day-biting mosquitoes. Bed-nets therefore have only very limited or no benefit, in contrast to malaria.

10.6.1 Dengue Vaccines

Vector control is currently the mainstay for the control of dengue, but it is not sufficient. Several models have shown that vaccination against dengue would be the most cost-effective strategy. However, development of a safe and effective vaccine against a disease with such strong immunological ramifications poses considerable challenges [50]. A dengue vaccine has to protect reliably and long-term against all four serotypes for two reasons: first, to protect the individual against disease resulting from any serotype and second, to preclude the development of immune-mediated severe disease. Weak immune responses that wane below protective levels over time are not acceptable because of the severe consequences seen during secondary DENV infections [51]. The lack of an animal model, limited understanding of immune correlates of protection, and the difficulty of distinguishing cross-reactions from the development of type-specific antibodies create further challenges [50].

Nevertheless, the development of dengue vaccines has seen significant progress in recent years, and the pace toward clinical efficacy trials has accelerated substantially. The vaccine pipeline is now sufficiently advanced for it to be possible to have a first-generation dengue vaccine licensed within the next 5–7 years. In addition, a number of diverse candidates are at earlier stages of evaluation and could become second-generation vaccines [52].

The vaccine in furthest development is the chimeric tetravalent vaccine (developed by Sanofi Pasteur). For this vaccine, the structural genes (prM and E) of each of the four dengue viruses were inserted individually to replace those of yellow fever virus in the backbone of the yellow fever 17D vaccine [10]. This vaccine is currently in phase 3 trials. Other vaccines in development are the live attenuated vaccines, subunit vaccines, recombinant vaccines, DNA vaccines, and vector-based vaccines [10].

More work is required to bring a vaccine from licensing to programmatic use in dengue endemic areas. Depending on cost-effectiveness and national epidemiology, countries may decide to introduce dengue vaccines into the national immunization programs for routine administration. If the vaccine is to be used for infants, the dengue vaccination will need to be carried out on a schedule compatible with other vaccines, and absence of interference with other childhood vaccines need to be shown. Post-marketing surveillance is paramount to identify rare serious adverse events that were not picked up during phase 1–3 trials.

10.7 Conclusions

Due to the expanding geographical distribution of both the virus and the mosquito vector, increased frequency of epidemics, co-circulation of multiple virus serotypes, and the emergence of DHF in new areas, WHO classifies dengue as a major international public health concern [2, 5]. The reasons for this resurgence are complex and include unprecedented urbanization with substandard living conditions, lack of vector control, virus evolution, and international travel [1, 5, 23]. Of all these factors, urbanization has probably had the most impact on the amplification of dengue within a given country, and travel had the most impact for the spread of dengue from country to country and continent to continent. Modern rapid intercontinental transportation has had a major influence on the distribution and transmission dynamics of dengue. The development of dengue vaccines has seen significant progress in recent years.

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