

# Dengue fever

Milada Tavodova<sup>a</sup> MD PgDip

## Introduction

Dengue fever is caused by dengue viruses (DENV). Transmission of DENV has increased dramatically in the past two decades making DENV the most important human pathogens among arthropod-borne viruses (1). About 50-100 million dengue fever infections occur every year in tropical and subtropical countries (2) – see Figure 1.

The emergence of dengue haemorrhagic fever (DHF) in most tropical countries is a public health priority. Little is understood about dengue virus pathogenesis. No other animals develop symptoms and research has been limited to studies involving humans (1).

DENV comprise four serotypes (DENV 1 to 4) but are epidemiologically similar (3). Dengue viruses are RNA viruses with a positive RNA strand, which belongs to the family *Flaviviridae*. There is a high mutation rate increasing biodiversity (4) and possibly increasing disease severity and problems with vaccination (4).

## History of dengue fever

The earliest record appears in a Chinese medical encyclopaedia (5). It may have spread via sailing ships, where mosquitoes used the stored water as a breeding site and could maintain the transmission cycle.

The global epidemiology and transmission of dengue viruses changed in Southeast Asia during World War II. Troop movement accelerated the spread of viruses between populations and a few years later the first documented outbreaks of DHF occurred in Manila, Philippines in 1953/54 (6).

The successful eradication of *Aedes aegypti* in the Americas in 1970s reduced the spread of dengue fever. After this programme was abandoned, *A. aegypti* re-invaded most of the countries causing a significant health problem (7). The true prevalence of dengue fever in Africa is unclear because of inadequate surveillance (2, 7).

Dengue viruses originated from an animal reservoir. Two distinct DENV transmission cycles are recognised

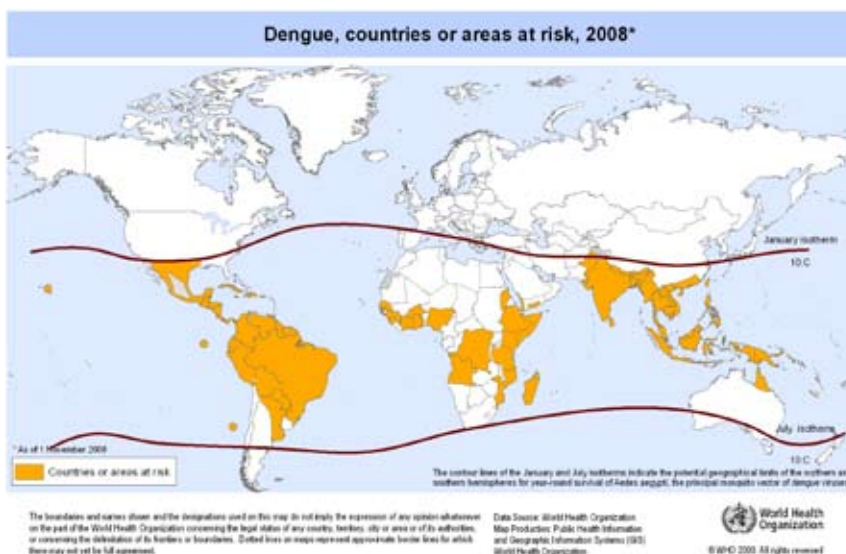


Figure 1. Dengue fever risk map 2008. (Source: WHO)

(Figure 2):

- endemic/ epidemic cycle and
- sylvatic /zoonotic cycle.

Endemic and epidemic cycles involve the human host and viruses are transmitted by *A. aegypti*, *A. albopictus* and other mosquitoes as secondary vectors (3). The sylvatic transmission cycle involves monkeys and several different *Aedes* mosquitoes identified in Asia and West Africa (7).

## Transmission to humans

Transmission to humans is through the bite of an infected mosquito, *A. aegypti* (Figure 3). This mosquito lays its eggs in containers found around the home (e.g. old car tyres, water storage containers). The adult mosquitoes feed on humans during daylight hours. There are two peaks of biting activity, early morning for 2 to 3 hours after daybreak and in the afternoon for several hours before dark. *A. aegypti* females often feed on several persons during a single blood meal hence increasing the transmission rate (5).

The incubation period is 3 - 14 days (average 4 to 7 days). There follows an acute febrile period of 2 - 10 days accompanied by nonspecific symptoms. During this period dengue viruses circulate in the peripheral blood. During this viraemic stage other biting mosquitoes become infected.

## Clinical picture

Dengue fever is mostly occurs in children and young adults (8). Clinical features vary with the age of the patient

<sup>a</sup> Pathology Department, Kings Mill Hospital, Sutton in Ashfield, UK  
[milada.tavodova@gmail.com](mailto:milada.tavodova@gmail.com)

## MAIN ARTICLES

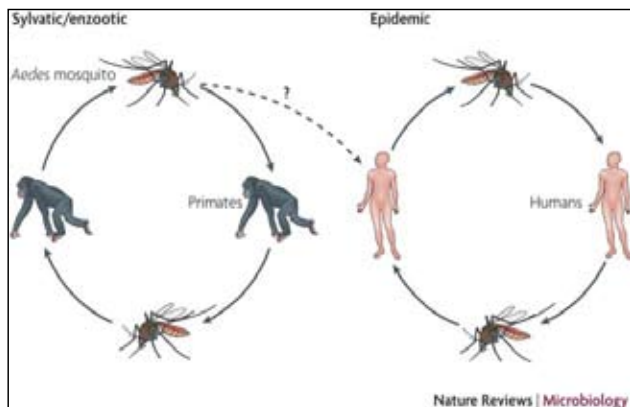


Figure 2. The two DENV transmission cycles. (Source: Nature reviews Microbiology 2007; 5: 518 – 528)

although clinically occult infection occurs in about 80% (9). There are four presentations (Figure 3):

- Non-specific febrile illness
- Classical dengue fever
- Dengue haemorrhagic fever
- Dengue haemorrhagic fever with dengue shock syndrome, encephalopathy and liver failure

**Non-specific febrile illness:** A maculo-papular rash occurs mostly in young children. Upper respiratory features, especially pharyngitis, are common (10).

**Classical dengue fever (DF)** is primarily a disease of older children and adults. It begins abruptly followed by three phases – febrile, critical and recovery (Figure 4). The fever may be biphasic lasting 3 to 7 days and accompanied by a variety of symptoms including severe headache, retro-orbital pain, fatigue, nausea, vomiting, generalised aches, arthralgia and myalgia, hence the term “break bone disease”(9). A flushed skin (face and neck) and maculo-papular rash are common (11). Haemorrhagic manifestations range from mild to severe; cutaneous petechiae and purpura, gum bleeding, epistaxis, gastrointestinal haemorrhage all can occur (5).

Recovery may be prolonged with weakness and depression (10). Laboratory findings include neutropaenia, lymphocytosis, thrombocytopenia and elevated liver enzymes.

**Dengue haemorrhagic fever (DHF)** is primarily a disease of children under 15 years in hyperendemic areas. It usually follows a secondary dengue infection and is characterized by high fever, haemorrhages,

circulatory failure and hepatomegaly (11). Patients either recover or progress to the plasma leakage stage remaining ill despite normalisation of temperature. Plasma leakage is characterized by tachycardia and hypotension with sweating, restlessness and cold extremities. Most patients recover, but in severe cases patients may develop circulatory shock (11). Mortality may reach 10 – 20% without early appropriate treatment but can be reduced to less than 1% with aggressive fluid replacement therapy.

Leucopenia and thrombocytopenia (less than 100,000/mm<sup>3</sup>) are usually found between days 3 and 8. Elevated liver enzymes are common.

**Dengue shock syndrome (DSS)** is associated with almost 50% mortality. Warning signs include sustained abdominal pain, vomiting, irritability or somnolence, a fall in body temperature and decrease in platelet count (10). Patients die from multi-organ failure and disseminated intravascular coagulation. DSS may be accompanied by encephalopathy caused by metabolic and electrolyte disturbances (11).

Haemostatic disturbances result from vascular changes, thrombocytopenia and coagulation disorders arising from, for example, a decreased fibrinogen level, and increased level of fibrinogen degradation products (5). Other reported complications include liver failure, disseminated intravascular coagulation, myocarditis and acute renal failure.

### Pathogenesis

This is poorly understood. It is likely that viral, immunopathogenic and other host factors have a role. The main risk factors for severe disease include the virulence of the strain of the virus, previous infection with heterotypic DENV, age and genetic background of the person (12).

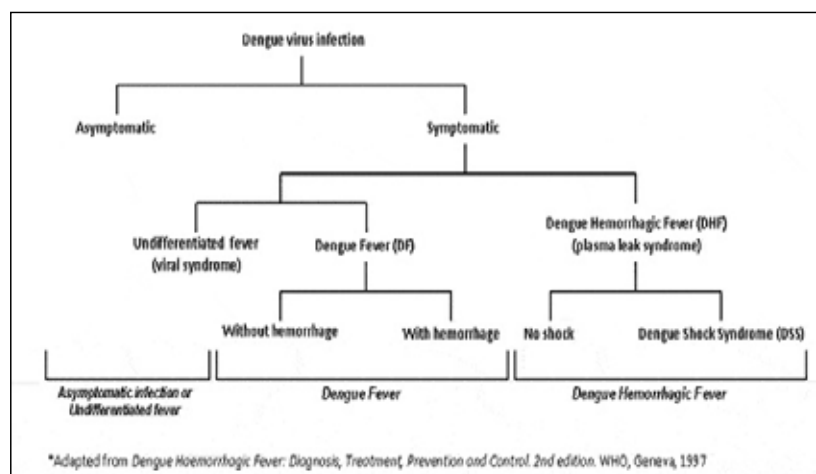


Figure 3. Dengue fever flow chart. (Source: WHO 1997 Dengue haemorrhagic fever: Diagnosis, Treatment, Prevention and Control, 2nd edition)

The two main theories of pathogenesis (5) are:

1. The secondary-infection or immune enhancement hypothesis. This implies that patients having a second infection with heterologous virus serotype have a significantly higher chance of developing DHF and DSS (13). Pre-existing antibodies cross-react with the virus and form antigen-antibody complexes, which then bind to the cell membrane of leucocytes. Because the antibody is heterologous, the virus is not neutralised. This facilitates virus entry to cells resulting in higher viral titres (5, 13). Higher viral titres may result in an amplified cascade of cytokines and complement activation causing endothelial dysfunction, platelets destruction and consumption of coagulation factors leading to plasma leakage and haemorrhage (10).

2. The other hypothesis assumes that dengue viruses vary and some are associated with higher virulence, severe disease and have greater epidemic potential (14).

### Laboratory diagnosis

Laboratory diagnosis depends on virus isolation and identification of virus-specific antibodies. Each method has its advantages and limitations and requires laboratories with the necessary infrastructure and technical expertise (15). Dengue viruses can be isolated from serum, plasma or leucocytes during the febrile phase of the disease (within 6 days) and from post-mortem specimens of liver, lung, spleen, lymph nodes, cerebrospinal fluid or pleural/ascitic fluid.

Serological diagnosis is more readily available. It is complicated by the existence of cross-reactive antigenic determinants shared by all four dengue virus serotypes and members of the flavivirus family (2).

IgM antibodies are the first to appear and are detectable in 50% of patients by days 3 – 5 after onset of illness, increasing to 80% by day 5. IgG antibody is detectable at low titres at the end of first week, increasing thereafter and still detectable after several months. During secondary dengue infection antibody titres rise rapidly and react broadly against many flaviviruses (15).

Molecular methods (nucleic acid detection assays) may identify virus within 24 – 48 hours, but these methods are expensive and require experienced personnel.

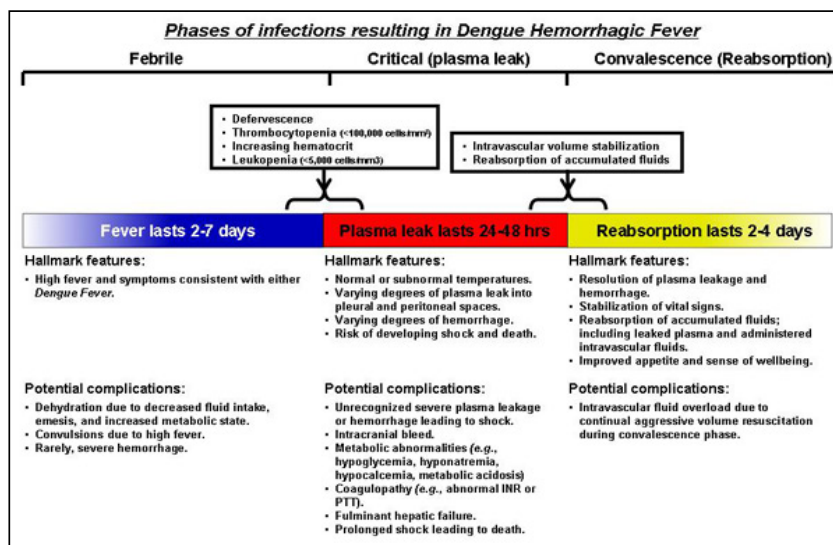


Figure 4. Phases of infection resulting in dengue haemorrhagic fever. (Source: Centers for Disease Control and Prevention, Atlanta, USA)

### Management of dengue infections

There is no specific therapy. Uncomplicated dengue infection usually resolves spontaneously. Patients with life threatening complications should be managed in hospital with supportive treatment. Fluid replacement and close monitoring of fluid and electrolytes balance are vital. Isotonic solutions (e.g. 0.9% saline, Ringer's lactate or Hartmann's solution) should be used (15). Signs of successful therapy are:

- Improving central and peripheral circulation (decreasing tachycardia, increasing blood pressure, capillary refill time <math>< 2 \text{ seconds}</math>) and
- Improving end-organ perfusion e.g. stable conscious level, urine output  $\geq 0.5 \text{ ml/kg/hour}$ , decreasing metabolic acidosis (15).

Give paracetamol for fever and analgesia. Avoid aspirin, ibuprofen and other non-steroidal anti-inflammatory agents as they may aggravate gastritis or bleeding (15). Acetylsalicylic acid (aspirin) may be associated with Reye's syndrome.

Monitor patients at least 6 hourly in 24 hours and particularly around the time of defervescence of symptoms as shock may develop. The indications for hospitalisation are:

- Poor oral intake
- Bleeding
- Change in level of consciousness
- Laboratory evidence of DHF
- Pregnancy, infancy, old age, obesity and diabetes

## MAIN ARTICLES

mellitus (15).

### Impact of global changes to the spread of dengue viruses.

Several factors contribute to the increase of dengue viruses (Figure 5):

- **Increasing human population** and urbanisation were critical factors in the past enabling the spread of viruses. The dengue virus broke free of its sylvatic cycle and established itself as the endemic human disease we see today (7).
- **Increased urbanisation.** The industrialisation and urbanisation are creating large populations of susceptible hosts and fertile habitats for mosquito vectors.
- **Poverty** associated with rapid population growth leads to concentration of people without the necessary infrastructure for the safe storage and distribution of water and drainage. Used containers and tyres provide breeding sites for mosquito vectors.
- **Decreased vector control** in areas where dengue is epidemic.
- **Human travel** and particularly air travel.

#### References

1. Ricco-Hesse R. Dengue Virus Evolution and Virulence Models *Clinical Infectious Diseases* 2007; 44: 1462–1466.
2. Gubler DJ. Epidemic dengue/dengue haemorrhagic fever as a public health, social and economic problem in the 21st century *Trends in Microbiology* 2002; 10 (2): 100 – 103.
3. Wang E, Ni H, Xu R, et al. Evolutionary Relationship of Endemic/Epidemic and Sylvatic Dengue Viruses. *Journal of Virology* 2000; 74 (7): 3227 – 3234.
4. Holmes EC, Burch SS. The causes and consequences of genetic variation in dengue virus. *Trends in Microbiology* 2000; 8 (2): 74 – 77.
5. Gubler DJ. Dengue and dengue haemorrhagic fever. *Clinical Microbiology Reviews* 1998; 11: 480-496.
6. Halstead SB. Dengue haemorrhagic fever – a public health problem and a field for research. *Bull World Health* 1980; 58: 1 – 21.
7. Holmes EC, Twiddy SS. The origin, emergence and evolutionary genetics of dengue virus. *Infection, Genetics and Evolution* 2003; 3: 19 – 28.

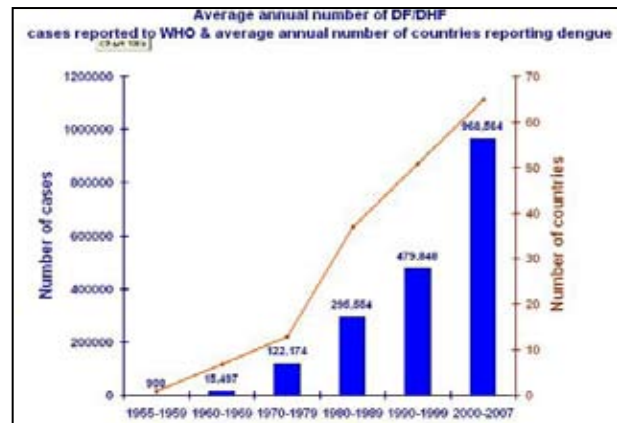


Figure 5. Average annual number of DF/DHF cases. (Source: WHO -<http://www.who.int/csr/disease/dengue/impact/en/>)

8. Garg A, Garg J, Rao YK et al. Prevalence of dengue among clinically suspected febrile episodes at a teaching hospital in North India. *Journal of Infectious Diseases and Immunity* 2011; 3 (5): 85 – 89.
9. Reiter P. Yellow fever and dengue: a threat to Europe? *Euro Surveill* 2010; 15 (10): 11 – 16.
10. Gibbons RV, Vaughn DW. Dengue: an escalating problem. *BMJ* 2002; 324: 1563 – 1566.
11. Gurugama P, Garg P, Wijewickrama A, Seneviratne SL. Dengue viral infections *Indian J Dermatol* 2010; 55: 68 – 78.
12. Mackenzie JS, Gubler DJ, Petersen LR. Emerging flaviviruses: the spread and resurgence of Japanese encephalitis, West Nile and dengue viruses. *Nature Medicine Supplement* 2004; 10(12): S98 – S109.
13. Halstead SB. Pathogenesis of dengue: challenges to molecular biology *Science* 1988; 239: 476-481
14. Ricco-Hesse R. Microevolution and virulence of Dengue viruses *Advances in Virus Research* 2003; 59: 315 – 340.
15. WHO. Dengue - Guidelines for diagnosis, treatment, prevention and control 2009. <http://apps.who.int/tdr/svc/publications/training-guideline-publications/dengue-diagnosis-treatment>.

Acknowledgements: I thank the World Health Organization, the Centers for Disease Control and Prevention, Atlanta and Dr Steve Whitehead for permission to use their images - and Dr Aleksandar Vodovnik for his encouragement and technical support.

Many thanks to John Vaughan and all the other reviewers for their help in preparing this issue