

CHAPTER 42



Dengue and Yellow Fever

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While the most important viral haemorrhagic fevers numerically (dengue and yellow fever) are transmitted exclusively by arthropods, other arboviral haemorrhagic fevers (Crimean–Congo and Rift Valley fevers) can also be transmitted directly by body fluids. A third group of haemorrhagic fever viruses (Lassa, Ebola, Marburg) are only transmitted directly, and are not transmitted by arthropods at all. The directly transmissible viral haemorrhagic fevers are discussed in Chapter 41.

Dengue

Dengue virus is numerically the most important arbovirus infecting humans, with an estimated 100 million cases per year and 2.5 billion people at risk. There are four serotypes of dengue virus, transmitted by *Aedes* mosquitoes, and it is unusual among arboviruses in that humans are the natural hosts. Dengue fever ('breakbone fever') has been around for many hundreds of years; dengue haemorrhagic fever (DHF) emerged as an apparently new disease in South East Asia in the 1950s.

Epidemiology

Dengue has spread dramatically since the end of World War II, in what has been described as a global pandemic. Virtually every country between the tropics of Capricorn and Cancer is now affected (Fig. 42.1).

Factors implicated in the spread of dengue viruses include poor control of its principal vec-

tor (*Aedes aegypti*) as well as reinfestation of this insect into Central and South America (it was largely eradicated in the 1960s). Other factors include intercontinental transport of car tyres containing *Aedes albopictus* eggs, overcrowding of refugee and urban populations and increasing human travel. In hyperendemic areas of Asia, disease is seen mainly in children.

Aedes mosquitoes are 'peri-domestic': they breed in collections of fresh water around the house (e.g. water storage jars). They feed on humans (anthrophilic), mainly by day, and feed repeatedly on different hosts (enhancing their role as vectors).

Clinical features

Dengue virus may cause a non-specific febrile illness or asymptomatic infection, especially in young children. However, there are two main clinical dengue syndromes: dengue fever (DF) and dengue haemorrhagic fever (DHF).

Dengue fever

This is a classical fever–arthralgia–rash syndrome (Chapter 40), with retro-orbital pain, photophobia, lymphadenopathy and, in about 50% of patients, a rash. This is usually maculopapular, but may be mottling or flushing. In addition, there may be petechiae and other bleeding manifestations including gum, nose or gastrointestinal haemorrhage, but these do not define it as DHF according to WHO criteria—see below (Table 42.1). About one-third of patients have a positive tourniquet test (a blood pressure cuff inflated to half way between

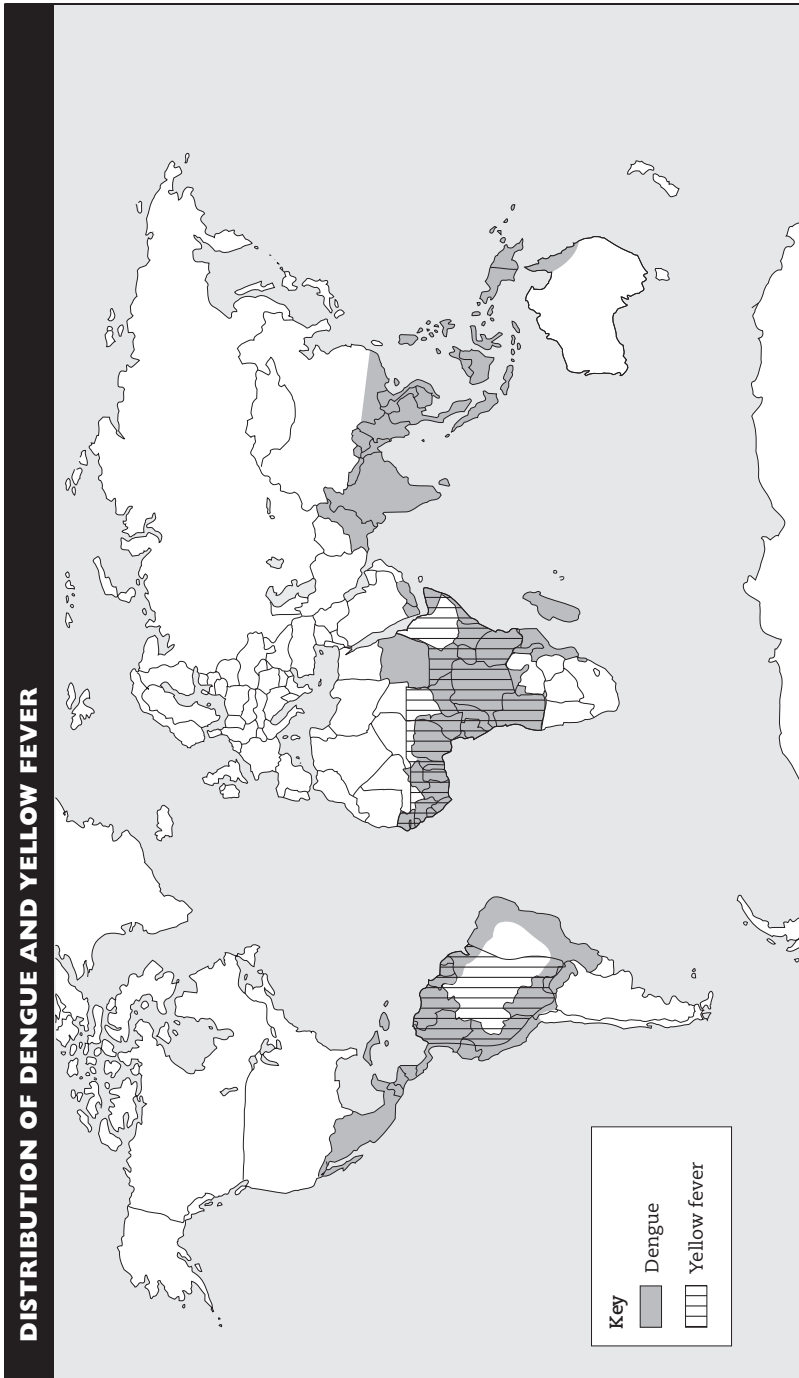


Fig. 42.1 Map showing the approximate distribution of dengue and yellow fever viruses.

DISTINGUISHING DF FROM DHF

	Plasma leakage*	Platelets (μL)	Circulatory collapse	Haemorrhagic manifestations
DF	No	Variable	Absent	Variable
DHF I	Present	< 100 000	Absent	Positive tourniquet test (or easy bruising)
DHF II	Present	< 100 000	Absent	Spontaneous bleeding† with or without positive tourniquet test
DHF III	Present	< 100 000	PP < 20 mmHg‡	Spontaneous bleeding and/or positive tourniquet test
DHF IV	Present	< 100 000	Pulse and BP undetectable	Spontaneous bleeding and/or positive tourniquet test

BP, blood pressure; DF, dengue fever; DHF, dengue haemorrhagic fever; PP, pulse pressure.
 * Identified by haematocrit 20% above normal, or clinical signs of plasma leakage.
 † Skin petechiae, mucosal or gastrointestinal bleeding.
 ‡ Pulse pressure less than 20 mmHg, or hypotension for age.

Table 42.1 World Health Organization criteria for distinguishing dengue fever (DF) and dengue haemorrhagic fever (DHF) grades I–IV. DHF grades III and IV are collectively known as dengue shock syndrome (DSS).

systolic and diastolic pressure for 5 min produces 20 or more petechiae in a 2.5-cm square on the forearm).

Dengue hemorrhagic fever

Initially, patients have a non-specific febrile illness, which may include a petechial rash. Then on the third to seventh day of illness, as the fever subsides, there is a massive increase in vascular permeability (this is the major pathophysiological process). This leads to plasma leakage from the blood vessels into the tissue, causing an elevated haematocrit, oedema and effusions. In addition, there is thrombocytopenia and haemorrhagic manifestations. If a positive tourniquet test is the only such manifestation, then this is defined as DHF grade I (Table 42.1). If there is spontaneous bleeding this is grade II. In grade III, the plasma leakage is sufficient to cause shock (defined in children as a pulse pressure < 20 mmHg). In grade IV, the blood pressure is unrecordable. Collectively, grades III and IV are known as dengue shock syndrome (DSS). Patients with DHF are restless

or lethargic, and often have tender hepatomegaly or abdominal pain.

DIFFERENTIAL DIAGNOSIS OF DENGUE**Fever with arthralgia or rash**

- *Arboviruses*: Chikungunya, O'nyong nyong, sindbis, West Nile, Ross River, Oropouche, sandfly fevers, Colorado tick fever.
- *Other viruses*: rubella, measles, herpes, enteroviruses.
- *Bacteria*: meningococcus, typhoid.
- *Spirochaetes*: leptospirosis, Lyme disease, relapsing fevers.
- *Rickettsiae*: tick and endemic typhus, Rocky Mountain spotted fever.
- *Parasites*: malaria.

Fever with haemorrhage

- *Arboviruses*: yellow fever, Crimean–Congo haemorrhagic fever, Rift Valley fever, Omsk haemorrhagic fever.
- *Other viruses*: hantaviruses, fulminant hepatitis (A–E); Lassa; South American haemorrhagic fevers, Ebola, Marburg.
- Any severe sepsis with disseminated intravascular coagulation (DIC).
- Drug reactions.

Box 42.1 Differential diagnosis of dengue.

Investigations

Leucopenia and thrombocytopenia are common. In the first few days of illness dengue virus can be isolated from serum or detected by polymerase chain reaction (PCR). After the fever subsides, IgM and then IgG antibodies can be detected by ELISA. New enzyme immunoassay kits allow rapid diagnosis in the field. A lateral chest X-ray may show a pleural effusion in DHF.

Management

Dengue fever

Most cases are self-limiting. Oral fluids should be encouraged, and paracetamol given. Patients may have a maculopapular recovery rash and prolonged lethargy and depression after recovery are common.

Dengue haemorrhagic fever

For grades I and II DHF, oral fluids should be encouraged, vital signs closely monitored, as well as haematocrit and platelet count, which may warn of deterioration to grades III and IV. For grades III and IV (dengue shock syndrome), central venous pressure (CVP) should be monitored if possible. Intravenous crystalloid (10–20 mL/kg/h) should be given, followed by intravenous colloid if shock persists. Patients should be watched carefully for fluid overload, and infusions reduced accordingly.

Other severe manifestations of dengue infection

These include hepatitis, or fulminant hepatic failure (Reye-like syndrome) as well as neurological complications (metabolic encephalopathy, cerebral oedema or, occasionally, viral encephalitis).

Pathogenesis of dengue haemorrhagic fever

Current evidence suggests two mechanisms may be important:

I Antibody-dependent enhancement—antibodies against one dengue virus serotype (from a previous infection) enhance the entry of a second dengue virus into macrophages, leading to a more severe infection.

2 Viral strain differences—e.g. increased virulence of South-East Asian strains of dengue-2 virus.

Prevention

Prevention is by control of *Aedes* mosquitoes. Methods include treating stored water with larvicides (e.g. temephos), educating people to remove collections of water around the house (e.g. in rubbish), and spraying with insecticide during epidemics.

Future developments include tetravalent vaccines (effective against all four dengue serotypes), which are in development, for example, live attenuated vaccines and recombinant copy DNA infectious clone vaccines.

Yellow fever

Epidemiology

Yellow fever virus is naturally transmitted between primates by various mosquitoes in jungle cycles in Central America and Africa (Fig. 42.1). *Aedes aegypti* transmits the virus to humans in urban cycles. The disease has re-emerged in South America since the 1970s, when the *Aedes* eradication programme was relaxed. There are an estimated 200 000 cases, with 30 000 deaths annually.

Clinical features

The illness is biphasic and often mild. Severe disease is characterized by jaundice, fulminant hepatic failure and gastrointestinal bleeding. Faget's sign is the failure of the heart rate to increase with a rising temperature and is indicative of cardiac damage. Elevated liver function tests, leucopenia, thrombocytopenia and clotting abnormalities may occur. Liver histology reveals Councilman bodies, which also occur in Crimean–Congo haemorrhagic fever and Rift Valley fever.

Control

Yellow fever control consists of use of the highly effective 17D live attenuated vaccine. Vector control is as for dengue fever.

Further reading

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