Dengue is a viral infection transmitted by mosquitoes. It causes more illness and death than any other arboviral infection, and its control is a priority for the WHO. Dengue viruses are flaviviruses closely related to yellow fever virus and Japanese encephalitis virus. There are four serotypes (1, 2, 3 and 4). Infection with one serotype does not induce solid immunity to the others, and individuals may be infected with dengue more than once.

Dengue is transmitted from infected to susceptible humans by day-biting *Aedes (Stegomyia) aegypti* mosquitoes. This mosquito lives in urban environments, breeding in small collections of clean water in and around human habitats. Dengue is not transmitted directly between humans; therefore, special infection control measures are not required for suspected cases in hospital.

**Epidemiology**

Dengue is found throughout the tropics and subtropics (Figure 1). It is most common in South East Asia, but there have recently been dramatic increases elsewhere, including the Indian subcontinent and the Western hemisphere. It is estimated that 40–80 million individuals are infected with dengue virus each year. Travellers to tropical and subtropical countries are at risk of dengue. Most cases imported into the UK are acquired in South Asia. Dengue is uncommon in travellers to Africa. Bite avoidance is currently the only available protection against infection, but is difficult because of the habits of the mosquito vector (see above).

**Determinants of disease severity**

Key studies have shown that peak viral titre early in the course of infection correlates with disease severity in humans. It follows that host and viral factors that increase or reduce the success of viral replication are critical determinants of disease outcome. There is considerable epidemiological evidence that second infection with dengue virus is a major risk factor predisposing individuals to severe disease. Several lines of evidence suggest that pre-circulating antidengue antibody may increase dengue virus replication by increasing infection of target cells (known as antibody-dependent enhancement of infection). In addition, recent data suggest that the immune response during second infection may be skewed towards the previously encountered serotype and may therefore be less effective at controlling viral replication. Particular viral strains are also associated with severe clinical disease, perhaps reflecting increased ability to replicate in target cells.

*Michael Jacobs* is Senior Lecturer and Honorary Consultant Physician in Infectious Diseases at Royal Free and University College Medical School, London, UK. Conflicts of interest: none declared.
Clinical and laboratory features

Dengue virus infection may be subclinical, or may result in a febrile illness with or without bleeding and/or shock. Conventionally, symptomatic patients have been classified into two groups, classical dengue fever and dengue haemorrhagic fever (DHF) (Figure 2). However, individual patients may have varying degrees of bleeding and/or shock (and sometimes other serious complications such as encephalitis), and therefore the clinical utility and specificity of the current classification is debated.

**Dengue fever** begins abruptly 3–15 (usually 5–8) days after a bite from an infected mosquito. The fever is often accompanied by severe headache, retro-orbital pain, and intense myalgia and arthralgia (‘break-bone fever’). A blanching rash (see page 10) typically appears after a few days and is a useful clue. Many febrile illnesses may present with similar clinical features, none of which is diagnostic for dengue fever. WHO guidelines emphasize that it is inappropriate to adopt a clinical definition of dengue fever.

Dengue fever usually lasts 4–7 days and is followed by complete recovery. Severe complications are uncommon. Bleeding may occur without evidence of vascular leak (therefore not fulfilling the current case definition of DHF – see below). Adults are particularly severely affected, and gastrointestinal bleeding and menorrhagia are well-recognized complications. It is increasingly appreciated that encephalopathy or encephalitis may occur in dengue fever. Dengue encephalopathy may result in neurological sequelae.

**DHF** is usually clinically indistinguishable from dengue fever during the initial phase of the illness. After 2–7 days, more serious manifestations become apparent, reflecting disordered haemostasis and increased vascular permeability. The WHO has proposed diagnostic criteria for DHF based on clinical observation and simple laboratory tests (Figure 3). Vascular leak is the key feature that distinguishes DHF from dengue fever. The WHO recognizes four grades of DHF according to clinical evidence of disease severity (Figure 4). The critical stage of the disease is reached at or soon after defervescence, when plasma leakage is maximal. If the patient is adequately supported during this phase, resolution occurs within 24–48 hours and spontaneous clinical recovery is expected.

Identification of patients at high risk of progression to DHF before the clinical features of severe disease manifest would greatly assist clinical decision-making (e.g. which patients to hospitalize). In Thai children, the only statistically significant differences in initial findings between those with dengue fever and those who subsequently developed DHF were lower platelet counts and higher plasma aspartate aminotransferase (AST) levels in the DHF group. Normal AST was a strong negative predictor of subsequent DHF.
in DHF, but a single high dose of methylprednisolone had no benefit in a prospective, randomized, double-blind, placebo-controlled study, and data to support the use of corticosteroids are generally lacking. Carbazochrome sodium sulfonate (AC-17) is marketed in Asian countries to counteract vascular permeability, and particularly as a specific agent for DHF, but a recent randomized, double-blind, placebo-controlled study demonstrated no benefit.

Prevention and control

Vector control – elimination of peri-domestic mosquito breeding sites is effective, but even in favourable settings it has been difficult to sustain the effort required to eliminate the vector over a wide area and for a prolonged period of time. Additional biological control strategies may contribute to vector control in the future.

Vaccination – effective vaccines are available for the closely related mosquito-borne flaviviruses yellow fever (live attenuated) and Japanese encephalitis (inactivated), but there is currently no vaccine for dengue. The dengue group of flaviviruses is unique in that the four serotypes can cause sequential infections of increased severity (see above), and any candidate dengue vaccine should induce solid immunity to all four serotypes. This presents a particular challenge.