**Dengue Fever**

**Wikipedia Clinical Review**

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(figure 1) Classic skin rash from Dengue fever

## Introduction

**Dengue fever** ([UK](http://en.wikipedia.org/wiki/British_English)[/](http://en.wikipedia.org/wiki/Wikipedia:IPA_for_English)[ˈdɛŋɡeɪ](http://en.wikipedia.org/wiki/Wikipedia:IPA_for_English" \l "Key)[/](http://en.wikipedia.org/wiki/Wikipedia:IPA_for_English) or [US](http://en.wikipedia.org/wiki/American_English) [/](http://en.wikipedia.org/wiki/Wikipedia:IPA_for_English)[ˈdɛŋɡiː](http://en.wikipedia.org/wiki/Wikipedia:IPA_for_English" \l "Key)[/](http://en.wikipedia.org/wiki/Wikipedia:IPA_for_English)), also known as **breakbone fever**, is an infectious [tropical disease](http://en.wikipedia.org/wiki/Tropical_disease) caused by the [dengue virus](http://en.wikipedia.org/wiki/Dengue_virus). Symptoms include [fever](http://en.wikipedia.org/wiki/Fever), [headache](http://en.wikipedia.org/wiki/Headache), [muscle](http://en.wikipedia.org/wiki/Myalgia) and [joint pains](http://en.wikipedia.org/wiki/Arthralgia), and a characteristic [skin rash](http://en.wikipedia.org/wiki/Skin_rash) that is [similar to measles](http://en.wikipedia.org/wiki/Morbilliform). In a small proportion of cases the disease develops into the life-threatening **dengue hemorrhagic fever**, resulting in [bleeding](http://en.wikipedia.org/wiki/Bleeding), [low levels of blood platelets](http://en.wikipedia.org/wiki/Thrombocytopenia) and blood plasma leakage, or into **dengue shock syndrome**, where[dangerously low blood pressure](http://en.wikipedia.org/wiki/Shock_(circulatory)) occurs.

Dengue is transmitted by several species of [mosquito](http://en.wikipedia.org/wiki/Mosquito) within the [genus](http://en.wikipedia.org/wiki/Genus) [*Aedes*](http://en.wikipedia.org/wiki/Aedes), principally [*A. aegypti*](http://en.wikipedia.org/wiki/Aedes_aegypti). The virus has four different types; infection with one type usually gives lifelong [immunity](http://en.wikipedia.org/wiki/Immunity_(medical)) to that type, but only short-term immunity to the others. Subsequent infection with a different type increases the risk of severe complications. As there is no [vaccine](http://en.wikipedia.org/wiki/Vaccine), prevention is sought by reducing the habitat and the number of mosquitoes and limiting exposure to bites.

Treatment of acute dengue is supportive, using either oral or intravenous [rehydration](http://en.wikipedia.org/wiki/Rehydration) for mild or moderate disease, and [intravenous fluids](http://en.wikipedia.org/wiki/Intravenous_therapy) and [blood transfusion](http://en.wikipedia.org/wiki/Blood_transfusion) for more severe cases. The [incidence](http://en.wikipedia.org/wiki/Incidence_(epidemiology))of dengue fever has increased dramatically since the 1960s, with around 50–100 million people infected yearly. Early descriptions of the condition date from 1779, and its viral cause and the transmission were elucidated in the early 20th century. Dengue has become a global problem since the [Second World War](http://en.wikipedia.org/wiki/World_War_II) and is [endemic](http://en.wikipedia.org/wiki/Endemic_(epidemiology)) in more than 110 countries. Apart from eliminating the mosquitoes, work is ongoing on a vaccine, as well as medication targeted directly at the virus.

## Signs and symptoms

(Figure 5) Schematic depiction of the symptoms of dengue fever

Typically, people infected with dengue virus are [asymptomatic](http://en.wikipedia.org/wiki/Asymptomatic) (80%) or only have mild symptoms such as an uncomplicated fever.[[1]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-White10-0)[[2]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp14-1)[[3]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Euro10-2) Others have more severe illness (5%), and in a small proportion it is life-threatening.[[1]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-White10-0)[[3]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Euro10-2) The [incubation period](http://en.wikipedia.org/wiki/Incubation_period) (time between exposure and onset of symptoms) ranges from 3–14 days, but most often it is 4–7 days.[[4]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gubler379-3) Therefore, travelers returning from endemic areas are unlikely to have dengue if fever or other symptoms start more than 14 days after arriving home.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) Children often experience symptoms similar to those of the [common cold](http://en.wikipedia.org/wiki/Common_cold) and [gastroenteritis](http://en.wikipedia.org/wiki/Gastroenteritis) (vomiting and diarrhea),[[6]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-India10-5) and generally have less severe symptoms than adults,[[7]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-NEJM-6) but are more susceptible to the severe complications.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4)

### Clinical course

The characteristic symptoms of dengue are sudden-onset fever, headache (typically located behind the eyes), muscle and joint pains, and a rash. The alternative name for dengue, "break-bone fever", comes from the associated muscle and joint pains.[[1]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-White10-0)[[8]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Chen-7) The course of infection is divided into three phases: febrile, critical, and recovery.[[9]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp25-8)

The febrile phase involves high fever, often over 40 °C (104 °F), and is associated with generalized pain and a headache; this usually lasts two to seven days.[[8]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Chen-7)[[9]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp25-8) At this stage, a rash occurs in 50–80% of those with symptoms.[[8]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Chen-7)[[10]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Fitz2009-9) It occurs in the first or second day of symptoms as [flushed skin](http://en.wikipedia.org/wiki/Erythema), or later in the course of illness (days 4–7), as a [measles-like](http://en.wikipedia.org/wiki/Morbilliform) rash.[[10]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Fitz2009-9)[[11]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-ER2010-10) Some [petechiae](http://en.wikipedia.org/wiki/Petechia) (small red spots that do not disappear when the skin is pressed, which are caused by broken [capillaries](http://en.wikipedia.org/wiki/Capillary)) can appear at this point,[[9]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp25-8) as may some mild bleeding from the [mucous membranes](http://en.wikipedia.org/wiki/Mucous_membrane) of the mouth and nose.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4)[[8]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Chen-7) The fever itself is classically [biphasic](http://en.wikipedia.org/wiki/Fever" \l "Types) in nature, breaking and then returning for one or two days, although there is wide variation in how often this pattern actually happens.[[11]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-ER2010-10)[[12]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gould-11)

In some people, the disease proceeds to a critical phase, which follows the resolution of the high fever and typically lasts one to two days.[[9]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp25-8)During this phase there may be significant fluid accumulation in the [chest](http://en.wikipedia.org/wiki/Thoracic_cavity) and [abdominal cavity](http://en.wikipedia.org/wiki/Abdominal_cavity) due to increased [capillary permeability](http://en.wikipedia.org/wiki/Vascular_permeability) and leakage. This leads to [depletion of fluid from the circulation](http://en.wikipedia.org/wiki/Hypovolemia) and [decreased blood supply to vital organs](http://en.wikipedia.org/wiki/Hypoperfusion).[[9]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp25-8) During this phase, organ dysfunction and severe [bleeding](http://en.wikipedia.org/wiki/Bleeding), typically from the [gastrointestinal tract](http://en.wikipedia.org/wiki/Gastrointestinal_tract), may occur.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4)[[9]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp25-8) [Shock](http://en.wikipedia.org/wiki/Shock_(circulatory)) (dengue shock syndrome) and hemorrhage (dengue hemorrhagic fever) occur in less than 5% of all cases of dengue,[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) however those who have previously been infected with other [serotypes](http://en.wikipedia.org/wiki/Serotype) of dengue virus ("secondary infection") are at an increased risk.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4)[[13]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Life10-12)

The recovery phase occurs next, with resorption of the leaked fluid into the bloodstream.[[9]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp25-8) This usually lasts two to three days.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) The improvement is often striking, but there may be severe [itching](http://en.wikipedia.org/wiki/Itch) and a [slow heart rate](http://en.wikipedia.org/wiki/Bradycardia).[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4)[[9]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp25-8) Another rash may occur with either a [maculopapular](http://en.wikipedia.org/wiki/Maculopapular) or a[vasculitis](http://en.wikipedia.org/wiki/Vasculitis)-like appearance followed by peeling of the skin.[[14]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-NEJM2012-13) During this stage, a [fluid overload](http://en.wikipedia.org/wiki/Fluid_overload) state may occur; if it [affects the brain](http://en.wikipedia.org/wiki/Cerebral_edema), it may cause a [reduced level of consciousness](http://en.wikipedia.org/wiki/Altered_level_of_consciousness) or [seizures](http://en.wikipedia.org/wiki/Epileptic_seizure).[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) A feeling of [fatigues](http://en.wikipedia.org/wiki/Fatigues) may last for weeks afterwards.[[14]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-NEJM2012-13)

### Complications.

Dengue can occasionally affect several other [body systems](http://en.wikipedia.org/wiki/Biological_system),[[9]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp25-8) either in isolation or along with the classic dengue symptoms.[[6]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-India10-5) A decreased level of consciousness occurs in 0.5–6% of severe cases, which is attributable either to [infection of the brain by the virus](http://en.wikipedia.org/wiki/Encephalitis) or indirectly as a result of impairment of vital organs, for example, the [liver](http://en.wikipedia.org/wiki/Hepatic_encephalopathy).[[6]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-India10-5)[[12]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gould-11)

Other neurological disorders have been reported in the context of dengue, such as [transverse myelitis](http://en.wikipedia.org/wiki/Transverse_myelitis) and [Guillain-Barré syndrome](http://en.wikipedia.org/wiki/Guillain-Barré_syndrome).[[6]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-India10-5) [Infection of the heart](http://en.wikipedia.org/wiki/Myocarditis) and [acute liver failure](http://en.wikipedia.org/wiki/Acute_liver_failure) are among the rarer complications.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4)[[9]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp25-8)

## Cause

### Virology

(figure 3) A [TEM](http://en.wikipedia.org/wiki/Transmission_electron_microscopy) [micrograph](http://en.wikipedia.org/wiki/Micrograph) showing dengue virus [virions](http://en.wikipedia.org/wiki/Virion) (the cluster of dark dots near the center)

Dengue fever virus (DENV) is an [RNA virus](http://en.wikipedia.org/wiki/RNA_virus) of the family [*Flaviviridae*](http://en.wikipedia.org/wiki/Flaviviridae); genus [*Flavivirus*](http://en.wikipedia.org/wiki/Flavivirus). Other members of the same genus include [yellow fever virus](http://en.wikipedia.org/wiki/Yellow_fever), [West Nile virus](http://en.wikipedia.org/wiki/West_Nile_virus), [St. Louis encephalitis virus](http://en.wikipedia.org/wiki/St._Louis_encephalitis), [Japanese encephalitis virus](http://en.wikipedia.org/wiki/Japanese_encephalitis), [tick-borne encephalitis virus](http://en.wikipedia.org/wiki/Tick-borne_encephalitis_virus), [Kyasanur forest disease virus](http://en.wikipedia.org/wiki/Kyasanur_forest_disease), and [Omsk hemorrhagic fever virus](http://en.wikipedia.org/wiki/Omsk_hemorrhagic_fever).[[12]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gould-11) Most are transmitted by [arthropods](http://en.wikipedia.org/wiki/Arthropod) (mosquitoes or [ticks](http://en.wikipedia.org/wiki/Tick)), and are therefore also referred to as [arboviruses](http://en.wikipedia.org/wiki/Arbovirus) (*ar*thropod-*bo*rne viruses).[[12]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gould-11)

The dengue virus [genome](http://en.wikipedia.org/wiki/Genome) (genetic material) contains about 11,000 [nucleotide bases](http://en.wikipedia.org/wiki/Nucleotide_base), which [code](http://en.wikipedia.org/wiki/Genetic_code) for the three different types of protein molecules (C, prM and E) that form the [virus particle](http://en.wikipedia.org/wiki/Virion) and seven other types of protein molecules (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) that are only found in infected host cells and are required for replication of the virus.[[13]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Life10-12)[[15]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Guzman10-14) There are four strains of the virus, which are called[serotypes](http://en.wikipedia.org/wiki/Serovar), and these are referred to as DENV-1, DENV-2, DENV-3 and DENV-4.[[2]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp14-1) All four serotypes can cause the full spectrum of disease.[[13]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Life10-12) Infection with one serotype is believed to produce lifelong immunity to that serotype but only short term protection against the others.[[2]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp14-1)[[8]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Chen-7)

The severe complications on secondary infection occurs particularly if someone previously exposed to serotype DENV-1 then contracts serotype DENV-2 or serotype DENV-3, or if someone previously exposed to type DENV-3 then acquires DENV-2.[[15]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Guzman10-14)

### Transmission

(figure 4) The mosquito [*Aedes aegypti*](http://en.wikipedia.org/wiki/Aedes_aegypti) feeding off a human host

Dengue virus is primarily transmitted by [*Aedes*](http://en.wikipedia.org/wiki/Aedes) mosquitoes, particularly [*A. aegypti*](http://en.wikipedia.org/wiki/Aedes_aegypti).[[2]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp14-1) These mosquitoes usually live between the [latitudes](http://en.wikipedia.org/wiki/Latitude) of 35° North and 35° South below an [elevation](http://en.wikipedia.org/wiki/Elevation) of 1,000 metres (3,300 ft).[[2]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp14-1) They bite primarily during the day.[[16]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp59-15) Other *Aedes* species that transmit the disease include[*A. albopictus*](http://en.wikipedia.org/wiki/Asian_tiger_mosquito), [*A. polynesiensis*](http://en.wikipedia.org/wiki/Aedes_polynesiensis) and [*A. scutellaris*](http://en.wikipedia.org/wiki/Aedes_scutellaris).[[2]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp14-1) Humans are the primary [host](http://en.wikipedia.org/wiki/Host_(biology)) of the virus,[[2]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp14-1)[[12]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gould-11) but it also circulates in nonhuman [primates](http://en.wikipedia.org/wiki/Primate).[[17]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-16) An infection can be acquired via a single bite.[[18]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Yellow10-17) A female mosquito that takes a blood meal from a person infected with dengue fever becomes itself infected with the virus in the cells lining its gut. About 8–10 days later, the virus spreads to other tissues including the mosquito's [salivary glands](http://en.wikipedia.org/wiki/Salivary_gland) and is subsequently released into its saliva. The virus seems to have no detrimental effect on the mosquito, which remains infected for life. *Aedes aegypti* prefers to lay its eggs in artificial water containers, to live in close proximity to humans, and to feed off people rather than other vertebrates.[[19]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-18)

Dengue can also be transmitted via infected [blood products](http://en.wikipedia.org/wiki/Blood_products) and through [organ donation](http://en.wikipedia.org/wiki/Organ_donation).[[20]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-19)[[21]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-20) In countries such as [Singapore](http://en.wikipedia.org/wiki/Singapore), where dengue is endemic, the risk is estimated to be between 1.6 and 6 per 10,000 [transfusions](http://en.wikipedia.org/wiki/Blood_transfusions).[[22]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-21) [Vertical transmission](http://en.wikipedia.org/wiki/Vertical_transmission) (from mother to child) during pregnancy or at birth has been reported.[[23]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-pmid20130380-22) Other person-to-person modes of transmission have also been reported, but are very unusual.[[8]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Chen-7)

### Predisposition

Severe disease is more common in babies and young children, and in contrast to many other infections it is more common in children that are relatively well nourished.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) Women are more at risk than men.[[15]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Guzman10-14) Dengue can be life-threatening in people with [chronic diseases](http://en.wikipedia.org/wiki/Chronic_disease) such as[diabetes](http://en.wikipedia.org/wiki/Diabetes_mellitus) and [asthma](http://en.wikipedia.org/wiki/Asthma).[[15]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Guzman10-14)

[Polymorphisms](http://en.wikipedia.org/wiki/Polymorphism_(biology)) (normal variations) in particular [genes](http://en.wikipedia.org/wiki/Gene) have been linked with an increased risk of severe dengue complications. Examples include the genes coding for the proteins known as [TNFα](http://en.wikipedia.org/wiki/Tumor_necrosis_factor-alpha), [mannan-binding lectin](http://en.wikipedia.org/wiki/Mannan-binding_lectin),[[1]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-White10-0) [CTLA4](http://en.wikipedia.org/wiki/CTLA4), [TGFβ](http://en.wikipedia.org/wiki/Transforming_growth_factor_beta),[[13]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Life10-12) [DC-SIGN](http://en.wikipedia.org/wiki/DC-SIGN), and particular [forms](http://en.wikipedia.org/wiki/Allele) of [human leukocyte antigen](http://en.wikipedia.org/wiki/Human_leukocyte_antigen).[[15]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Guzman10-14) A common genetic abnormality in Africans, known as [glucose-6-phosphate dehydrogenase deficiency](http://en.wikipedia.org/wiki/Glucose-6-phosphate_dehydrogenase_deficiency), appears to increase the risk.[[24]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Martina09-23) Polymorphisms in the genes for the [vitamin D receptor](http://en.wikipedia.org/wiki/Calcitriol_receptor) and [FcγR](http://en.wikipedia.org/wiki/Fc_receptor" \l "Fc-gamma_receptors) seem to offer protection against severe disease in secondary dengue infection.[[15]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Guzman10-14)

## Mechanism

When a mosquito carrying dengue virus bites a person, the virus enters the skin together with the mosquito's saliva. It binds to and enters [white blood cells](http://en.wikipedia.org/wiki/White_blood_cell), and reproduces inside the cells while they move throughout the body. The white blood cells respond by producing a number of signaling proteins, such as [interferon](http://en.wikipedia.org/wiki/Interferon), which are responsible for many of the symptoms, such as the fever, the flu-like symptoms and the severe pains. In severe infection, the virus production inside the body is greatly increased, and many more organs (such as the [liver](http://en.wikipedia.org/wiki/Liver) and the [bone marrow](http://en.wikipedia.org/wiki/Bone_marrow)) can be affected, and fluid from the bloodstream leaks through the wall of small blood vessels into body cavities. As a result, less blood circulates in the blood vessels, and the blood pressure becomes so low that it cannot supply sufficient blood to vital organs. Furthermore, dysfunction of the bone marrow leads to reduced numbers of platelets, which are necessary for effective blood clotting; this increases the risk of bleeding, the other major complication of dengue fever.[[24]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Martina09-23)

### Viral replication

Once inside the skin, dengue virus binds to [Langerhans cells](http://en.wikipedia.org/wiki/Langerhans_cell) (a population of [dendritic cells](http://en.wikipedia.org/wiki/Dendritic_cell) in the skin that identifies pathogens).[[24]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Martina09-23) The virus[enters the cells](http://en.wikipedia.org/wiki/Receptor-mediated_endocytosis) through binding between viral proteins and [membrane proteins](http://en.wikipedia.org/wiki/Membrane_protein) on the Langerhans cell, specifically the [C-type lectins](http://en.wikipedia.org/wiki/C-type_lectin) called DC-SIGN, [mannose receptor](http://en.wikipedia.org/wiki/Mannose_receptor) and [CLEC5A](http://en.wikipedia.org/wiki/CLEC5A).[[13]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Life10-12) DC-SIGN, a non-specific receptor for foreign material on dendritic cells, seems to be the main point of entry.[[15]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Guzman10-14) The dendritic cell moves to the nearest [lymph node](http://en.wikipedia.org/wiki/Lymph_node). Meanwhile, the virus genome is replicated in membrane-bound vesicles on the cell's[endoplasmic reticulum](http://en.wikipedia.org/wiki/Endoplasmic_reticulum), where the cell's protein synthesis apparatus produces new viral proteins, and the viral RNA is copied. Immature virus particles are transported to the [Golgi apparatus](http://en.wikipedia.org/wiki/Golgi_apparatus), the part of the cell where some of the proteins receive necessary sugar chains ([glycoproteins](http://en.wikipedia.org/wiki/Glycoprotein)). The now mature new viruses bud on the surface of the infected cell and are released by [exocytosis](http://en.wikipedia.org/wiki/Exocytosis). They are then able to enter other white blood cells, such as [monocytes](http://en.wikipedia.org/wiki/Monocyte) and [macrophages](http://en.wikipedia.org/wiki/Macrophage).[[13]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Life10-12)

The initial reaction of infected cells is to produce [interferon](http://en.wikipedia.org/wiki/Interferon), a [cytokine](http://en.wikipedia.org/wiki/Cytokine) that raises a number of defenses against viral infection through the [innate immune system](http://en.wikipedia.org/wiki/Innate_immune_system) by augmenting the production of a large group of proteins mediated by the [JAK-STAT pathway](http://en.wikipedia.org/wiki/JAK-STAT_signaling_pathway). Some serotypes of dengue virus appear to have mechanisms to slow down this process. Interferon also activates the [adaptive immune system](http://en.wikipedia.org/wiki/Adaptive_immune_system), which leads to the generation of[antibodies](http://en.wikipedia.org/wiki/Antibody) against the virus as well as [T cells](http://en.wikipedia.org/wiki/T_cell) that directly attack any cell infected with the virus.[[13]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Life10-12) Various antibodies are generated; some bind closely to the viral proteins and target them for [phagocytosis](http://en.wikipedia.org/wiki/Phagocytosis) (ingestion by [specialized cells](http://en.wikipedia.org/wiki/Phagocyte) and destruction), but some bind the virus less well and appear instead to deliver the virus into a part of the phagocytes where it is not destroyed but is able to replicate further.[[13]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Life10-12)

### Severe disease

It is not entirely clear why secondary infection with a different strain of dengue virus places people at risk of dengue hemorrhagic fever and dengue shock syndrome. The most widely accepted hypothesis is that of [antibody-dependent enhancement](http://en.wikipedia.org/wiki/Antibody-dependent_enhancement) (ADE). The exact mechanism behind ADE is unclear. It may be caused by poor binding of non-neutralizing antibodies and delivery into the wrong compartment of white blood cells that have ingested the virus for destruction.[[13]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Life10-12)[[15]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Guzman10-14) There is a suspicion that ADE is not the only mechanism underlying severe dengue-related complications,[[1]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-White10-0) and various lines of research have implied a role for [T cells](http://en.wikipedia.org/wiki/T_cell) and soluble factors such as [cytokines](http://en.wikipedia.org/wiki/Cytokine) and the [complement system](http://en.wikipedia.org/wiki/Complement_system).[[24]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Martina09-23)

Severe disease is marked by two problems: dysfunction of [endothelium](http://en.wikipedia.org/wiki/Endothelium) (the cells that line blood vessels) and disordered [blood clotting](http://en.wikipedia.org/wiki/Coagulation).[[6]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-India10-5)Endothelial dysfunction leads to the leakage of fluid from the blood vessels into the chest and abdominal cavities, while coagulation disorder is responsible for the bleeding complications. Higher viral load in the blood and involvement of other organs (such as the [bone marrow](http://en.wikipedia.org/wiki/Bone_marrow) and the [liver](http://en.wikipedia.org/wiki/Liver)) are associated with more severe disease. Cells in the affected organs die, leading to the release of cytokines and activation of both coagulation and [fibrinolysis](http://en.wikipedia.org/wiki/Fibrinolysis) (the opposing systems of blood clotting and clot degradation). These alterations together lead to both endothelial dysfunction and coagulation disorder.[[24]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Martina09-23)

## Diagnosis

|  |  |
| --- | --- |
| **Warning signs**[[25]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp10-24) | |
| Abdominal pain |  |
| Ongoing vomiting |  |
| Liver enlargement |  |
| Mucosal bleeding |  |
| High [hematocrit](http://en.wikipedia.org/wiki/Hematocrit) with low [platelets](http://en.wikipedia.org/wiki/Platelets) |  |
| Lethargy |  |

(figure 6: )

The diagnosis of dengue is typically made clinically, on the basis of reported symptoms and [physical examination](http://en.wikipedia.org/wiki/Physical_examination); this applies especially in endemic areas.[[1]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-White10-0) However, early disease can be difficult to differentiate from other [viral infections](http://en.wikipedia.org/wiki/Viral_infections).[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) A probable diagnosis is based on the findings of fever plus two of the following: [nausea](http://en.wikipedia.org/wiki/Nausea) and vomiting, rash, generalized pains, [low white blood cell count](http://en.wikipedia.org/wiki/Leukopenia), positive [tourniquet test](http://en.wikipedia.org/wiki/Tourniquet_test), or any warning sign (see table) in someone who lives in an [endemic](http://en.wikipedia.org/wiki/Endemic_(epidemiology)) area.[[25]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp10-24) Warning signs typically occur before the onset of severe dengue.[[9]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp25-8) The tourniquet test, which is particularly useful in settings where no laboratory investigations are readily available, involves the application of a [blood pressure cuff](http://en.wikipedia.org/wiki/Sphygmomanometer) for five minutes, followed by the counting of any [petechial](http://en.wikipedia.org/wiki/Petechial) hemorrhages; a higher number makes a diagnosis of dengue more likely.[[9]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp25-8)

The diagnosis should be considered in anyone who develops a fever within two week of being in the [tropics](http://en.wikipedia.org/wiki/Tropics) or [subtropics](http://en.wikipedia.org/wiki/Subtropics).[[14]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-NEJM2012-13) It can be difficult to distinguish dengue fever and [chikungunya](http://en.wikipedia.org/wiki/Chikungunya), a similar viral infection that shares many symptoms and occurs in similar parts of the world to dengue.[[8]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Chen-7) Often, investigations are performed to exclude other conditions that cause similar symptoms, such as[malaria](http://en.wikipedia.org/wiki/Malaria), [leptospirosis](http://en.wikipedia.org/wiki/Leptospirosis), [typhoid fever](http://en.wikipedia.org/wiki/Typhoid_fever), and [meningococcal disease](http://en.wikipedia.org/wiki/Meningococcal_disease).[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4)

The earliest change detectable on laboratory investigations is a low white blood cell count, which may then be followed by [low platelets](http://en.wikipedia.org/wiki/Thrombocytopenia) and [metabolic acidosis](http://en.wikipedia.org/wiki/Metabolic_acidosis).[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) In severe disease, plasma leakage results in [hemoconcentration](http://en.wikipedia.org/wiki/Hemoconcentration) (as indicated by a rising [hematocrit](http://en.wikipedia.org/wiki/Hematocrit)) and [hypoalbuminemia](http://en.wikipedia.org/wiki/Hypoalbuminemia).[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) [Pleural effusions](http://en.wikipedia.org/wiki/Pleural_effusion) or [ascites](http://en.wikipedia.org/wiki/Ascites) can be detected by physical examination when large,[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) but the demonstration of fluid on [ultrasound](http://en.wikipedia.org/wiki/Medical_ultrasonography) may assist in the early identification of dengue shock syndrome.[[1]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-White10-0)[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) The use of ultrasound is limited by lack of availability in many settings.[[1]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-White10-0)

### Classification

The [World Health Organization](http://en.wikipedia.org/wiki/World_Health_Organization)'s 2009 classification divides dengue fever into two groups: uncomplicated and severe.[[1]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-White10-0)[[25]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp10-24) This replaces the 1997 WHO classification, which needed to be simplified as it had been found to be too restrictive, though the older classification is still widely used.[[25]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp10-24)The 1997 classification divided dengue into undifferentiated fever, dengue fever, and dengue hemorrhagic fever.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4)[[26]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHO97-25) Dengue hemorrhagic fever was subdivided further into grades I–IV. Grade I is the presence only of easy bruising or a positive tourniquet test in someone with fever, grade II is the presence of spontaneous bleeding into the skin and elsewhere, grade III is the clinical evidence of [shock](http://en.wikipedia.org/wiki/Shock_(circulatory)), and grade IV is shock so severe that [blood pressure](http://en.wikipedia.org/wiki/Blood_pressure) and [pulse](http://en.wikipedia.org/wiki/Pulse) cannot be detected.[[26]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHO97-25) Grades III and IV are referred to as "dengue shock syndrome".[[25]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp10-24)[[26]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHO97-25)

### Laboratory tests

Dengue fever may be diagnosed by microbiological laboratory testing.[[25]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp10-24) This can be done by virus isolation in [cell cultures](http://en.wikipedia.org/wiki/Cell_culture), [nucleic acid detection](http://en.wikipedia.org/wiki/Nucleic_acid_test) by [PCR](http://en.wikipedia.org/wiki/Polymerase_chain_reaction), viral [antigen](http://en.wikipedia.org/wiki/Antigen) detection or specific [antibodies](http://en.wikipedia.org/wiki/Antibodies) (serology).[[15]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Guzman10-14)[[27]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp90-26) Virus isolation and nucleic acid detection are more accurate than antigen detection, but these tests are not widely available due to their greater cost.[[27]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp90-26) All tests may be negative in the early stages of the disease.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4)[[15]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Guzman10-14) PCR however is more accurate in the first seven days and a test available as July of 2012 which can run on equipment used to diagnose influenza will result in improved avaliability.[[28]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-27)

These laboratory tests are only of diagnostic value during the acute phase of the illness with the exception of serology. Tests for dengue virus-specific antibodies, types [IgG](http://en.wikipedia.org/wiki/IgG) and [IgM](http://en.wikipedia.org/wiki/IgM), can be useful in confirming a diagnosis in the later stages of the infection. Both IgG and IgM are produced after 5–7 days. The highest levels ([titres](http://en.wikipedia.org/wiki/Titre)) of IgM are detected following a primary infection, but IgM is also produced in secondary and tertiary infections. The IgM becomes undetectable 30–90 days after a primary infection, but earlier following re-infections. IgG, by contrast, remains detectable for over 60 years and, in the absence of symptoms, is a useful indicator of past infection. After a primary infection the IgG reaches peak levels in the blood after 14–21 days. In subsequent re-infections, levels peak earlier and the titres are usually higher. Both IgG and IgM provide protective immunity to the infecting serotype of the virus. In the laboratory test the IgG and the IgM antibodies can cross-react with other flaviviruses, such as [yellow fever virus](http://en.wikipedia.org/wiki/Yellow_fever), which can make the interpretation of the serology difficult.[[8]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Chen-7)[[15]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Guzman10-14)[[29]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gubler10-28) The detection of IgG alone is not considered diagnostic unless blood samples are collected 14 days apart and a greater than fourfold increase in levels of specific IgG is detected. In a person with symptoms, the detection of IgM is considered diagnostic.[[29]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gubler10-28)

## Prevention

(figure 7) A 1920s photograph of efforts to disperse standing water and thus decrease mosquito populations

There are no approved [vaccines](http://en.wikipedia.org/wiki/Vaccine) for the dengue virus.[[1]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-White10-0) Prevention thus depends on control of and protection from the bites of the mosquito that transmits it.[[16]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp59-15)[[30]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp137-29) The World Health Organization recommends an Integrated Vector Control program consisting of five elements: (1) Advocacy, social mobilization and legislation to ensure that public health bodies and communities are strengthened, (2) collaboration between the health and other sectors (public and private), (3) an integrated approach to disease control to maximize use of resources, (4) evidence-based decision making to ensure any interventions are targeted appropriately and (5) capacity-building to ensure an adequate response to the local situation.[[16]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp59-15)

The primary method of controlling *A. aegypti* is by eliminating its [habitats](http://en.wikipedia.org/wiki/Habitat).[[16]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp59-15) This is done by emptying containers of water or by adding [insecticides](http://en.wikipedia.org/wiki/Insecticide) or [biological control agents](http://en.wikipedia.org/wiki/Biological_control_agent) to these areas,[[16]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp59-15) although spraying with [organophosphate](http://en.wikipedia.org/wiki/Organophosphate) or [pyrethroid](http://en.wikipedia.org/wiki/Pyrethroid) insecticides is not thought to be effective.[[3]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Euro10-2) Reducing open collections of water through environmental modification is the preferred method of control, given the concerns of negative health effect from insecticides and greater logistical difficulties with control agents.[[16]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp59-15) People can prevent mosquito bites by wearing clothing that fully covers the skin, using [mosquito netting](http://en.wikipedia.org/wiki/Mosquito_net) while resting, and/or the application of [insect repellent](http://en.wikipedia.org/wiki/Insect_repellent) ([DEET](http://en.wikipedia.org/wiki/DEET) being the most effective).[[18]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Yellow10-17)

## Management

There are no specific treatments for dengue fever.[[1]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-White10-0) Treatment depends on the symptoms, varying from [oral rehydration therapy](http://en.wikipedia.org/wiki/Oral_rehydration_therapy) at home with close follow-up, to hospital admission with administration of [intravenous fluids](http://en.wikipedia.org/wiki/Intravenous_therapy) and/or [blood transfusion](http://en.wikipedia.org/wiki/Blood_transfusion).[[31]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp32-30) A decision for hospital admission is typically based on the presence of the "warning signs" listed in the table above, especially in those with preexisting health conditions.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4)

Intravenous hydration is usually only needed for one or two days.[[31]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp32-30) The rate of fluid administration is titrated to a [urinary output](http://en.wikipedia.org/wiki/Urination) of 0.5–1 mL/kg/hr, stable [vital signs](http://en.wikipedia.org/wiki/Vital_signs) and normalization of [hematocrit](http://en.wikipedia.org/wiki/Hematocrit).[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) Invasive medical procedures such as [nasogastric intubation](http://en.wikipedia.org/wiki/Nasogastric_intubation), [intramuscular injections](http://en.wikipedia.org/wiki/Intramuscular_injection) and arterial punctures are avoided, in view of the bleeding risk.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) [Paracetamol](http://en.wikipedia.org/wiki/Paracetamol) (acetaminophen) is used for fever and discomfort while[NSAIDs](http://en.wikipedia.org/wiki/NSAIDs) such as [ibuprofen](http://en.wikipedia.org/wiki/Ibuprofen) and [aspirin](http://en.wikipedia.org/wiki/Aspirin) are avoided as they might aggravate the risk of bleeding.[[31]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp32-30) Blood transfusion is initiated early in patients presenting with unstable vital signs in the face of a *decreasing hematocrit*, rather than waiting for the hemoglobin concentration to decrease to some predetermined "transfusion trigger" level.[[32]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp40-31) [Packed red blood cells](http://en.wikipedia.org/wiki/Packed_red_blood_cells) or [whole blood](http://en.wikipedia.org/wiki/Whole_blood) are recommended, while [platelets](http://en.wikipedia.org/wiki/Platelet) and [fresh frozen plasma](http://en.wikipedia.org/wiki/Fresh_frozen_plasma) are usually not.[[32]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp40-31)

During the recovery phase intravenous fluids are discontinued to prevent a state of [fluid overload](http://en.wikipedia.org/wiki/Hypervolemia).[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) If fluid overload occurs and vital signs are stable, stopping further fluid may be all that is needed.[[32]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp40-31) If a person is outside of the critical phase, a [loop diuretic](http://en.wikipedia.org/wiki/Loop_diuretic) such as [furosemide](http://en.wikipedia.org/wiki/Furosemide) may be used to eliminate excess fluid from the circulation.[[32]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp40-31)

## Epidemiology

*See also:* [*Dengue fever outbreaks*](http://en.wikipedia.org/wiki/Dengue_fever_outbreaks)

(figure 2) Dengue distribution in 2006.  
Red: Epidemic dengue and *Ae. aegypti*  
Aqua: Just *Ae. Aegypti*

Most people with dengue recover without any ongoing problems.[[25]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp10-24) The mortality is 1–5% without treatment,[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) and less than 1% with adequate treatment;[[25]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp10-24) however severe disease carries a mortality of 26%.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) Dengue is [endemic](http://en.wikipedia.org/wiki/Endemism) in more than 110 countries.[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) It infects 50 to 100 million people worldwide a year, leading to half a million hospitalizations,[[1]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-White10-0) and approximately 12,500–25,000 deaths.[[6]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-India10-5)[[33]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-32)

The most common viral disease transmitted by [arthropods](http://en.wikipedia.org/wiki/Arthropod),[[13]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Life10-12) dengue has a [disease burden](http://en.wikipedia.org/wiki/Disease_burden) estimated to be 1600 [disability-adjusted life years](http://en.wikipedia.org/wiki/Disability-adjusted_life_year) per million population, which is similar to other childhood and tropical diseases such as [tuberculosis](http://en.wikipedia.org/wiki/Tuberculosis).[[15]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Guzman10-14) As a tropical disease dengue is deemed only second in importance to[malaria](http://en.wikipedia.org/wiki/Malaria),[[5]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Peads10-4) though the World Health Organization counts dengue as one of sixteen [neglected tropical diseases](http://en.wikipedia.org/wiki/Neglected_diseases).[[34]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-33)

The incidence of dengue increased 30 fold between 1960 and 2010.[[35]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp3-34) This increase is believed to be due to a combination of urbanization, population growth, increased international travel, and [global warming](http://en.wikipedia.org/wiki/Global_warming).[[1]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-White10-0) The geographical distribution is around the equator with 70% of the total 2.5 billion people living in endemic areas from Asia and the Pacific.[[35]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp3-34) In the United States, the rate of dengue infection among those who return from an endemic area with a fever is 2.9–8.0%,[[18]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Yellow10-17) and it is the second most common infection after malaria to be diagnosed in this group.[[8]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Chen-7)

Until 2003, dengue was classified as a potential [bioterrorism](http://en.wikipedia.org/wiki/Bioterrorism) agent, but subsequent reports removed this classification as it was deemed too difficult to transfer and only caused [hemorrhagic fever](http://en.wikipedia.org/wiki/Hemorrhagic_fever) in a relatively small proportion of people.[[36]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Barrett09-35)

Like most arboviruses, dengue virus is maintained in nature in cycles that involve preferred blood-sucking vectors and vertebrate hosts. The viruses are maintained in the forests of Southeast Asia and Africa by transmission from female *Aedes* mosquitoes—of species other than *A. aegypti*—to her offspring and to lower primates. In rural settings the virus is transmitted to humans by *A. aegypti* and other species of *Aedes* such as [*A. albopictus*](http://en.wikipedia.org/wiki/Aedes_albopictus). In towns and cities, the virus is primarily transmitted to humans by *A. aegypti*, which is highly domesticated. In all settings the infected lower primates or humans greatly increase the number of circulating dengue viruses. This is called amplification.[[37]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-36) The urban cycle is the most important to infections of humans and dengue infections are primarily confined to towns and cities.[[38]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gubler377-37) In recent decades, the expansion of villages, towns and cities in endemic areas, and the increased mobility of humans has increased the number of epidemics and circulating viruses. Dengue fever, which was once confined to Southeast Asia, has now spread to Southern China, countries in the Pacific Ocean and America,[[38]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gubler377-37) and might pose a threat to Europe.[[3]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Euro10-2)

## History

## The first record of a case of probable dengue fever is in a Chinese medical encyclopedia from the [Jin Dynasty](http://en.wikipedia.org/wiki/Jin_Dynasty_(265–420)) (265–420 AD) which referred to a "water poison" associated with flying insects[39][40]. There have been descriptions of epidemics in the 17th century, but the most plausible early reports of dengue epidemics are from 1779 and 1780, when an epidemic swept Asia, Africa and North America.[[40]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gubler98-39) From that time until 1940, epidemics were infrequent.[[40]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gubler98-39)

In 1906, transmission by the *Aedes* mosquitoes was confirmed, and in 1907 dengue was the second disease (after [yellow fever](http://en.wikipedia.org/wiki/Yellow_fever)) that was shown to be caused by a virus.[[41]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Henchal-40) Further investigations by [John Burton Cleland](http://en.wikipedia.org/wiki/John_Burton_Cleland) and [Joseph Franklin Siler](http://en.wikipedia.org/wiki/Joseph_Franklin_Siler) completed the basic understanding of dengue transmission.[[41]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Henchal-40)

The marked spread of dengue during and after the [Second World War](http://en.wikipedia.org/wiki/World_War_II) has been attributed to ecologic disruption. The same trends also led to the spread of different serotypes of the disease to new areas, and to the emergence of dengue hemorrhagic fever. This severe form of the disease was first reported in the [Philippines](http://en.wikipedia.org/wiki/Philippines) in 1953; by the 1970s, it had become a major cause of [child mortality](http://en.wikipedia.org/wiki/Child_mortality) and had emerged in the Pacific and the Americas.[[40]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gubler98-39) Dengue hemorrhagic fever and dengue shock syndrome were first noted in Central and South America in 1981, as DENV-2 was contracted by people who had previously been infected with DENV-1 several years earlier.[[12]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Gould-11)

The origins of the word "dengue" are not clear, but one theory is that it is derived from the [Swahili](http://en.wikipedia.org/wiki/Swahili_language) phrase *Ka-dinga pepo*, which describes the disease as being caused by an [evil spirit](http://en.wikipedia.org/wiki/Evil_spirit).[[39]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-EID06-38) The Swahili word *dinga* may possibly have its origin in the Spanish word *dengue*, meaning fastidious or careful, which would describe the gait of a person suffering the bone pain of dengue fever.[[42]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-41) However, it is possible that the use of the Spanish word derived from the similar-sounding Swahili.[[39]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-EID06-38) Slaves in the West Indies having contracted dengue were said to have the posture and gait of a[dandy](http://en.wikipedia.org/wiki/Dandy), and the disease was known as "dandy fever".[[43]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-42)[[44]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Hal08-43)

The term "break-bone fever" was first applied by physician and [Founding Father](http://en.wikipedia.org/wiki/Founding_Fathers_of_the_United_States) [Benjamin Rush](http://en.wikipedia.org/wiki/Benjamin_Rush), in a 1789 report of the 1780 epidemic in[Philadelphia](http://en.wikipedia.org/wiki/Philadelphia). In the report he uses primarily the more formal term "bilious remitting fever".[[36]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Barrett09-35)[[45]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-44) The term dengue fever came into general use only after 1828.[[44]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Hal08-43) Other historical terms include "breakheart fever" and "la dengue".[[44]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Hal08-43) Terms for severe disease include "infectious thrombocytopenic purpura" and "Philippine", "Thai", or "Singapore hemorrhagic fever".[[44]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Hal08-43)

## Research

(figure 8)Public health officers releasing*P. reticulata* [fry](http://en.wikipedia.org/wiki/Spawn_(biology)) into an [artificial lake](http://en.wikipedia.org/wiki/Artificial_lake) in the [Lago Norte](http://en.wikipedia.org/wiki/Lago_Norte) district of [Brasília](http://en.wikipedia.org/wiki/Brasília), Brazil, as part of a vector control effort.

Research efforts to prevent and treat dengue include various means of vector control,[[46]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp71-45) vaccine development, and [antiviral drugs](http://en.wikipedia.org/wiki/Antiviral_drug).[[30]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp137-29)

With regards to vector control, a number of novel methods have been used to reduce mosquito numbers with some success including the placement of the guppy ([*Poecilia reticulata*](http://en.wikipedia.org/wiki/Poecilia_reticulata)) or [copepods](http://en.wikipedia.org/wiki/Copepods) in standing water to eat the mosquito larvae.[[46]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp71-45) Another effort is to infect mosquitoes with [*wolbachia*](http://en.wikipedia.org/wiki/Wolbachia) which leads to subsequent resistance of mosquitoes to the dengue virus.[[14]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-NEJM2012-13)

There are ongoing programs working on a dengue vaccine to cover all four serotypes.[[30]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp137-29) One of the concerns is that a vaccine could increase the risk of severe disease through antibody-dependent enhancement.[[47]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Webster-46) The ideal vaccine is safe, effective after one or two injections, covers all serotypes, does not contribute to ADE, is easily transported and stored, and is both affordable and cost-effective.[[47]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Webster-46) As of 2009, a number of vaccines were undergoing testing.[[15]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Guzman10-14)[[36]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Barrett09-35)[[47]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Webster-46) It is hoped that the first products will be commercially available by 2015.[[30]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-WHOp137-29)

Apart from attempts to control the spread of the *Aedes* mosquito and work to develop a vaccine against dengue, there are ongoing efforts to develop [antiviral drugs](http://en.wikipedia.org/wiki/Antiviral_drug) that would be used to treat attacks of dengue fever and prevent severe complications.[[48]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Sampath-47)[[49]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Noble-48) Discovery of the structure of the viral proteins may aid the development of effective drugs.[[49]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Noble-48) There are several plausible targets. The first approach is inhibition of the viral[RNA-dependent RNA polymerase](http://en.wikipedia.org/wiki/RNA-dependent_RNA_polymerase) (coded by NS5), which copies the viral genetic material, with [nucleoside analogs](http://en.wikipedia.org/wiki/Nucleoside_analog). Secondly, it may be possible to develop specific [inhibitors](http://en.wikipedia.org/wiki/Protease_inhibitor_(pharmacology)) of the viral [protease](http://en.wikipedia.org/wiki/Protease) (coded by NS3), which [splices](http://en.wikipedia.org/wiki/Protein_splicing) viral proteins.[[50]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-pmid19519486-49) Finally, it may be possible to develop [entry inhibitors](http://en.wikipedia.org/wiki/Entry_inhibitor), which stop the virus entering cells, or inhibitors of the [5′ capping](http://en.wikipedia.org/wiki/5'_cap) process, which is required for viral replication.[[48]](http://en.wikipedia.org/wiki/Dengue_fever" \l "cite_note-Sampath-47)

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