Dengue fever: a Wikipedia clinical review

James M Heilman, Jacob De Wolff, Graham M Beards, Brian J Basden

ABSTRACT

Dengue fever, also known as breakbone fever, is a mosquito-borne infectious tropical disease caused by the dengue virus. Symptoms include fever, headache, muscle and joint pains, and a characteristic skin rash that is similar to measles. In a small proportion of cases, the disease develops into life-threatening dengue hemorrhagic fever, which results in bleeding, thrombocytopenia, and leakage of blood plasma, or into dengue shock syndrome, in which dangerously low blood pressure occurs. Treatment of acute dengue fever is supportive, with either oral or intravenous rehydration for mild or moderate disease and use of intravenous fluids and blood transfusion for more severe cases. Along with attempts to eliminate the mosquito vector, work is ongoing to develop a vaccine and medications targeted directly at the virus.

James M. Heilman, MD, CCFP(EM), is the Emergency Department Head at the East Kootenay Regional Hospital, Cranbrook, British Columbia, and is also a Clinical Instructor in the Department of Emergency Medicine, The University of British Columbia, Vancouver, British Columbia. **Jacob De Wolff,** MRCP(UK), is a Consultant in Acute Medicine and High Dependency Medicine at Northwick Park Hospital, Harrow, Middlesex, UK. **Graham M. Beards,** DSc, FIBMS, is a Clinical and Biomedical Scientist in blood science at Walsall Manor Hospital, Walsall, UK. **Brian J. Basden,** BSc, is a Researcher with Battelle Memorial Institute, Atlanta, Georgia.

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Correspondence: Dr. James Heilman, East Kootenay Regional Hospital, 13–24th Avenue N, Cranbrook BC V1C 3H9; jmh649@gmail.com

➢ Dengue fever, also known as breakbone fever, is a mosquito-borne infectious tropical disease caused by the dengue virus. This disease occurs primarily in the equatorial regions of Africa, the Americas, South-East Asia, and the Western Pacific.[1] The incidence of dengue fever has increased dramatically since the 1960s,[2] with current estimates of incidence ranging from 50 million[2] to 528 million[3] people infected yearly. This increase is believed to be due to several factors, including global warming and urbanization.[2] Early descriptions of the condition date from 1779, and its viral cause and mechanism of transmission were elucidated in the early 20th century.[4] Dengue has become a global problem since the Second World War and is endemic in more than 110 countries.[5]

After an incubation period of 3–10 days, the illness starts with acute onset of high fever, which is typically accompanied by headache, myalgia, arthralgia, and occasionally a characteristic maculopapular skin rash similar to measles (Figure 1).[6,7] Most infected people have few if any symptoms, and most of those who do have symptoms recover spontaneously.[3] In a small proportion of cases, the disease progresses to a more

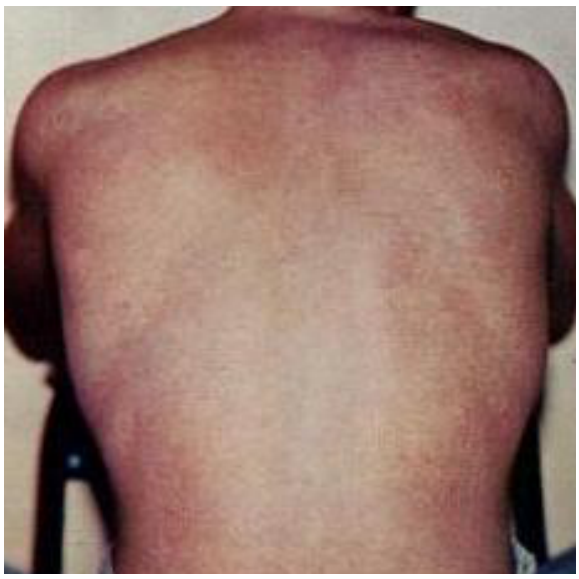

Figure 1
Maculopapular rash of dengue fever. Image file from Wikimedia Commons.

severe form, life-threatening dengue hemorrhagic fever, which is characterized by hemorrhage, thrombocytopenia, and leakage of blood plasma, or to dengue shock syndrome.[8]

Dengue is transmitted by several species of mosquito within the genus *Aedes*, principally *Aedes aegypti*.[8] The virus has 5 different types;[9] infection with a given type usually confers lifelong immunity to that type, but only short-term immunity to the others.[10] Subsequent infection with a different type increases the risk of severe complications.[10] As there is no commercially available vaccine, prevention is sought by reducing the habitat and the number of mosquitoes and limiting exposure to bites.[11]

Treatment of acute dengue is supportive,[7] with either oral or intravenous rehydration for mild or moderate disease and intravenous fluids and blood transfusion for more severe cases.[12] Apart from eliminating the mosquitoes, work is ongoing to develop a vaccine and medications targeting the virus.[13]

Clinical presentation

Signs and symptoms. Figure 2 (online) depicts the symptoms of dengue fever according to the phase of illness. Typically, people infected with dengue virus are asymptomatic (80%) or have only mild symptoms, such as uncomplicated fever.[2,14,15] Others have more severe illness (5%), and in a small proportion of cases (< 1%), it is life-threatening and causes death, despite treatment.[2,14,15] The incubation period (time between exposure and onset of symptoms) ranges from 3 to 14 days, but most often it is 4 to 7 days.[6] Therefore, travellers returning from endemic areas are unlikely to have dengue if fever or other symptoms start more than 14 days after they arrive home.[5] Children are more likely to have atypical presentation, often experiencing symptoms similar to those of the common cold or gastroenteritis (vomiting and diarrhea).[16] Children are also at greater risk of severe complications,[5,17] although their initial symptoms may be mild.[17]

Clinical course. The characteristic symptoms of dengue are sudden-onset fever, headache (typically located behind the eyes), muscle and joint pains, and a rash (Figure 3, online).[18] The alternative name for dengue, breakbone fever, comes from the associated muscle and joint pains.[2,10] The course of infection is divided into 3 phases: febrile, critical, and recovery.[18] The febrile phase involves high fever, potentially over 40°C (104°F), and is associated with generalized pain and a headache; this phase usually lasts 2–7 days.[10,18] Vomiting may also occur.[17] A rash occurs in 50%–80% of those with symptoms,[10,19] on the first or second day of symptoms as flushed skin, or later in the course of illness (days 4–7) as a measles-like maculopapular rash.[7,19] A rash described as "islands of white in a sea of red" has also been described.[20] Some petechiae may appear at this point,[18] as may some mild bleeding from the mucous membranes of the mouth and nose.[5,10] The fever pattern is classically biphasic or "saddleback," breaking and then returning for 1 or 2 more days.[7,20]

In some people, the disease proceeds to a critical phase as the fever resolves.[17] This phase is characterized by significant, diffuse leakage of plasma typically lasting 1–2 days.[18] This leakage can result in pulmonary edema and ascites, as well as hypovolemia and shock.[18] There may also be organ dysfunction and severe bleeding, typically from the gastrointestinal tract.[5,18] Shock (dengue shock syndrome) and hemorrhage (dengue hemorrhagic fever) occur in less than 5% of all cases of dengue;[5] however, those who have previously been infected with other serotypes of dengue virus (and are thus experiencing a secondary infection) are at increased risk.[5,21] This critical phase, though rare, is more common among children and young adults.[17]

Among those who have experienced the critical phase, the recovery phase occurs next, with resorption of the leaked fluid into the bloodstream[18] over a period of 2–3 days.[5] The improvement is often striking and may be accompanied by severe pruritus and bradycardia.[5,18] Another rash may occur, with either a maculopapular or a vasculitic appearance, which is followed by desquamation.[17] During this stage, a fluid-overloaded state may occur, in rare instances causing cerebral edema that leads to reduced level of consciousness or seizures.[5] Fatigue may last for weeks in adults.[17]

Associated problems. Dengue occasionally affects several other body systems,[18] either in isolation or along with the classic dengue symptoms.[16] Decreased level of consciousness occurs in 0.5%–6% of severe cases, attributable to encephalitis or, indirectly, to impairment of vital organs (e.g., hepatic encephalopathy).[16,20] Other neurologic disorders have been reported in the context of dengue, such as transverse myelitis and Guillain–Barré syndrome.[16] Myocarditis and acute liver failure are among the rarer complications.[5,18]

Cause

Virology. Dengue fever virus (DENV) is a single-stranded, positive-sense RNA virus of the family

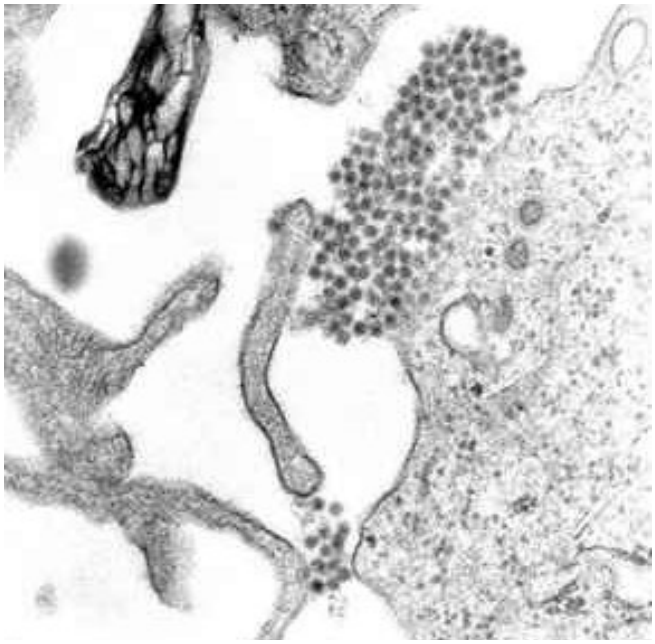

Figure 4
Dengue virus. Image file from Wikimedia Commons.

Flaviviridae and the genus *Flavivirus*. In Figure 4, a transmission electron micrograph, dengue virus virions appear as a cluster of dark dots near the centre of the image. Other members of the same genus include yellow fever virus, West Nile virus, St. Louis encephalitis virus, Japaneseencephalitisvirus,tick-borneencephalitisvirus, Kyasanur Forest disease virus, and Omsk hemorrhagic fever virus.[20] Most are transmitted by arthropods (mosquitoes or ticks) and are therefore also referred to as arboviruses (arthropod-borne viruses).[20]

The dengue virus genome (i.e., genetic material) contains about 11 000 nucleotide bases, which code for a single polyprotein that is cleaved post-translationally into 3 structural protein molecules (C, prM, and E) that form the virus particle and 7 nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5) that are found only in infected host cells and are required for viral replication.[21,22] The 5 strains of the virus (DENV-1, DENV-2, DENV-3, DENV-4, and DENV-5) are called serotypes because they differ in serum reactivity (antigenicity).[9,14,23] The fifth of these strains was first announced in 2013.[9]

Transmission. Dengue virus is transmitted primarily by *Aedes* mosquitoes, particularly *Aedes aegypti*[14] (Figure 5). These mosquitoes usually live between the latitudes of 35°N and 35°S below an elevation of 1000 m (3300 feet).[14] They typically bite during the day, particularly in the early morning and in the evening.[8,11] Other *Aedes* species that transmit the disease include *A. albopictus*, *A. polynesiensis*, and *A. scutellaris*.[14] Humans are the primary host of the virus,[14,20] which arose in nonhuman primates.[22] An infection can be acquired via a single bite.[24] A female mosquito that takes a blood meal from an infected person (during the potential 2- to 12-day range of the febrile, viremic period) becomes 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, and is subsequently released into its saliva. The virus seems to have no detrimental effect on the mosquito, which remains infected for life.[6] *Aedes aegypti* is particularly implicated, as it prefers to lay its eggs in artificial water containers, to live in close proximity to humans, and to feed on people rather than other vertebrates.[6]

Dengue can also be transmitted via infected blood products and through organ donation.[25,26] In countries such as Singapore, where dengue is endemic, the risk is estimated to be between 1.6 and 6 per 10 000 transfusions.[27] Vertical transmission (from mother to child) during pregnancy or at birth has been reported.[28] Other person-to-person modes of transmission have also been reported but are very unusual.[10] Dengue genetic types are region-specific, which suggests that establishment in new territories is relatively infrequent, despite dengue having emerged in new regions in recent decades.[17]

Predisposition. Severe disease is more common in babies and young children, but in contrast to many other infections, it is more common in children who are relatively well nourished.[5] Other risk factors for severe disease include female sex, high body mass index,[17] and high viral load.[29] Although each serotype can cause the full spectrum of disease,[21] virus strain is another risk

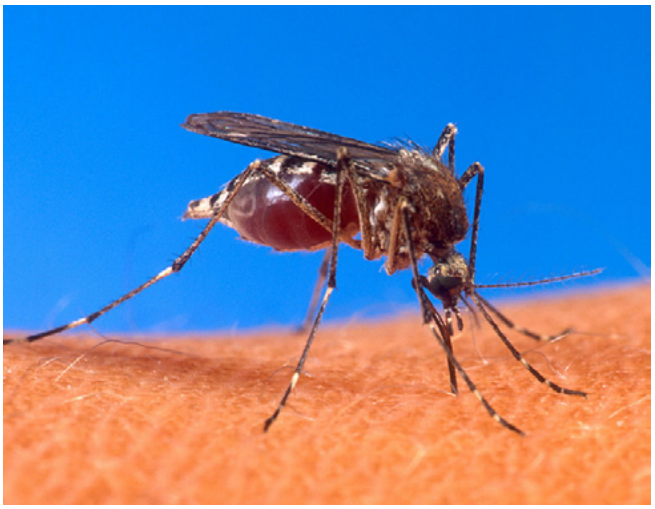

Figure 5
***Aedes aegypti* mosquito.** Image file from Wikimedia Commons.

factor for severe disease.[17] Infection with a given serotype is thought to produce lifelong immunity to that type, but only short-term protection against the other four.[10,14] The risk of severe disease from secondary infection increases if a person who was previously exposed to serotype DENV-1 contracts serotype DENV-2 or DENV-3, or if a person previously exposed to DENV-3 acquires DENV-2.[22] Dengue can be life-threatening for people with chronic diseases such as diabetes mellitus and asthma.[22]

Polymorphisms (normal variations) in particular genes have been linked to an increased risk of severe complications of dengue. Examples of affected genes include those coding for the proteins known as tumour necrosis factor α (TNFα), mannan-binding lectin,[2] cytotoxic T-lymphocyte-associated protein 4 (CTLA4), transforming growth factor β (TGFβ),[21] dendritic cell–specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), phospholipase C epsilon 1 (PLCE1), and particular forms of human leukocyte antigen from gene variations of HLA-B.[17,22] Glucose-6-phosphate dehydrogenase deficiency, a common genetic abnormality, particularly among people from Africa, appears to increase the risk.[29] Polymorphisms in the genes for the vitamin D receptor and Fc gamma receptor (FcγR) seem to offer protection against severe disease in secondary dengue infection.[22]

Mechanism of infection

When a mosquito carrying dengue virus bites a person, the virus enters the skin along with the mosquito's saliva. It binds to and enters white blood cells and then reproduces inside the cells while they move throughout the body. The white blood cells respond by producing a number of signalling proteins, including interferons and other cytokines, which are responsible for nonspecific symptoms such as fever, headache, joint pain, and muscle pain. In severe infection, virus production inside the body is greatly increased, and many more organs (such as the liver and the bone marrow) may be affected. Fluid from the bloodstream leaks through the wall of small blood vessels into body cavities because of endothelial dysfunction. As a result, less blood circulates, and shock may result. Furthermore, dysfunction of the bone marrow due to infection of the stromal cells leads to thrombocytopenia, which increases the risk of bleeding, the other major complication.[29]

Viral replication. Once inside the skin, dengue virus binds to Langerhans cells (dendritic cells in the skin that are engaged in surveillance for pathogens).[29] The virus enters these cells through binding of viral proteins with membrane proteins on the cells, specifically the C-type lectins known as DC-SIGN, mannose receptors, and C-type lectin domain family 5 member A (CLEC5A).[21] DC-SIGN, a nonspecific receptor for foreign material on dendritic cells, seems to be the main point of entry.[22] The dendritic cell then moves to the nearest lymph node. Meanwhile, the virus genome is translated in membrane-bound vesicles associated with the cell's endoplasmic reticulum, where the cell's protein synthesis apparatus produces new viral proteins that then copy the viral RNA and begin to assemble viral particles.[21] Immature virus particles are transported to the Golgi apparatus, the part of the cell where some of the proteins receive necessary sugar chains (glycoproteins), and the precursor membrane protein prM is cleaved to its M form. The mature new viruses bud inside the cell and are released by exocytosis. They are then able to enter other white blood cells, such as monocytes and macrophages.[21]

The initial reaction of infected cells is to produce interferon, a cytokine that raises a number of defences against viral infection through the innate immune system by augmenting the production of a large group of proteins (interferon-stimulated genes or ISGs), a process mediated by the Janus kinase signal transducer and activator of transcription pathway (also known as the JAK-STAT pathway).[21] Some serotypes of dengue virus appear to have mechanisms to slow down this process.[21] The ISGs also help to activate cells of the adaptive immune system, leading to the generation of antibodies specific for the virus, as well as T cells that directly attack infected cells.[21] Various antibodies are generated. Some of these antibodies bind tightly to the viral proteins and target them for phagocytosis (ingestion by specialized cells and destruction), but others 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.[21]

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. The exact mechanism behind antibody-dependent enhancement 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.[21,22] There is also a suspicion that

antibody-dependent enhancement is not the only mechanism underlying severe dengue-related complications,[2] and various lines of research have implied a role for T cells and soluble factors such as cytokines and the complement system.[29]

Severe disease is marked by capillary permeability (which allows protein-containing fluid to escape from blood vessels) and coagulopathy.[16,17] These features appear to be associated with a disordered state of the endothelial glycocalyx, which acts as a molecular filter of blood components.[17] Leaky capillaries (and the critical disease phase that results) are thought to be caused by an immune system response.[17] Other processes of interest include infected cells becoming necrotic, which affects both coagulation (blood clotting) and fibrinolysis (dissolution of blood clots), and thrombocytopenia, which also affects clotting.[29]

Diagnosis

The diagnosis of dengue is typically made clinically, on the basis of reported symptoms and physical examination, especially in endemic areas.[2] However, early dengue fever can be difficult to differentiate from other viral infections.[5] A probable diagnosis is based on findings of fever and 2 of the following: nausea and vomiting, rash, generalized pains, leukopenia, positive result on tourniquet test, or any warning sign (see Box 1) in someone who lives in an endemic area.[5,30] Warning signs typically occur before the onset of severe dengue.[18] The tourniquet test, which is particularly useful in settings where laboratory investigations are not readily available, involves applying a blood pressure cuff, inflating it to the midpoint between the diastolic and systolic pressure for 5 minutes, and then counting any petechial hemorrhages that occur. A higher number of petechiae makes diagnosis of dengue more likely; the lower limit for diagnosis is variably defined as 10–20 petechiae per 2.5 cm^2 (square inch).[18,31,32]

Box 1
Warning signs of dengue[17,30]

- Worsening abdominal pain
- Ongoing vomiting
- Enlargement of the liver
- Mucosal bleeding
- High hematocrit combined with low platelet count
- Lethargy or restlessness
- Serosal effusion

The diagnosis of dengue fever should be considered in anyone who experiences fever within 2 weeks of being in the tropics or subtropics.[17] It can be difficult to distinguish between dengue fever and chikungunya, a similar viral infection that shares many of the same symptoms and occurs in similar parts of the world.[10] Often, investigations are performed to exclude other conditions that cause similar symptoms, such as malaria, leptospirosis, viral hemorrhagic fever, typhoid fever, meningococcal disease, measles, and influenza.[5,33] Pleural effusions or ascites can be detected by physical examination if they are large,[5] and ultrasonographic demonstration of fluid may assist in the early identification of dengue shock syndrome.[2,5]

Classification. The 2009 classification of the World Health Organization (WHO) divides dengue fever into 2 groups: uncomplicated and severe.[2,34] According to this system, dengue that is associated with severe bleeding, severe organ dysfunction, or severe plasma leakage is considered severe, whereas all other cases are uncomplicated.[34] This simplified system replaces the 1997 WHO classification, which was found to be too restrictive, although it is still widely used,[34] including by the WHO's Regional Office for South-East Asia (as of 2011).[35] The 1997 classification divided dengue into undifferentiated fever, dengue fever, and dengue hemorrhagic fever.[5] Dengue hemorrhagic fever was subdivided further into grades I to IV, where grade I is the presence of only easy bruising or a positive tourniquet test result in someone with fever, grade II is the presence of spontaneous bleeding into the skin and elsewhere, grade III is clinical evidence of shock, and grade IV is shock so severe that blood pressure and pulse cannot be detected.[36] In this system, grades III and IV are referred to as "dengue shock syndrome."[34]

Laboratory tests. The graph shown in Figure 6 (online) illustrates the points when various laboratory tests for dengue fever become positive in relation to the course of illness, with day 0 being the first day of symptoms.[17] In the graph, "1st" refers to those with a primary infection, and "2nd" refers to those with a secondary infection.

The earliest change detectable on laboratory investigations is leukopenia, which may be followed by thrombocytopenia and metabolic acidosis.[5] A moderately elevated level of aminotransferase (aspartate aminotransferase and alanine aminotransferase) from the liver is commonly associated with thrombocytopenia and leukopenia.[17] In severe disease, plasma

leakage results in hemoconcentration (indicated by a rising hematocrit) and hypoalbuminemia.[5]

The diagnosis of dengue fever can be confirmed by microbiological laboratory testing.[30] This can be done by isolating virus in cell cultures, detecting its nucleic acid by polymerase chain reaction (PCR), and detecting viral antigens (such as NS1) or specific antibodies (i.e., serology).[22,37] Virus isolation and nucleic acid detection are more accurate than antigen detection, but these tests are not widely available because of their high cost.[37] Detection of NS1 during the febrile phase of a primary infection may be greater than 90% sensitive; however, sensitivity is only 60%–80% in subsequent infections.[17] All test results may be negative in the early stages of the disease.[5,22] PCR and viral antigen detection are more accurate in the first 7 days of infection.[17] A test approved in 2012, which is a DENV reverse transcription PCR assay, may improve access to PCR-based diagnosis.[38]

Except for serology tests, these laboratory investigations are of diagnostic value only during the acute phase of the illness. Tests for dengue virus–specific antibodies (immunoglobulins G and M [IgG and IgM]) can be useful in confirming the diagnosis in the later stages of the infection. Both IgG and IgM are produced after 5–7 days. The highest levels (titres) of IgM are detected following a primary infection, but IgM is also produced during re-infection. 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, IgG reaches peak levels in the blood after 14–21 days. During subsequent infections, levels peak earlier and titres are usually higher. Both IgG and IgM provide protective immunity to the infecting serotype of the virus.[6,10,22] In testing for IgG and IgM antibodies, there may be cross-reactivity with other flaviviruses, which may result in false positive results if there has been recent infection with or vaccination for yellow fever virus or Japanese encephalitis virus.[17] The detection of IgG alone is not considered diagnostic unless blood samples have been collected 14 days apart and a greater than 4-fold increase in levels of specific IgG over this period is detected. In a person with symptoms, the detection of IgM is considered diagnostic.[6]

Prevention

There are no approved vaccines for the dengue virus.[2] Prevention thus depends on control of, and protection from the bites of, the mosquito that transmits it.[11,13] The WHO recommends an integrated vector control program consisting of 5 elements: advocacy, social mobilization, and legislation to ensure that public health bodies and communities are strengthened; collaboration between health care and other sectors (public and private); an integrated approach to disease control to optimize use of resources; evidence-based decision-making to ensure that any interventions are targeted appropriately; and capacity-building to ensure an adequate response to the local situation.[11]

The primary method of controlling *A. aegypti* is by eliminating its habitats, which include standing water in urban areas (e.g., discarded tires, ponds, drainage ditches, and open barrels).[11] The photograph in Figure 7 (from the 1920s) depicts efforts to disperse standing water and thus decrease mosquito populations. If removal of habitat is not possible, another option is adding insecticides or biological control agents to standing water.[11] Reducing open collections of water through environmental modification is the preferred method of control, given the concerns about negative health effects from insecticides and the greater logistic difficulties associated with control agents.[11] Generalized spraying with organophosphate or pyrethroid

Figure 7
Dengue vector control, southern United States, 1920s.
Image file from Wikimedia Commons.

insecticides is sometimes done but is not thought to be effective.[15] People can prevent mosquito bites by wearing clothing that fully covers the skin, using repellent on clothing, or staying in air-conditioned, screened, or netted areas.[25] However, these methods appear not to be sufficiently effective, as the frequency of outbreaks appears to be increasing in some areas, probably because urbanization is increasing *Aedes* mosquito habitat; in addition, the range of the disease appears to be expanding, possibly because of climate change.[9]

Management

There are no specific antiviral drugs for dengue; however, maintaining proper fluid balance is important.[17] Treatment depends on the severity of symptoms.[12] Those who are able to drink, are passing urine, have no warning signs (as listed in Box 1), and are otherwise healthy can be managed at home with daily follow-up and oral rehydration therapy.[12] Those who have other health problems, who have warning signs, or who cannot manage regular follow-up should be admitted to hospital for care.[5,12] For those with severe dengue, care should be provided in an area with access to an intensive care unit.[12]

Intravenous hydration, if required, is typically needed for only 1 or 2 days.[12] The rate of fluid administration is titrated to a urinary output of 0.5–1 mL/kg per hour, stabilization of vital signs, and normalization of hematocrit.[5] The amount of fluid administered should be the smallest amount required to achieve these markers.[12] Invasive medical procedures such as nasogastric intubation, intramuscular injections, and arterial punctures are to be avoided, in view of the bleeding risk.[5] Paracetamol (acetaminophen) is used for fever and discomfort, and nonsteroidal anti-inflammatory drugs such as ibuprofen and acetylsalicylic acid are to be avoided, as they may aggravate the risk of bleeding. For patients presenting with unstable vital signs in the face of decreasing hematocrit, blood transfusion should be initiated early, rather than waiting for the hemoglobin concentration to decline to some predetermined "transfusion trigger" level. Packed red blood cells or whole blood is recommended; platelets and fresh frozen plasma are usually not recommended.[12]

During the recovery phase, intravenous fluids are discontinued to prevent fluid overload.[5] If fluid overload occurs and vital signs are stable, stopping administration of fluid may be all that is needed to eliminate the excess fluid. If the person is outside the critical phase, a loop diuretic such as furosemide may be used to eliminate excess fluid from the circulation.[12]

Epidemiology

Most people with dengue recover without any ongoing problems.[34] The fatality rate among those with severe disease is 1%–5%[5] and may be less than 1% with adequate treatment;[34] however, the fatality rate among those with shock can reach 26% if treatment is inadequate.[5] Dengue is endemic in more than 110 countries.[5] Figure 8 shows the distribution in 2006, with red indicating areas with *A. aegypti* and epidemic dengue, and aqua indicating *A. aegypti* without epidemic dengue. Current estimates of incidence range from 50 million[2] to 528 million[3] people infected yearly, leading to half a million hospital admissions[2] and about 25 000 deaths.[16]

Infections are most commonly acquired in the urban environment.[6] In recent decades, the expansion of villages, towns, and cities in endemic areas and the increased mobility of people have increased the number of epidemics and circulating dengue serotypes. Dengue fever, which was once confined to South-East Asia, has

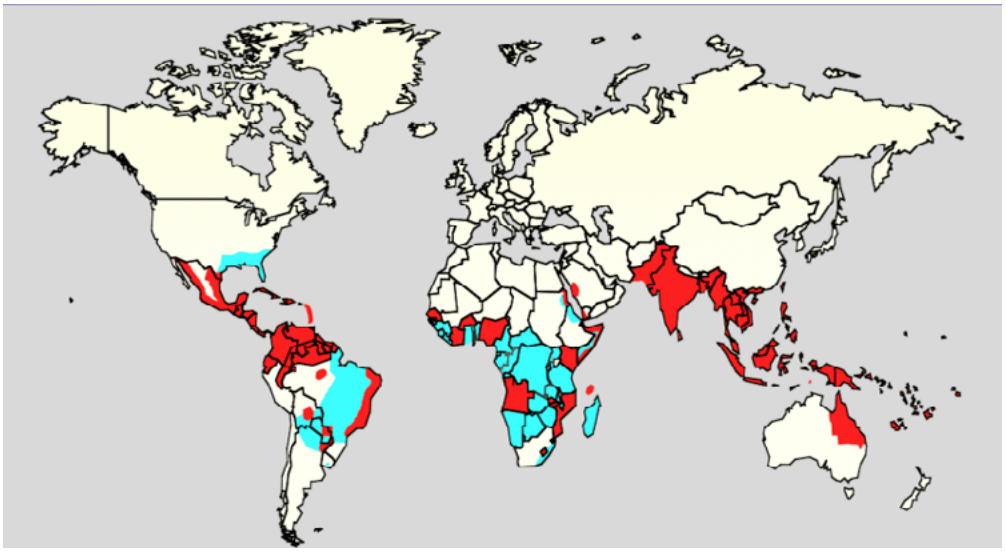

Figure 8
Global dengue distribution in 2006. Image file from Wikimedia Commons.

now spread to southern China, as well as countries in the Pacific Ocean, Africa, and the Americas.[1,6] It could also pose a threat to Europe.[15] During the period 2000 to 2009, 12 countries in South-East Asia were estimated to have about 3 million infections and 6000 deaths annually.[39] Dengue fever has been reported in at least 22 countries in Africa, but is likely present in most African countries, with 20% of the continental population at risk.[1]

The incidence of dengue increased 30-fold between 1960 and 2010.[40] This increase is believed to have been due to a combination of urbanization, population growth, increased international travel, and global warming.[2] The virus is geographically distributed around the equator. Of the 2.5 billion people living in endemic areas, 70% are in Asia and the Pacific.[41] Infection with dengue virus is second only to malaria as a diagnosed cause of fever among travellers returning from the developing world.[10] It is the most common viral disease transmitted by arthropods,[21] and the disease burden is estimated to be 1600 disability-adjusted life years per million population.[22] The WHO counts dengue fever as 1 of 17 neglected tropical diseases.[42]

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 South-East Asia and Africa by transmission from female *Aedes* mosquitoes—of species other than *A. aegypti*—to their offspring and to lower primates. In towns and cities, the virus is primarily transmitted by the highly domesticated *A. aegypti.* In rural settings, the virus is transmitted to humans by *A. aegypti* and other species of *Aedes* such as *A. albopictus.*[6] Both of these species had expanding ranges in the second half of the 20th century.[17] In all settings, the infected lower primates or humans greatly increase the number of circulating dengue viruses, in a process called amplification.[6]

History

The first record of a case of probable dengue fever is in a Chinese medical encyclopedia from the Jin dynasty (AD 265–420), which referred to a "water poison" associated with flying insects.[4,43] The primary vector, *A. aegypti,* spread out of Africa in the 15th to 19th centuries in part because of increased globalization secondary to the slave trade.[17] 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. From that time until 1940, epidemics were infrequent.[4] In 1906, transmission by the *Aedes* mosquitoes was confirmed, and in 1907 dengue was the second disease (after yellow fever) that was shown to be caused by a virus.[44] Further investigations by John Burton Cleland and Joseph Franklin Siler completed the basic understanding of dengue transmission.[44]

The marked spread of dengue during and after the Second World War has been attributed to ecologic disturbances. 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 in 1953; by the 1970s, it had become a major cause of child mortality and had emerged in the Pacific and the Americas.[4] 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 been infected with DENV-1 several years earlier.[20]

Etymology. The origins of the word "dengue" are unclear, but one theory is that it is derived from the Swahili phrase "Ka-dinga pepo," which describes the disease as being caused by an evil spirit.[43] The Swahili word "dinga" may 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.[45] However, it is possible that use of the Spanish word derived from the similar-sounding Swahili word.[43] Slaves in the West Indies who had contracted dengue were said to have the posture and gait of a dandy, and the disease was known there as "dandy fever."[46,47] The term "break-bone fever" was applied by physician and United States Founding Father Benjamin Rush in a 1789 report of the 1780 epidemic in Philadelphia. In the report's title he also used the term "bilious remitting fever."[48] The term "dengue fever" came into general use only after 1828. Other historical terms include "breakheart fever" and "la dengue." Terms for severe disease include "infectious thrombocytopenic purpura" and "Philippine," "Thai," or "Singapore hemorrhagic fever."[47]

Future directions

Research efforts to prevent and treat dengue include various means of vector control,[49] vaccine development, and antiviral drugs.[13]

With regard to vector control, a number of novel methods have been used to reduce mosquito numbers,

with some success, including placement of the guppy (*Poecilia reticulata*) or copepods in standing water to eat the mosquito larvae.[49] For example, Figure 9 shows public health officers releasing *P. reticulata* fry into an artificial lake in the Lago Norte district of Brasília, Brazil, as part of a vector-control effort. Attempts are ongoing to infect the mosquito population with bacteria of the *Wolbachia* genus, which makes the mosquitoes partially resistant to dengue virus.[17]

Programs are underway to develop a dengue vaccine that will cover serotypes 1 through 4,[13] and now that there is a fifth serotype, it will need to be factored in to these efforts.[9] One of the concerns is that a vaccine could increase the risk of severe disease through antibody-dependent enhancement.[50] The ideal vaccine would be safe, would be effective after 1 or 2 injections, would cover all serotypes, would not contribute to antibody-dependent enhancement, would be easily transported and stored, and would be both affordable and cost-effective.[50] As of 2012, a number of vaccines were undergoing testing.[8,50] The most well developed of these is based on a weakened combination of the yellow fever virus and the first 4 dengue serotypes.[8,51] It is hoped that the first products will be commercially available by 2016.[13]

In addition to attempts to control the spread of *Aedes* mosquitos and work to develop a vaccine against dengue, efforts are being made to develop antiviral drugs that would be used to treat attacks of dengue fever and prevent severe complications.[52,53] Discovery of the structure of the viral proteins may aid in the development of effective drugs.[53] There are several plausible targets. One approach uses nucleoside analogues to inhibit the viral RNA–dependent RNA polymerase (within the NS5 protein), which copies the viral genetic material. It may also be possible to develop specific inhibitors of the viral protease (within the NS3 protein), which cleaves functional proteins from the viral polyprotein.[54] Finally, it may be possible to develop entry inhibitors that will prevent the virus from entering cells or inhibitors of the 5′ capping process that is required for viral replication.[52]

Figure 8
Public health officers release *Poecilia reticulata* (guppy) fry into an artificial lake in Brasília, Brazil, as part of dengue vector control. Image file from Wikimedia Commons.

Conclusions

The world has seen large increases in the rates of dengue fever over the past 50 years. Although this disease occurs most commonly in the tropics and subtropics, many cases are now being seen among returning travellers in all areas of the world.

Most cases can be managed with oral rehydration and close follow-up. Occasionally, the judicious use of intravenous fluids is required to maintain sufficient urinary output and perfusion. Even less commonly, dengue may cause severe disease requiring blood transfusions and admission for intensive care.

While efforts are being made to develop a vaccine, prevention currently relies primarily on reducing the habitat of the vector, *A. aegypti*, and avoiding its bite. Habitat reduction involves decreasing mosquitos' access to stagnant bodies of water or, if that is not possible, applying insecticide.

Contributors: James Heilman brought the article to Wikipedia's "good article" status (i.e., an article with no obvious problems, approaching the quality of a professional encyclopedia) on January 16, 2011, by rewriting the majority of the original version of the article, on the basis of the best available sources. He (along with Jacob De Wolff) brought the article to Wikipedia's "featured article" status (i.e., an article that is deemed to be professional, outstanding, and thorough) on July 4, 2011. During the writing process of the article, he made 453 edits. Following peer review by *Open Medicine*, he made more than 99 edits. Jacob de Wolff provided peer review to bring the article to "good article" status. He led the improvements to "featured article" status in collaboration with James Heilman and Graham Beards. During the writing process of the article he made 197 edits. Graham Beards worked on improving the virology aspects of the article during the push for "featured article" status. During the writing process of the article, he made 52 edits. Following peer review by *Open Medicine*, he made more than 10 edits, including the addition of Figure 4. Brian Basden (along with James Heilman) worked to update the article with recent literature (i.e., published since it reached "featured article" status). During the writing process of the article, he made 76 edits; following peer review by *Open Medicine*, he made more than 12 edits. In addition to these 4 main contributors, another 1369 people and bots made edits to this article since it was first created on Wikipedia in February 2002. A full list of all contributions is available from: https://en.wikipedia.org/w/index.php?title=Dengue_fever&action=history

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