Dengue Fever

Wikipedia Clinical Review

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Words: 4 544
Keywords: Dengue fever, Dengue hemorrhagic fever, Dengue/Classification, Dengue/Complications, Dengue/Epidemiology, Dengue/History, Dengue/Diagnosis, Dengue/Virology Dengue/Prevention, Dengue/Immunology, Differential Diagnosis, Tropical Disease, Arbovirus Infections, Wikimedicine, Wikipedia

(figure 1) Classic skin rash from Dengue fever

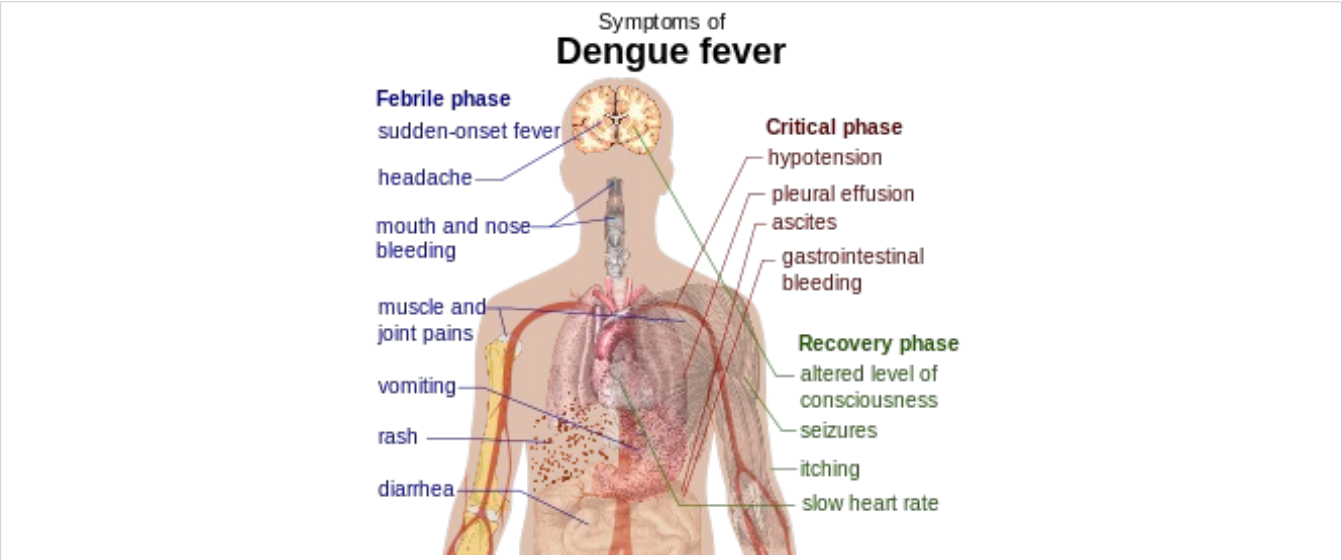
1Introduction

Dengue fever (UK/ˈdɛŋgeɪ/ or US /ˈdɛŋgiː/), also known as **breakbone fever**, is an 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 the life-threatening **dengue hemorrhagic fever**, resulting in bleeding, low levels of blood platelets and blood plasma leakage, or into **dengue shock syndrome**, wheredangerously low blood pressure occurs.

Dengue is transmitted by several species of mosquito within the genus *Aedes*, principally *A. aegypti*. The virus has four different types; infection with one type usually gives lifelong immunity 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, 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 for mild or moderate disease, and intravenous fluids and blood transfusion for more severe cases. The incidenceof 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 and is endemic 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.

2Signs and symptoms



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

Typically, people infected with dengue virus are asymptomatic (80%) or only have mild symptoms such as an uncomplicated fever.[1][2][3] Others have more severe illness (5%), and in a small proportion it is life-threatening.[1][3] The incubation period (time between exposure and onset of symptoms) ranges from 3–14 days, but most often it is 4–7 days.[4] 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] Children often experience symptoms similar to those of the common cold and gastroenteritis (vomiting and diarrhea),[6] and generally have less severe symptoms than adults,[7] but are more susceptible to the severe complications.[5]

1Clinical 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][8] The course of infection is divided into three phases: febrile, critical, and recovery.[9]

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][9] At this stage, a rash occurs in 50–80% of those with symptoms.[8][10] It occurs in the first or second day of symptoms as flushed skin, or later in the course of illness (days 4–7), as a measles-like rash.[10][11] Some petechiae (small red spots that do not disappear when the skin is pressed, which are caused by broken capillaries) can appear at this point,[9] as may some mild bleeding from the mucous membranes of the mouth and nose.[5][8] The fever itself is classically biphasic in nature, breaking and then returning for one or two days, although there is wide variation in how often this pattern actually happens.[11][12]

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]During this phase there may be significant fluid accumulation in the chest and abdominal cavity due to increased capillary permeability and leakage. This leads to depletion of fluid from the circulation and decreased blood supply to vital organs.[9] During this phase, organ dysfunction and severe bleeding, typically from the

gastrointestinal tract, may occur.[5][9] 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 ("secondary infection") are at an increased risk.[5][13]

The recovery phase occurs next, with resorption of the leaked fluid into the bloodstream.[9] This usually lasts two to three days.[5] The improvement is often striking, but there may be severe itching and a slow heart rate.[5][9] Another rash may occur with either a maculopapular or avasculitis-like appearance followed by peeling of the skin.[14] During this stage, a fluid overload state may occur; if it affects the brain, it may cause a reduced level of consciousness or seizures.[5] A feeling of fatigues may last for weeks afterwards.[14]

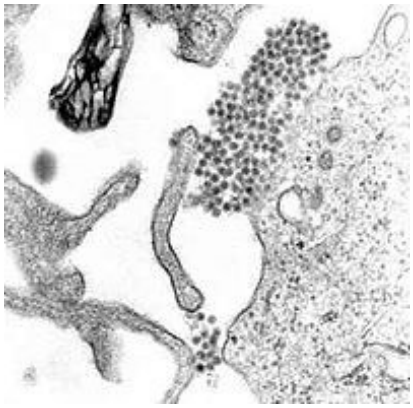
2**Complications.**

Dengue can occasionally affect several other body systems,[9] either in isolation or along with the classic dengue symptoms.[6] 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 or indirectly as a result of impairment of vital organs, for example, the liver.[6][12]

Other neurological disorders have been reported in the context of dengue, such as transverse myelitis and Guillain-Barré syndrome.[6] Infection of the heart and acute liver failure are among the rarer complications.[5][9]

3Cause

1Virology



(figure 3) A TEM micrograph showing dengue virus virions (the cluster of dark dots near the center)

Dengue fever virus (DENV) is an RNA virus of the family *Flaviviridae*; genus *Flavivirus*. Other members of the same genus include yellow fever virus, West Nile virus, St. Louis encephalitis virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kyasanur forest disease virus, and Omsk hemorrhagic fever virus.[12] Most are transmitted by arthropods (mosquitoes or ticks), and are therefore also referred to as arboviruses (*ar*thropod-*bo*rne viruses).[12]

The dengue virus genome (genetic material) contains about 11,000 nucleotide bases, which code for the three different types of protein molecules (C, prM and E) that form the virus particle 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][15] There are four strains of the

virus, which are calledserotypes, and these are referred to as DENV-1, DENV-2, DENV-3 and DENV-4.[2] All four serotypes can cause the full spectrum of disease.[13] Infection with one serotype is believed to produce lifelong immunity to that serotype but only short term protection against the others.[2][8]

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]

2Transmission

(figure 4) The mosquito *Aedes aegypti* feeding off a human host

Dengue virus is primarily transmitted by *Aedes* mosquitoes, particularly *A. aegypti*.[2] These mosquitoes usually live between the latitudes of 35° North and 35° South below an elevation of 1,000 metres (3,300 ft).[2] They bite primarily during the day.[16] Other *Aedes* species that transmit the disease include*A. albopictus*, *A. polynesiensis* and *A. scutellaris*.[2] Humans are the primary host of the virus,[2][12] but it also circulates in nonhuman primates.[17] An infection can be acquired via a single bite.[18] 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 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]

Dengue can also be transmitted via infected blood products and through organ donation.[20][21] In countries such as Singapore, where dengue is endemic, the risk is estimated to be between 1.6 and 6 per 10,000 transfusions.[22] Vertical transmission (from mother to child) during pregnancy or at birth has been reported.[23] Other person-to-person modes of transmission have also been reported, but are very unusual.[8]

3Predisposition

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] Women are more at risk than men.[15] Dengue can be life-threatening in people with chronic diseases such asdiabetes and asthma.[15]

Polymorphisms (normal variations) in particular genes have been linked with an increased risk of severe dengue complications. Examples include the genes coding for the proteins known as TNFα,

mannan-binding lectin,[1] CTLA4, TGFβ,[13] DC-SIGN, and particular forms of human leukocyte antigen.[15] A common genetic abnormality in Africans, known as glucose-6-phosphate dehydrogenase deficiency, appears to increase the risk.[24] Polymorphisms in the genes for the vitamin D receptor and FcγR seem to offer protection against severe disease in secondary dengue infection.[15]

4Mechanism

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, 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, 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 and the 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]

1Viral replication

Once inside the skin, dengue virus binds to Langerhans cells (a population of dendritic cells in the skin that identifies pathogens).[24] The virusenters the cells through binding between viral proteins and membrane proteins on the Langerhans cell, specifically the C-type lectins called DC-SIGN, mannose receptor and CLEC5A.[13] DC-SIGN, a non-specific receptor for foreign material on dendritic cells, seems to be the main point of entry.[15] The dendritic cell moves to the nearest lymph node. Meanwhile, the virus genome is replicated in membrane-bound vesicles on the cell'sendoplasmic 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, the part of the cell where some of the proteins receive necessary sugar chains (glycoproteins). The now mature new viruses bud on the surface of the infected cell and are released by exocytosis. They are then able to enter other white blood cells, such as monocytes and macrophages.[13]

The initial reaction of infected cells is to produce interferon, a cytokine that raises a number of defenses against viral infection through the innate immune system by augmenting the production of a large group of proteins mediated by the JAK-STAT pathway. Some serotypes of dengue virus appear to have mechanisms to slow down this process. Interferon also activates the adaptive immune system, which leads to the generation ofantibodies against the virus as well as T cells that directly attack any cell infected with the virus.[13] Various antibodies are generated; some bind closely to the viral proteins and target them for phagocytosis (ingestion by specialized cells 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]

2Severe 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 (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][15] There is a suspicion that ADE is not the only mechanism underlying severe dengue-related

complications,[1] and various lines of research have implied a role for T cells and soluble factors such as cytokines and the complement system.[24]

Severe disease is marked by two problems: dysfunction of endothelium (the cells that line blood vessels) and disordered blood clotting.[6]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 and the 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 (the opposing systems of blood clotting and clot degradation). These alterations together lead to both endothelial dysfunction and coagulation disorder.[24]

5

6Diagnosis

Warning signs[25]
Abdominal pain
Ongoing vomiting
Liver enlargement
Mucosal bleeding
High hematocrit with low platelets
Lethargy

(figure 6:)

The diagnosis of dengue is typically made clinically, on the basis of reported symptoms and physical examination; this applies especially in endemic areas.[1] However, early disease can be difficult to differentiate from other viral infections.[5] A probable diagnosis is based on the findings of fever plus two of the following: nausea and vomiting, rash, generalized pains, low white blood cell count, positive tourniquet test, or any warning sign (see table) in someone who lives in an endemic area.[25] Warning signs typically occur before the onset of severe dengue.[9] The tourniquet test, which is particularly useful in settings where no laboratory investigations are readily available, involves the application of a blood pressure cuff for five minutes, followed by the counting of any petechial hemorrhages; a higher number makes a diagnosis of dengue more likely.[9]

The diagnosis should be considered in anyone who develops a fever within two week of being in the tropics or subtropics.[14] It can be difficult to distinguish dengue fever and chikungunya, a similar viral infection that shares many symptoms and occurs in similar parts of the world to dengue.[8] Often, investigations are performed to exclude other conditions that cause similar symptoms, such asmalaria, leptospirosis, typhoid fever, and meningococcal disease.[5]

The earliest change detectable on laboratory investigations is a low white blood cell count, which may then be followed by low platelets and metabolic acidosis.[5] In severe disease, plasma leakage results in hemoconcentration (as indicated by a rising hematocrit) and hypoalbuminemia.

[5] Pleural effusions or ascites can be detected by physical examination when large,[5] but the demonstration of fluid on ultrasound may assist in the early identification of dengue shock syndrome.[1][5] The use of ultrasound is limited by lack of availability in many settings.[1]

1Classification

The World Health Organization's 2009 classification divides dengue fever into two groups: uncomplicated and severe.[1][25] 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]The 1997 classification divided dengue into undifferentiated fever, dengue fever, and dengue hemorrhagic fever.[5][26] 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, and grade IV is shock so severe that blood pressure and pulse cannot be detected.[26] Grades III and IV are referred to as "dengue shock syndrome".[25][26]

2Laboratory tests

Dengue fever may be diagnosed by microbiological laboratory testing.[25] This can be done by virus isolation in cell cultures, nucleic acid detection by PCR, viral antigen detection or specific antibodies (serology).[15][27] 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] All tests may be negative in the early stages of the disease.[5][15] 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]

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 and 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) 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, which can make the interpretation of the serology difficult.[8][15][29] 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]

7Prevention

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

There are no approved vaccines for the dengue virus.[1] Prevention thus depends on control of and protection from the bites of the mosquito that transmits it.[16][30] 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]

The primary method of controlling *A. aegypti* is by eliminating its habitats.[16] This is done by emptying containers of water or by adding insecticides or biological control agents to these areas, [16] although spraying with organophosphate or pyrethroid insecticides is not thought to be effective.[3] 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] People can prevent mosquito bites by wearing clothing that fully covers the skin, using mosquito netting while resting, and/or the application of insect repellent (DEET being the most effective).[18]

8 Management

There are no specific treatments for dengue fever.[1] Treatment depends on the symptoms, varying from oral rehydration therapy at home with close follow-up, to hospital admission with administration of intravenous fluids and/or blood transfusion.[31] 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]

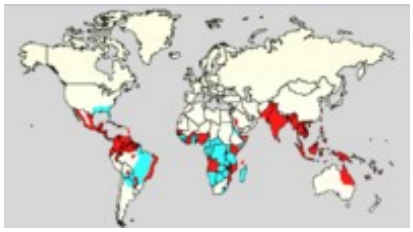
Intravenous hydration is usually only needed for one or two days.[31] The rate of fluid administration is titrated to a urinary output of 0.5–1 mL/kg/hr, stable vital signs and normalization of hematocrit.[5] Invasive medical procedures such as nasogastric intubation, intramuscular injections and arterial punctures are avoided, in view of the bleeding risk.[5] Paracetamol (acetaminophen) is used for fever and discomfort whileNSAIDs such as ibuprofen and aspirin are avoided as they might aggravate the risk of bleeding.[31] 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] Packed red blood cells or whole blood are recommended, while platelets and fresh frozen plasma are usually not.[32]

During the recovery phase intravenous fluids are discontinued to prevent a state of fluid overload.[5] If fluid overload occurs and vital signs are stable, stopping further fluid may be all that is needed.[32] If a person is outside of the critical phase, a loop diuretic such as furosemide may be used to eliminate excess fluid from the circulation.[32]

9Epidemiology

See also: 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] The mortality is 1–5% without treatment,[5] and less than 1% with adequate treatment;[25] however severe disease carries a mortality of 26%.[5] Dengue is endemic in more than 110 countries.[5] It infects 50 to 100 million people worldwide a year, leading to half a million hospitalizations,[1] and approximately 12,500–25,000 deaths.[6][33]

The most common viral disease transmitted by arthropods,[13] dengue has a disease burden estimated to be 1600 disability-adjusted life years per million population, which is similar to other childhood and tropical diseases such as tuberculosis.[15] As a tropical disease dengue is deemed only second in importance tomalaria,[5] though the World Health Organization counts dengue as one of sixteen neglected tropical diseases.[34]

The incidence of dengue increased 30 fold between 1960 and 2010.[35] This increase is believed to be due to a combination of urbanization, population growth, increased international travel, and global warming.[1] 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] 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] and it is the second most common infection after malaria to be diagnosed in this group.[8]

Until 2003, dengue was classified as a potential bioterrorism agent, but subsequent reports removed this classification as it was deemed too difficult to transfer and only caused hemorrhagic fever in a relatively small proportion of people.[36]

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*. 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] The urban cycle is the most important to infections of humans and dengue infections are primarily confined to towns and cities.[38] 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] and might pose a threat to Europe.[3]

10

11History

12The first record of a case of probable dengue fever is in a Chinese medical encyclopedia from the Jin Dynasty (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] From that time until 1940, epidemics were infrequent.[40]
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.[41] Further investigations by John Burton Cleland and Joseph Franklin Siler completed the basic understanding of dengue transmission.[41]

The marked spread of dengue during and after the Second World War 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 in 1953; by the 1970s, it had become a major cause of child mortality and had emerged in the Pacific and the Americas.[40] 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]

1

The origins of the word "dengue" are not clear, 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.[39] 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] However, it is possible that the use of the Spanish word derived from the similar-sounding Swahili.[39] Slaves in the West Indies having contracted dengue were said to have the posture and gait of a dandy, and the disease was known as "dandy fever".[43][44]

The term "break-bone fever" was first applied by physician and Founding Father Benjamin Rush, in a 1789 report of the 1780 epidemic in Philadelphia. In the report he uses primarily the more formal term "bilious remitting fever".[36][45] The term dengue fever came into general use only after 1828.[44] Other historical terms include "breakheart fever" and "la dengue".[44] Terms for severe disease include "infectious thrombocytopenic purpura" and "Philippine", "Thai", or "Singapore hemorrhagic fever".[44]

13

14Research

(figure 8)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.

Research efforts to prevent and treat dengue include various means of vector control,[46] vaccine development, and antiviral drugs.[30]

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*) or copepods in standing water to eat the mosquito larvae.[46] Another effort is to infect mosquitoes with *wolbachia* which leads to subsequent resistance of mosquitoes to the dengue virus.[14]

There are ongoing programs working on a dengue vaccine to cover all four serotypes.[30] One of the concerns is that a vaccine could increase the risk of severe disease through antibody-dependent enhancement.[47] 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] As of 2009, a number of vaccines were undergoing testing.[15][36][47] It is hoped that the first products will be commercially available by 2015.[30]

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 that would be used to treat attacks of dengue fever and prevent severe complications.[48][49] Discovery of the structure of the viral proteins may aid the development of effective drugs.[49] There are several plausible targets. The first approach is inhibition of the viralRNA-dependent RNA polymerase (coded by NS5), which copies the viral genetic material, with nucleoside analogs. Secondly, it may be possible to develop specific inhibitors of the viral protease (coded by NS3), which splices viral proteins.[50] Finally, it may be possible to develop entry inhibitors, which stop the virus entering cells, or inhibitors of the 5′ capping process, which is required for viral replication.[48]

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