The Aedes Aegypti Mosquito[1]

Dengue Epidemic in Puerto Rico 2024

Diagnosis and Treatment of Mosquito-Borne Dengue Illness

By

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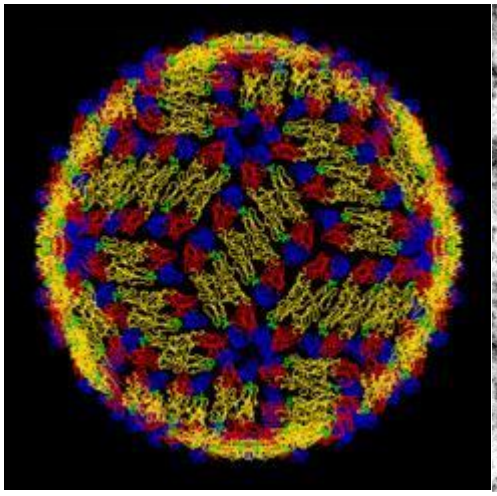
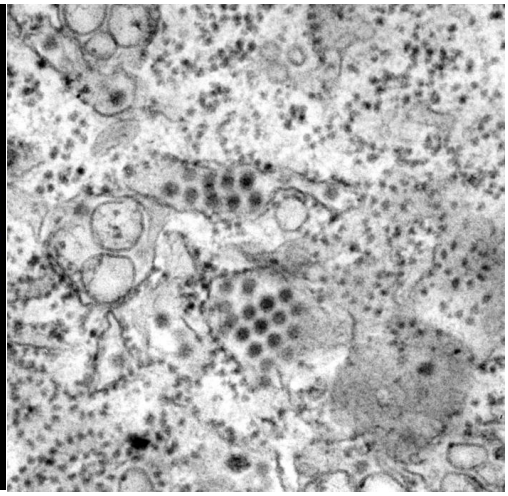
On March 26, 2024 Puerto Rico declared a dengue epidemic after having 549 cases, including 341 hospitalizations and 29 severe cases year to date through March 10th.[2]

No other animal infects and causes disease as effectively as mosquitos, which are the deadliest animals in the world to humans. Infections caused by mosquitos kill over 700,000 people a year.[3] In this article we will look at mosquito borne dengue virus illness.



Structure of a dengue virus[4]



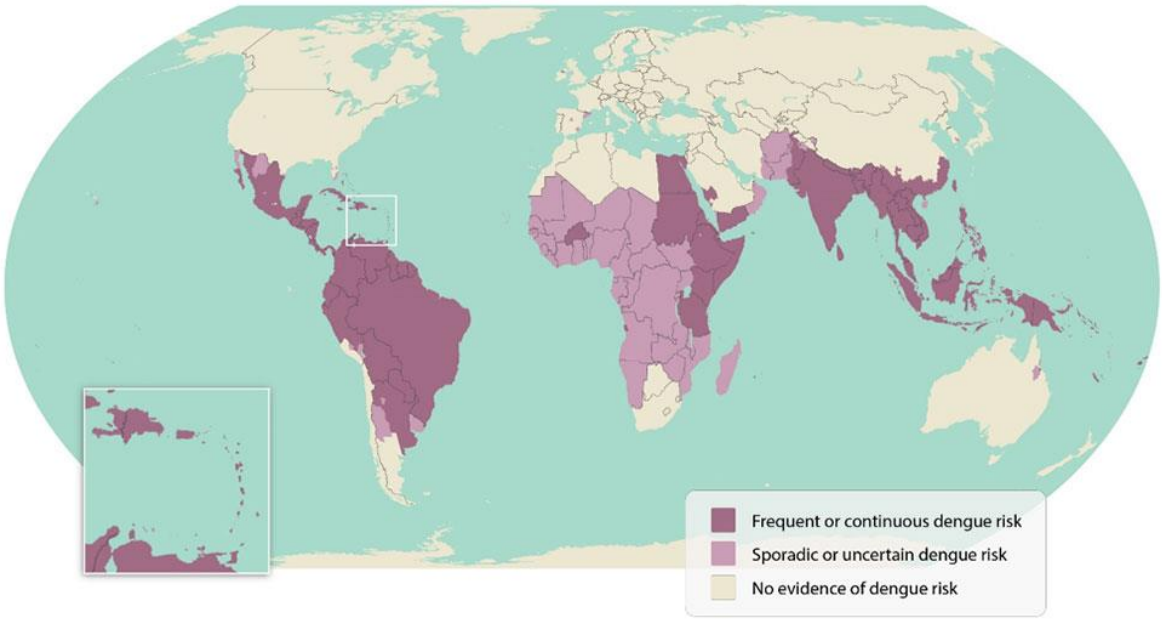
Dengue viruses in tissue[5]

Dengue viruses are Flaviviruses, transmitted through the bite of infected Aedes aegypti or Aedes albopictus mosquitos. Dengue is caused by one of four related viruses: Dengue virus 1, 2, 3, and 4. For this reason, a person can be infected as many as four times with the different dengue viruses.[6]

The history of dengue is not well known, but a dengue-like outbreak in humans was recorded in a Chinese medical encyclopedia in 992. In the 1700s dengue was known as breakbone fever. Queen Luisa of Spain used the word dengue while writing about her recovery from it in 1801. No one is sure about dengue's etymology, but the word dengue in Spanish means affectation, or careful, and may have described the stiff, painful movements of people with dengue fever. Another theory is that the name came from a Swahili phrase "Ka dinga pepo", or "disease caused by an evil spirit".[7]

Dengue is common in more than 100 countries around the world. About three billion people live in endemic areas, and every year up to 400 million people get infected with dengue, approximately 100 million people get symptomatic illness, and 22,000 die from severe dengue.[7]

Dengue is common in the U.S. territories of Puerto Rico, the U.S. Virgin Islands, and American Samoa. Nearly all dengue cases reported in the U.S. mainland are from travelers infected elsewhere. In 2023, there were 2,890 cases of dengue reported in the U.S. including Puerto Rico.[8] Dengue is a frequent cause of infection in Central and South America, East Africa, Southeast Asia and the Pacific Islands.[9]



Global Dengue Risk Map[9]

World Health Organization(WHO) Clinical Dengue Definitions[10]

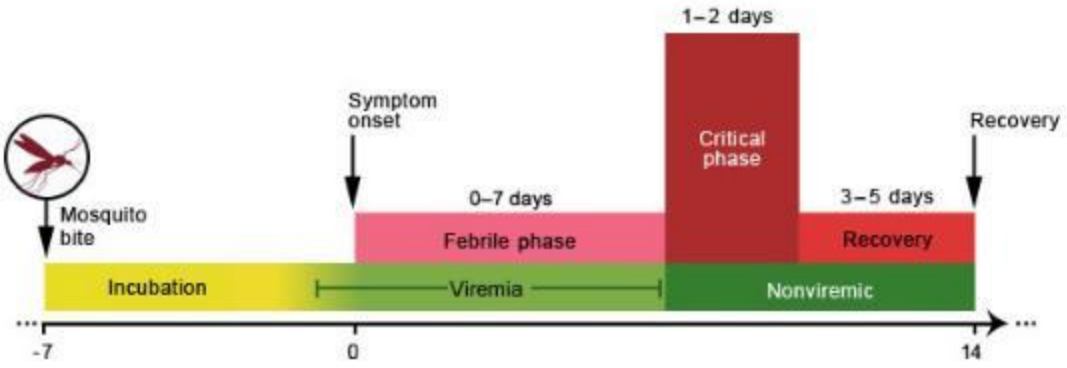
Dengue is defined by a combination of ≥2 clinical findings in a febrile person who traveled to, or lives in a dengue-endemic area. Clinical findings include nausea, vomiting, rash, aches and pains, a positive tourniquet test, leukopenia, or the following warning signs which may predict severe dengue: abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, and liver enlargement.

Severe dengue is defined as dengue with any of the following symptoms: severe plasma leakage leading to shock or fluid accumulation with respiratory distress; severe bleeding; or severe organ impairment such as elevated liver transaminases ≥1,000 IU/L, impaired consciousness, or heart impairment.

Dengue Clinical Disease and Treatment[10]

Most dengue infections are asymptomatic, with only 25% of dengue virus infections estimated to be symptomatic. It commonly presents as a mild to moderate, nonspecific, acute febrile illness. Approximately 5% of patients with dengue progress to severe dengue, a life-threatening disease. The early clinical findings of severe dengue are nonspecific, but recognizing early signs of shock, and promptly initiating intensive care unit therapy can reduce the risk of death to <0.5%.

A study of antibody dependent enhancement of dengue in children, found that the level of serum antibodies from a first infection determined the risk of severe dengue disease on reinfection. The presence of high dengue antibody titers in an individual are protective, but people with intermediate antibody titers had a much higher likelihood of developing severe dengue, even greater than those with low antibody titers. In that study the chances of getting severe dengue during a second infection was 1.6% in the high antibody titer group, 11.4% in the intermediate antibody titer group, and 6.6% in low antibody titer group. It is thought that particularly with intermediate dengue antibody titers, some binding of antibodies to the dengue virus occurs, but the antibody does not necessarily neutralize the virus. This creates a virus-antibody complex that appears to facilitate viral entry into host cells, and can trigger an immune cascade that leads to severe dengue. This is felt to be the reason why a dengue re-infection with a different strain, or first infection after dengue vaccination, may increase the risk of contracting severe dengue.[11]

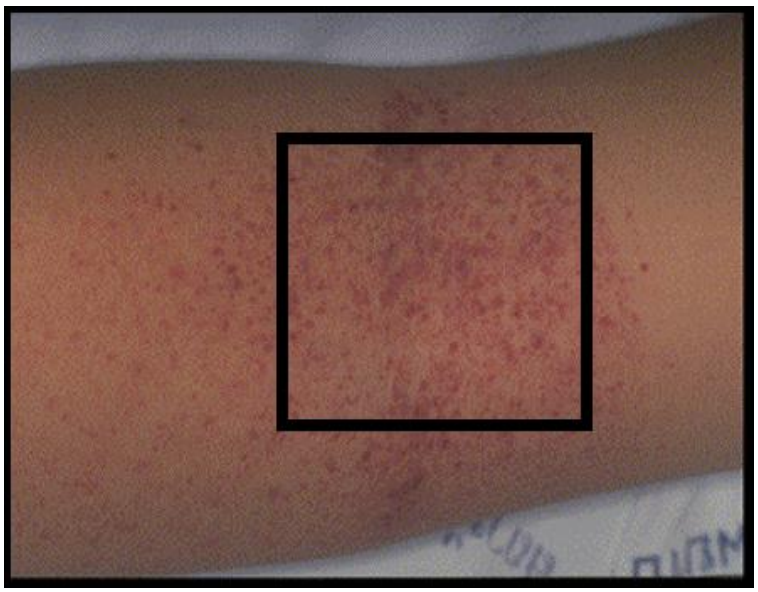


Clinical Course of Dengue[12]

Dengue begins abruptly after a typical incubation period of five to seven days, and has three phases: febrile, critical, and convalescent or recovery.

Febrile Phase

The febrile phase lasts two to seven days and can be biphasic. Other signs and symptoms may include severe headache, retro-orbital eye pain, muscle, joint, bone pain, and/or a macular (reddened and flat) or maculopapular (reddened flat with some raised areas) rash. Some patients have an injected oropharynx and facial erythema (redness) the first 24–48 hours after onset. Bleeding may occur from thrombocytopenia (low platelets), or in more ill patients from a coagulopathy (blood clotting disorder). Thrombocytopenia results from transient bone marrow suppression, and increased peripheral destruction of platelets in dengue.[13] In this phase, patients may have minor hemorrhagic manifestations such as ecchymosis(blood vessel leakage under the skin over 1 centimeter), purpura (blood vessel leakage between 4 and 10 millimeters), epistaxis (nosebleeds), bleeding gums, or hematuria (bloody urine). Petechiae (blood vessel leakage less than 4mm) may occur, and a positive tourniquet test may aid in the diagnosis of dengue. A positive tourniquet test result is ten or more petechiae per one square inch in the arm, after inflating a blood pressure cuff halfway between the systolic and diastolic pressures for two minutes.[14]



Positive Tourniquet Test[14]

Critical Phase

The critical phase of dengue begins at defervescence, and typically lasts 24–48 hours. Most patients clinically improve during this phase, but there can be substantial plasma leakage due to a marked increase in vascular permeability. Patients with severe plasma leakage and third spacing may have pleural effusions, ascites, hypoproteinemia, or hemoconcentration. Liver enlargement may occur.[13] Once hypotension develops, irreversible shock and death may ensue despite resuscitation. Patients can also develop severe hemorrhagic manifestations such as hematemesis (vomiting blood), bloody stools, or menorrhagia (heavy menstrual bleeding). Increased activated partial thromboplastin time (APTT), and a reduction in fibrinogen levels may be seen in severe dengue.[13] Uncommon complications include myocarditis, pancreatitis, and encephalitis.

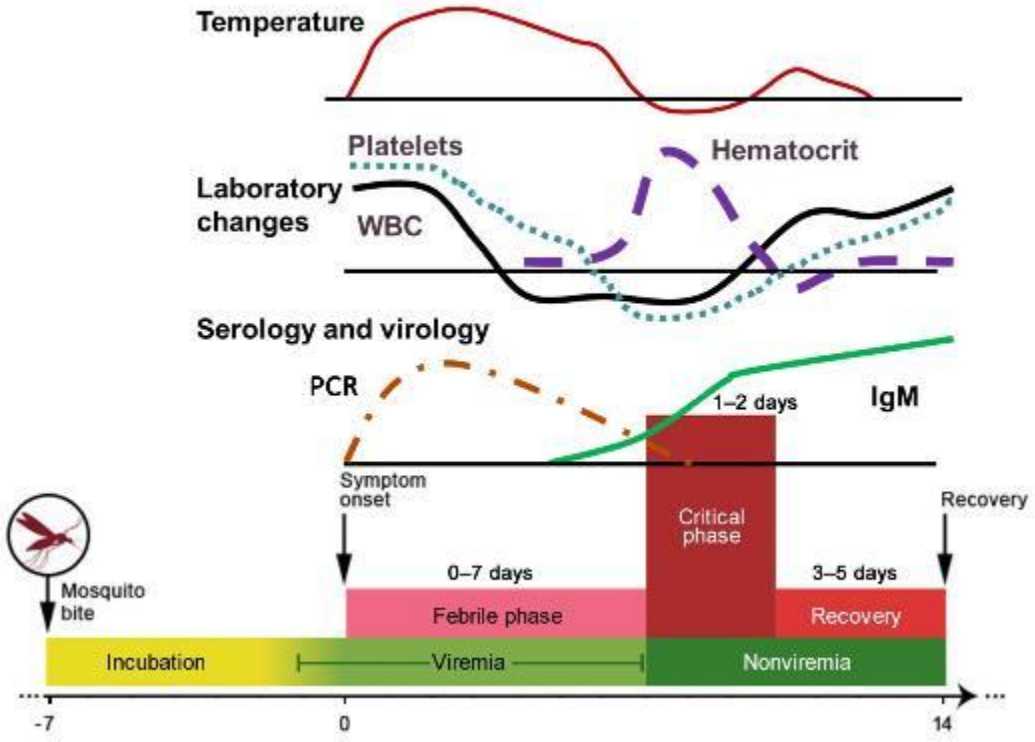
Convalescent/Recovery Phase[10]

In severe dengue, as plasma leakage and third spacing subsides, the patient enters the convalescent or recovery phase, and begins to reabsorb extravasated intravenous fluids, pleural effusions and ascites. As a patient's hemodynamic status stabilizes there is a significant diuresis of the excess extracellular fluid. The patient's hematocrit stabilizes, or may fall because of the dilutional effect of the reabsorbed fluid, and the white cell count usually starts to rise, followed by a recovery of platelet count. In the convalescent-phase rashes may desquamate (flake off) and become pruritic (itchy).

Dengue and Pregnancy[6]

There is limited data about dengue during pregnancy. Perinatal transmission can occur, and maternal infection may increase the likelihood of symptomatic infection in the newborn. In 41 perinatal transmission cases to fetuses described in the literature, all developed thrombocytopenia, most had evidence of plasma leakage typically with ascites or pleural effusions, and 39 were febrile. Nearly 40% had a hemorrhagic manifestation, and 25% were hypotensive at some point. Perinatally infected neonates typically become ill during the first week of life. Placental transfer of maternal dengue IgG antibodies from a previous infection does occur, but when the protective effect of these antibodies wanes, infants 6–12 months of age are at risk for severe dengue.

Laboratory Findings and Testing[15]



Course of a Dengue Infection[16]

Laboratory findings commonly include leukopenia, thrombocytopenia, hyponatremia (low blood white cells, platelets and sodium respectively), elevated aspartate aminotransferase and alanine aminotransferase (liver enzymes), and in the majority of cases, a normal erythrocyte sedimentation rate (marker of inflammation).[17]

During days one to seven after symptom onset, dengue virus RNA can be detected with molecular tests, such as an RT-PCR(reverse transcriptase polymerase chain reaction). NS1 is a dengue virus protein that also can be detected by some commercial tests. An IgM antibody level should also be drawn. A negative result from a molecular, NS1, or IgM antibody test is not conclusive. After seven days post symptom onset, patients with initially negative RT-PCR, NS1,and IgM (immunoglobulin M) antibody tests from the first seven days of illness should have a convalescent sample tested for IgM antibodies. During the convalescent phase, IgM antibodies are usually present and can be reliably detected. IgM antibodies against dengue virus can remain detectable for 3 months or longer after infection.

If a PCR or NS1 test is positive for dengue, a current dengue diagnosis is confirmed. If the PCR result is negative and the IgM antibody test is positive, the laboratory diagnosis is presumptive dengue virus infection.

Cross reactivity with other flaviviruses such West Nile, yellow fever, and Zika, is a limitation of dengue IgM antibody tests. Therefore, a patient with past flavivirus infection(s) may be falsely test positive for dengue virus IgM antibodies. To determine if dengue is causing the infection, IgM positive specimens should be tested for specific neutralizing antibodies by a plaque reduction neutralization test (PRNT).

Whenever a pregnant woman is tested for dengue, it is recommended Zika also be tested for using an RT-PCR test, as they may present similarly.

Treatment[18]

No specific antiviral agents or treatments exist for dengue. Supportive care is recommended and patients should try to stay well hydrated, and avoid aspirin and other NSAIDS because of their anticoagulant properties. Fever can be controlled with acetaminophen and possibly tepid sponge baths. Febrile patients should avoid mosquito bites to reduce risk of further transmission to other people.

In severe dengue, ICU care may be required. Prophylactic platelet transfusions in dengue patients are not beneficial, and may contribute to fluid overload. Administration of corticosteroids has not demonstrated any benefit, except in the case of autoimmune-related complication such as immune thrombocytopenia purpura.

A vaccine to prevent dengue, Dengvaxia, administered in three doses six months apart, is licensed and available in some countries for people aged 9-45 years old. The WHO recommends that the vaccine only be given to people with confirmed prior dengue virus infection, as previously uninfected people who are vaccinated and then get dengue have

a higher chance of developing severe dengue. In 2019, Dengvaxia was FDA approved for use in children 9-16 years old, with laboratory confirmed prior dengue virus infection, living in an endemic area such as the U.S. territories of American Samoa, Guam, Puerto Rico or the U.S. Virgin Islands.[19]

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