



World Health
Organization

Dengue Fever

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- Basic information on the dengue virus,
- Vector, and its transmission
- Disease surveillance and control
- Clinical manifestations of dengue and dengue hemorrhagic fever (DHF)
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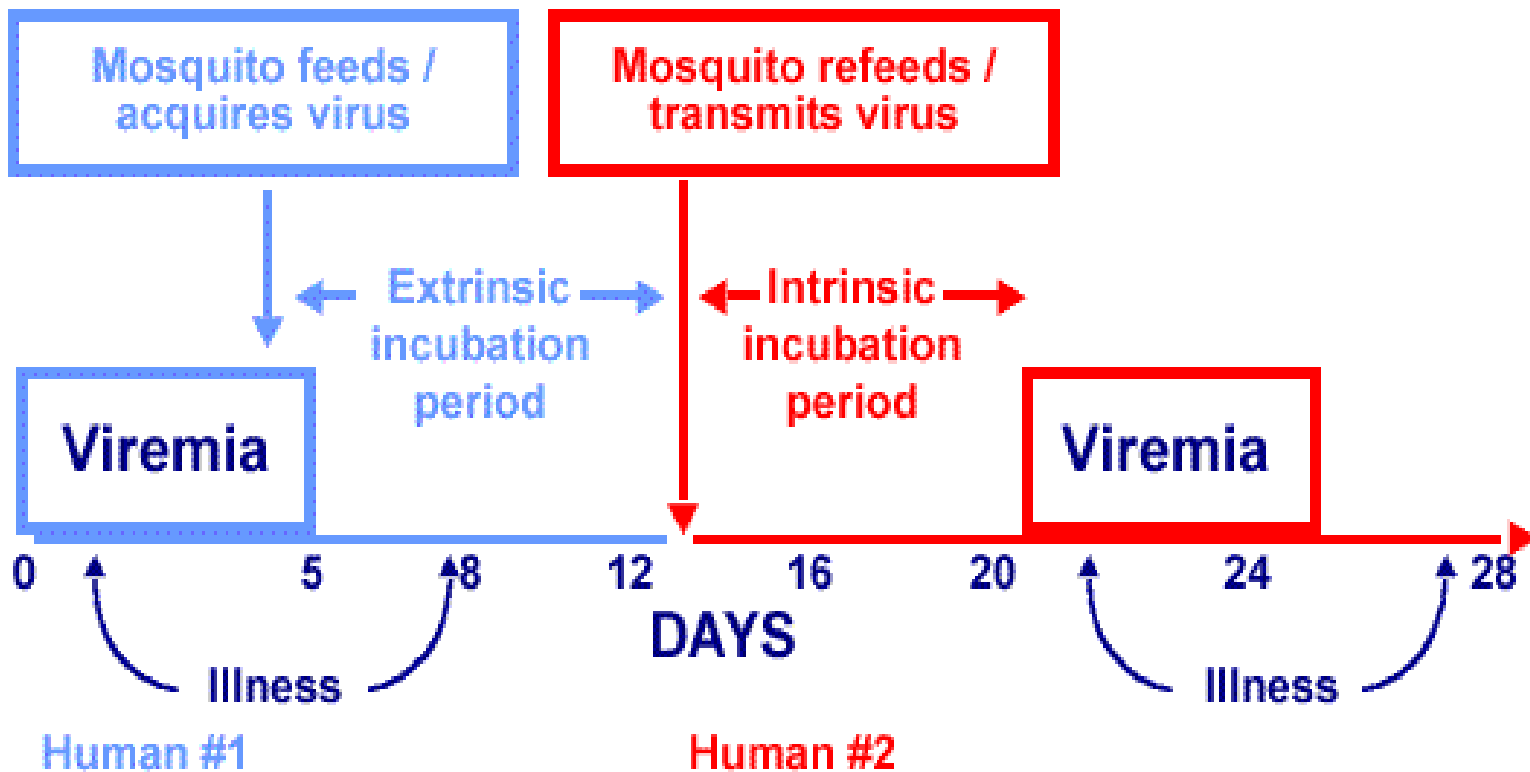
Dengue Virus

- Causes dengue and dengue hemorrhagic fever
- It is an arbovirus, and within this group it is a flavivirus, in the same family as the viruses that cause yellow fever, St. Louis encephalitis, West Nile fever, and Japanese encephalitis
- Transmitted by mosquitoes
- Composed of single-stranded RNA
- Has 4 serotypes (DEN-1, 2, 3, 4)

Dengue Viruses

- Each serotype provides specific lifetime immunity, and short-term cross-immunity
- All serotypes can cause severe and fatal disease
- Genetic variation within serotypes
- Some genetic variants within each serotype appear to be more virulent or have greater epidemic potential

Transmission of Dengue Virus by *Aedes aegypti*



- The transmission cycle of dengue virus by the mosquito *Aedes aegypti* begins with a dengue-infected person. This person will have virus circulating in the blood—a viremia that lasts for about five days.
- During the viremic period, an uninfected female *Aedes aegypti* mosquito bites the person and ingests blood that contains dengue virus. Although there is some evidence of transovarial transmission of dengue virus in *Aedes aegypti*, usually mosquitoes are only infected by biting a viremic person
- Then, within the mosquito, the virus replicates during an extrinsic incubation period of eight to twelve days.

- The mosquito then bites a susceptible person and transmits the virus to him or her, as well as to every other susceptible person the mosquito bites for the rest of its lifetime
- The virus then replicates in the second person and produces symptoms. The symptoms begin to appear an average of four to seven days after the mosquito bite—this is the intrinsic incubation period, within humans. While the intrinsic incubation period averages from four to seven days, it can range from three to 14 days

- The viremia begins slightly before the onset of symptoms. Symptoms caused by dengue infection may last three to 10 days, with an average of five days, after the onset of symptoms—so the illness persists several days after the viremia has ended

Replication and Transmission of Dengue Virus

1. The virus is inoculated into humans with the mosquito saliva
2. The virus localizes and replicates in various target organs, for example, local lymph nodes and the liver
3. The virus is then released from these tissues and spreads through the blood to infect white blood cells and other lymphatic tissues
4. The virus is then released from these tissues and circulates in the blood.

5. The mosquito ingests blood containing the virus
6. The virus replicates in the mosquito midgut, the ovaries, nerve tissue and fat body. It then escapes into the body cavity, and later infects the salivary glands
7. The virus replicates in the salivary glands and when the mosquito bites another human, the cycle continues

Aedes aegypti Mosquito



The most common epidemic vector of dengue in the world is the *Aedes aegypti* mosquito. It can be identified by the white bands or scale patterns on its legs and thorax.

Aedes aegypti

- Dengue transmitted by infected female mosquito
- Primarily a daytime feeder
- Lives around human habitation
- Lays eggs and produces larvae preferentially in artificial containers

Proactive Surveillance: Goals and Objectives

- Provide early and precise information
 - time
 - location
 - virus serotype
 - disease severity
- Predict dengue transmission and guide implementation of control measures
- Link clinical and entomologic surveillance

Vector Control Methods: Chemical Control

- Larvicides may be used to kill immature aquatic stages
- Ultra-low volume fumigation ineffective against adult mosquitoes
- Mosquitoes may have resistance to commercial aerosol sprays

Vector Control Methods: Biological and Environmental Control

❖ Biological control

- Largely experimental
- Option: place fish in containers to eat larvae

❖ Environmental control

- Elimination of larval habitats
- Most likely method to be effective in the long term

Purpose of Control

- Reduce female vector density to a level below which epidemic vector transmission will not occur
- Based on the assumption that eliminating or reducing the number of larval habitats in the domestic environment will control the vector
- The minimum vector density to prevent epidemic transmission is unknown

Programs to Minimize the Impact of Epidemics

- Teaching the medical community how to diagnose and manage dengue hemorrhagic fever (DHF)
- Implementing an emergency contingency plan to anticipate the logistical issues of hospitalizing large numbers of patients and to outline measures for community-wide vector control activities.
- Educating the general public to encourage and enable them to carry out vector control in their homes and neighborhoods

Clinical Manifestations of Dengue and Dengue Hemorrhagic Fever

- There are actually four dengue clinical syndromes:
 - Undifferentiated fever
 - Classic dengue fever
 - Dengue hemorrhagic fever, or DHF
 - Dengue shock syndrome, or DSS.
 - Dengue shock syndrome is actually a severe form of DHF

Undifferentiated Fever

- May be the most common manifestation of dengue
- Prospective study found that 87% of students infected were either asymptomatic or only mildly symptomatic
- Other prospective studies including all age-groups also demonstrate silent transmission

Clinical Characteristics of Dengue Fever

- Dengue fever is an acute viral illness characterized by:
 - Fever, often with sudden onset;
 - Severe headache, often described as retro-ocular;
 - Myalgias and arthralgias that can be very severe;
 - Nausea and vomiting;
 - A rash that may present at different stages of the illness, and whose appearance can be variable—it may be maculopapular, petechial, or erythematous. And
 - Hemorrhagic manifestations,

Signs and Symptoms of Encephalitis/Encephalopathy Associated with Acute Dengue Infection

- Some cases may present with or develop encephalitic or encephalopathic signs and symptoms, such as:
 - Decreased level of consciousness—including lethargy, confusion, and coma
 - Seizures;
 - Nuchal rigidity; and
 - Paresis.
 - Some of these cases may subsequently develop typical dengue hemorrhagic fever.

Hemorrhagic Manifestations of Dengue

- Skin hemorrhages:
petechiae, purpura, ecchymoses
- Gingival bleeding
- Nasal bleeding
- Gastrointestinal bleeding:
hematemesis, melena, hematochezia
- Hematuria
- Increased menstrual flow

Clinical Case Definition for Dengue Hemorrhagic Fever

- Fever, or recent history of acute fever
- Hemorrhagic manifestations
- Low platelet count (100,000/mm³ or less)
- Objective evidence of “leaky capillaries:”
 - ✓ Elevated hematocrit (20% or more over baseline)
 - ✓ low albumin
 - ✓ Pleural or other effusions

Clinical Case Definition for Dengue Shock Syndrome

- The four criteria for DHF
- Evidence of circulatory failure manifested indirectly by all of the following:
 - Rapid and weak pulse
 - Narrow pulse pressure (≤ 20 mm Hg) OR hypotension for age
 - Cold, clammy skin and altered mental status
 - Frank shock is direct evidence of circulatory failure

❖ **There are four grades of DHF, For all grades the four criteria for DHF must be met:**

➤ **Grade 1**

- Fever and nonspecific constitutional symptoms
- Positive tourniquet test is only hemorrhagic manifestation

➤ **Grade 2**

- Grade 1 manifestations + spontaneous bleeding

➤ **Grade 3**

- Signs of circulatory failure (rapid/weak pulse, narrow pulse pressure, hypotension, cold/clammy skin)

➤ **Grade 4**

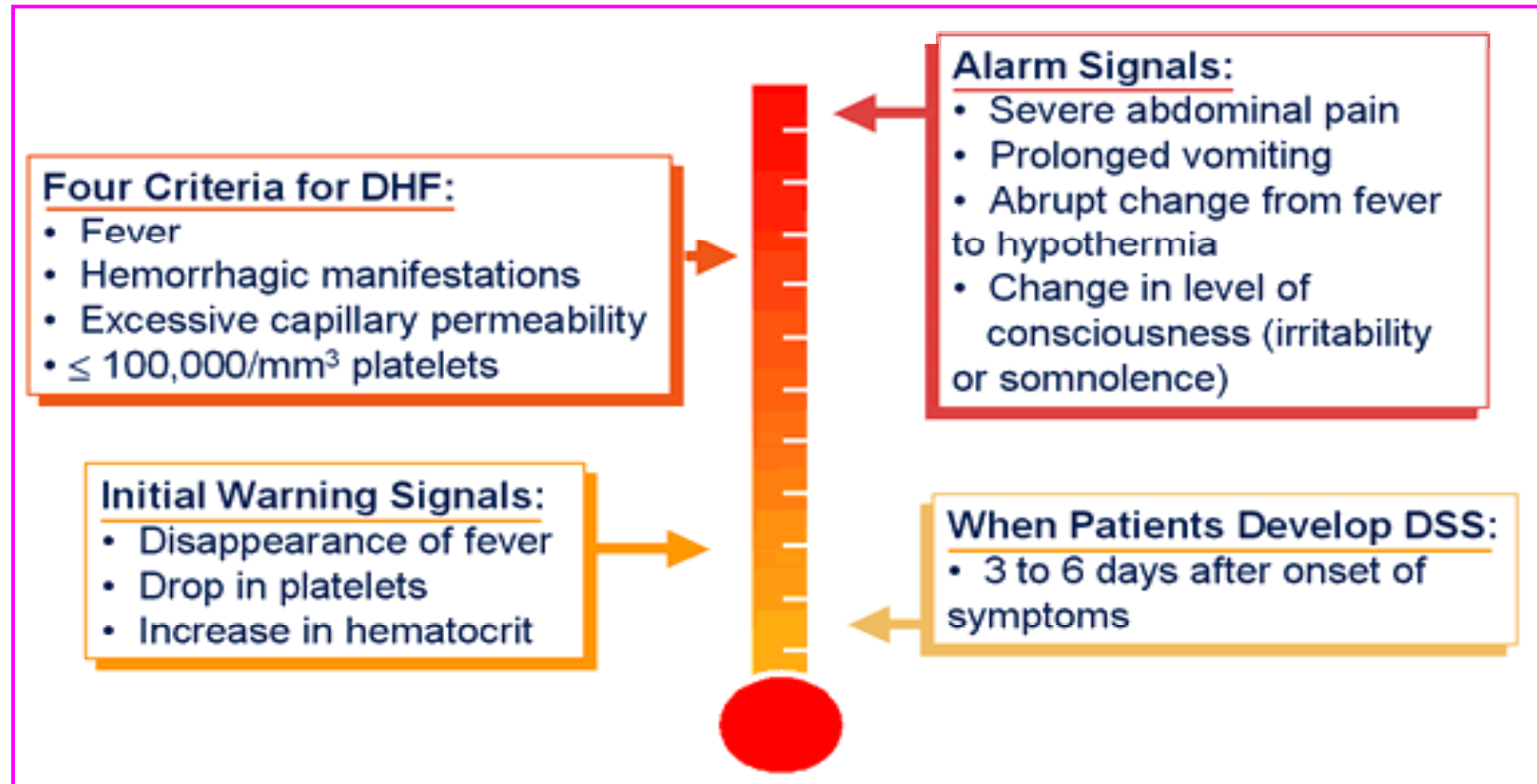
- Profound shock (undetectable pulse and BP)

Danger Signs in Dengue Hemorrhagic Fever

- Abdominal pain - intense and sustained
- Persistent vomiting
- Abrupt change from fever to hypothermia, with sweating and prostration
- Change in the mental status of the patient, going to be restlessness or somnolence.

All of these are signs of impending shock and should alert clinicians that the patient needs close observation and fluids.

Warning Signs for Dengue Shock



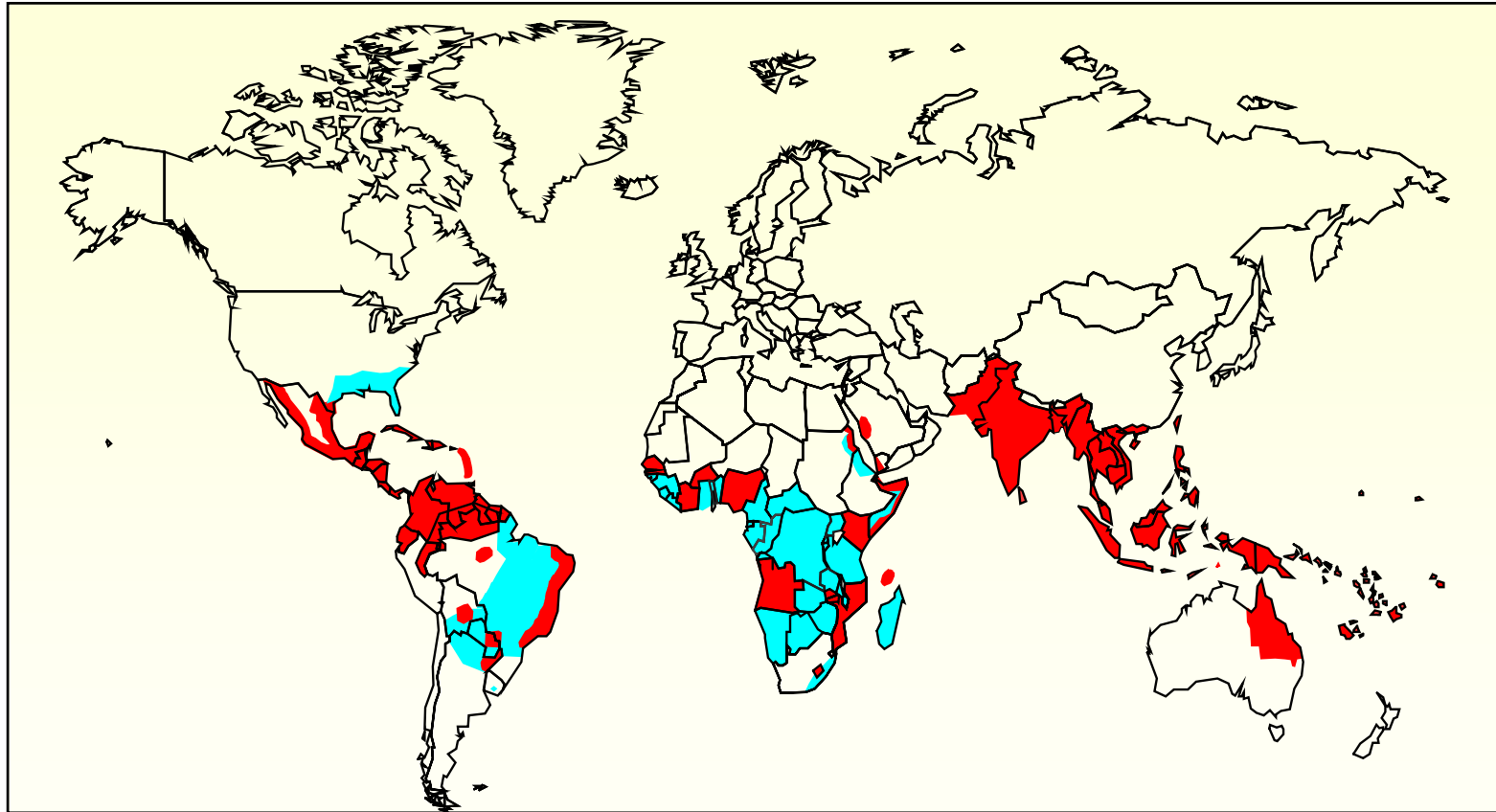
- This thermometer illustrates the developments in the illness that are progressive warning signs that DSS may occur
- The initial evaluation is made by determining how many days have passed since the onset of symptoms. Most patients who develop DSS do so 3-6 days after onset of symptoms
- If a patient is seven days into the illness, it is likely that the worst is over
- If the fever goes between three and six days after the symptoms began, this is a warning signal that the patient must be closely observed, as shock often occurs at or around the disappearance of fever
- Other early warning signs to be alert for include a drop in platelets, an increase in hematocrit, or other signs of plasma leakage

- If you document hemoconcentration and thrombocytopenia and other signs of DHF and the patient meets the criteria for DHF, the prognosis and the patient's risk category have changed. Though dengue fever does not often cause fatalities, a greater proportion of DHF cases are fatal
- The next concern would be observation of the danger signs—severe abdominal pain, change in mental status, vomiting and abrupt change from fever to hypothermia. These often herald the onset of DSS
- The goal of treatment is to prevent shock. The plasma leakage syndrome is self-limited. If you can support the patient through the plasma leakage phase and provide sufficient fluids to prevent shock, the illness will resolve itself

Unusual Presentations of Severe Dengue Fever

- Encephalopathy
- Liver failure or fulminant hepatitis, demonstrated by increased transaminases and bilirubin, and prolonged prothrombin time (PT and PTT)
- Cardiomyopathy—conduction defects, myocarditis;
- Severe gastrointestinal hemorrhage

World Distribution of Dengue 1999



- Areas infested with *Aedes aegypti*
- Areas with *Aedes aegypti* and recent epidemic dengue

Disease Pathogenesis

➤ **Risk Factors Reported for DHF:**

- Virus strain: DHF can occur in primary infection with certain genetic strains of virus
- Pre-existing anti-dengue antibody, either caused by previous infection or to maternal antibodies passed to infants
- Host genetics—for example, race seems to be a factor: data from Cuba suggest that whites may be at greater risk, and blacks at lower risk. And
- Age—in Southeast Asia, children are most affected, though in the Americas, all age- groups are affected

- Higher risk in secondary infections
- Higher risk in locations with two or more serotypes circulating simultaneously at high levels (hyperendemic transmission)

Diagnosis

➤ **General Recommendations for Medical Care**

- Epidemiologic considerations
 - Season of year
 - Travel history
- Diagnosis
- Treatment
- Follow-up

Differential Diagnosis of Dengue

- Influenza
- Measles
- Rubella
- Malaria
- Typhoid fever
- Leptospirosis
- Meningococccemia
- Rickettsial infections
- Bacterial sepsis
- Other viral hemorrhagic fevers

Clinical Evaluation in Dengue Fever

- The physical examination for suspected dengue should include an assessment of:
 - Blood pressure—both level and pulse pressure
 - Evidence of bleeding in the skin or other sites
 - Hydration status
 - Evidence of increased vascular permeability as evidenced by pleural effusions or ascites—and
 - Tourniquet test

Petechiae



patient with visible petechiae, a common hemorrhagic manifestation.

Tourniquet Test

- Inflate blood pressure cuff to a point midway between systolic and diastolic pressure for 5 minutes
- After deflating the cuff, wait for the skin to return to its normal color, and then count the number of petechiae visible in a one-inch-square area on the ventral surface of the forearm.
- Positive test: 20 or more petechiae per 1 inch² (6.25 cm²)

Positive Tourniquet Test

A typical positive result from a tourniquet test may look like. This patient has more than 20 petechiae per square inch



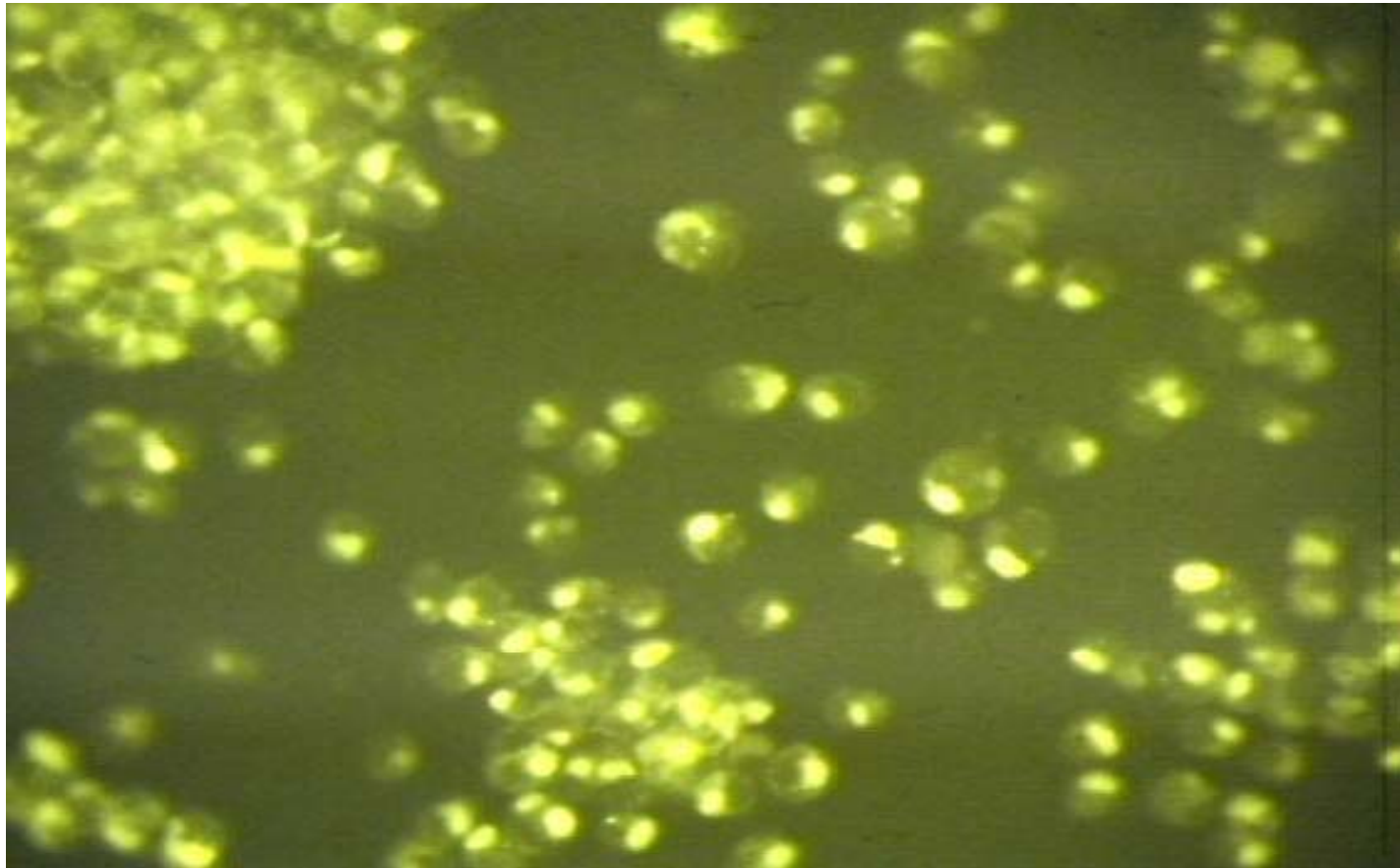
Laboratory Tests in Dengue Fever

- Clinical laboratory tests
 - CBC—WBC, platelets, hematocrit
 - Albumin
 - Liver function tests
 - Urine—check for microscopic hematuria
- Dengue-specific tests
 - Virus isolation
 - Serology

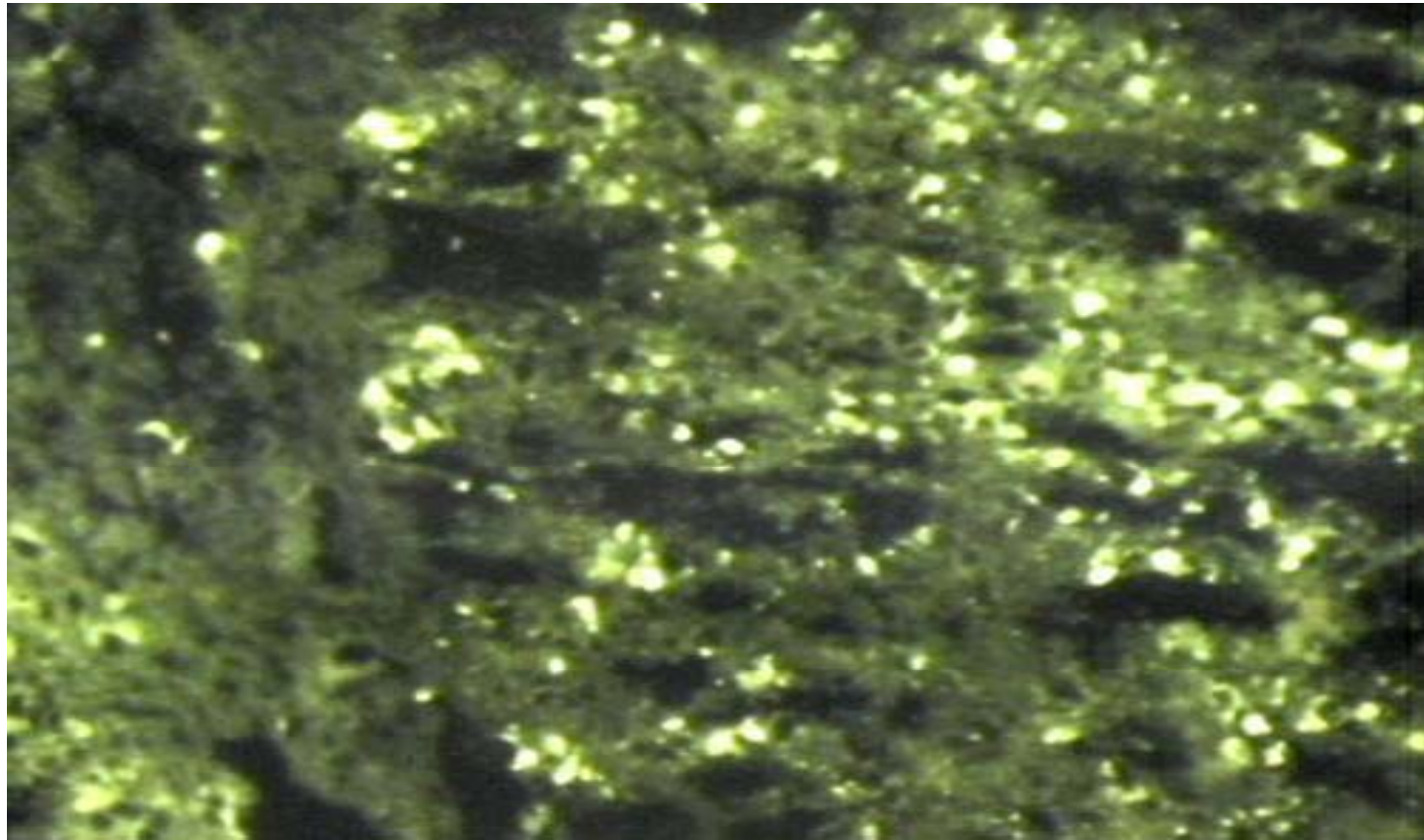
Laboratory Methods for Dengue Diagnosis, CDC Dengue Branch

- There are several diagnostic techniques to document an infection by the dengue virus. The two most important types of analysis are virus isolation and immunoglobulin M enzyme-linked immunoassay, or IgM ELISA.
- Virus isolation is attempted to determine the serotype of the infecting virus. This can be performed either by using mosquito cell cultures or by mosquito inoculation.
- The IgM ELISA is the basic test for serologic diagnosis

Virus Isolation: Cell Culture



Virus Isolation: Fluorescent Antibody Test



ELISA Plate



The ELISA detects the presence of anti-dengue IgM in a patient's blood sample, indicating a recent dengue infection. An ELISA plate is shown here. The more intense the color reaction, the greater the level of anti-dengue IgM antibody in the sample.

Collection and Processing of Samples for Laboratory Diagnosis

- The tests for diagnosis of dengue infection are time dependent
- *If the patient presents within the first 5 days after onset of symptoms, which is the acute phase of the illness, a blood sample should be drawn immediately, to be tested for virus isolation. Virus can be isolated most easily in samples drawn in the first days after onset of symptoms, although it has been isolated as long as 12 days after onset.*
- A convalescent-phase sample should also be drawn to test for IgM antibody. This sample should be drawn between 6 and 21 days after symptom onset
- *If the patient presents six or more days after symptom onset, the blood sample should be drawn as soon as possible. This sample should then be tested for serum IgM antibody*

Procedures for Diagnosing a Suspected Dengue Fatality

- When sending samples from a suspected fatality for processing, you should inform the laboratory carrying out the tests that the case was fatal. The samples you should collect include:
 - A blood sample to attempt virus isolation and serology. If an autopsy is performed, blood from the heart should be collected.
 - In addition to blood, the following tissue samples should be obtained: heart, liver, kidney, lung, intestines, spleen, lymph nodes, brain, and skin from areas where the rash occurred. If fresh tissues are available, they will be tested for virus isolation. If an autopsy has been performed and no fresh tissues are available, tissues fixed in formalin should be submitted for immunohistochemical studies

Treatment

- If the patient has no hemorrhagic manifestations and is well-hydrated, he or she can be sent home with instructions for "follow-up."
- If there are hemorrhagic manifestations or hydration status is borderline, the patient should be observed, either in an outpatient observation center or in the hospital
- If warning signs are present even without evidence of shock, or if DSS is present, the patient should be hospitalized

Patient Follow-Up

- Patients being treated at home should be instructed regarding the appearance of danger signs and told to return should any occur.
- Repeat clinical evaluation should be considered, with timing based on the physician's judgment, remembering that DSS most commonly occurs at 3-6 days after symptom onset.
- Patients with bleeding manifestations should have serial hematocrit and platelet levels checked at least daily until their temperature is normal for 1-2 days.
- If the blood sample was taken the first five days after the onset of symptoms, a convalescent-phase sample to measure IgM antibody is needed between 6-30 days after the onset of symptoms.
- A blood sample should be taken from all hospitalized patients at the time of discharge or death

Treatment of Dengue Fever

(Part 1)

- Fluids. Patients should be encouraged to take small, frequent sips of fluids. If the patient cannot be rehydrated by mouth, fluids should be administered intravenously. At times large amounts of intravenous fluids are needed.
- Rest
- Antipyretics— aspirin and nonsteroidal anti-inflammatory drugs such as ibuprofen should be avoided so that platelet function will not be impaired. And
- Monitoring of blood pressure, urine output, hematocrit, platelet count, and level of consciousness

Mosquito Barriers

- Only needed until fever subsides, to prevent *Aedes aegypti* mosquitoes from biting patients and acquiring virus
- Keep patient in screened sickroom or under a mosquito net

Treatment of Dengue Fever

(Part 2)

- Patients often develop dengue hemorrhagic fever after their fever disappears. So providers should continue monitoring vital signs and hydration status for 24 to 48 hours after defervescence
- If any doubt, provide intravenous fluids, guided by serial hematocrits, blood pressure, and urine output
- The volume of fluid needed is similar to the treatment of diarrhea with mild to moderate isotonic dehydration (5%-8% deficit)

Rehydrating Patients Over 40 kg

- Volume required for rehydration is twice the recommended maintenance requirement
- Formula for calculating maintenance volume:
 $1500 + 20 \times (\text{weight in kg} - 20)$
- For example, maintenance volume for 55 kg patient is: $1500 + 20 \times (55 - 20) = 2200$ ml
- For this patient, the rehydration volume would be 2×2200 , or 4400 ml

Treatment of Dengue Fever (Part 3)

- Avoid invasive procedures when possible
- Unknown if the use of steroids, intravenous immune globulin, or platelet transfusions to shorten the duration or decrease the severity of thrombocytopenia is effective
- Patients in shock may require treatment in an intensive care unit

Indications for Hospital Discharge

- Absence of fever for 24 hours (without anti-fever therapy) and return of appetite
- Visible improvement in clinical picture
- Stable hematocrit
- 3 days after recovery from shock
- Platelets $\geq 50,000/\text{mm}^3$
- No respiratory distress from pleural effusions/ascites

Common Misconceptions about Dengue Hemorrhagic Fever

- One commonly believed but false idea is that dengue plus bleeding equals dengue hemorrhagic fever
- The truth is that there are four established criteria for defining DHF, and the critical difference between dengue fever and DHF is not bleeding, but the increased vascular permeability that occurs in DHF—this is what causes shock and death
- DHF kills only by hemorrhage
 - Patient dies as a result of shock
- Poor management turns dengue into DHF
 - Poorly managed dengue can be more severe, but DHF is a distinct condition, which even well-treated patients may develop
- Positive tourniquet test = DHF
 - Tourniquet test is a nonspecific indicator of capillary fragility

More Common Misconceptions about Dengue Hemorrhagic Fever

- **DHF is a pediatric disease**
 - All age groups are involved in the Americas
- **DHF is a problem of low income families**
 - All socioeconomic groups are affected
- **Tourists will certainly get DHF with a second infection**
 - Tourists are at low risk to acquire DHF

Prevention

Early Eradication Campaigns Succeeded

- Adequate local and external funding for personnel, equipment and insecticides
- Emphasis on source reduction
- Effective residual insecticide
- Centralized, vertically-structured programs with military-type organization, strict supervision, high level of discipline

Dengue Vaccine?

- No licensed vaccine at present
- Effective vaccine must be tetravalent
- Field testing of an attenuated tetravalent vaccine currently underway
- Effective, safe and affordable vaccine will not be available in the immediate future

Vector Control Methods: Chemical Control

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Programs to Minimize the Impact of Epidemic

- Education of the medical community
- Implementation of emergency contingency plan
- Education of the general population

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