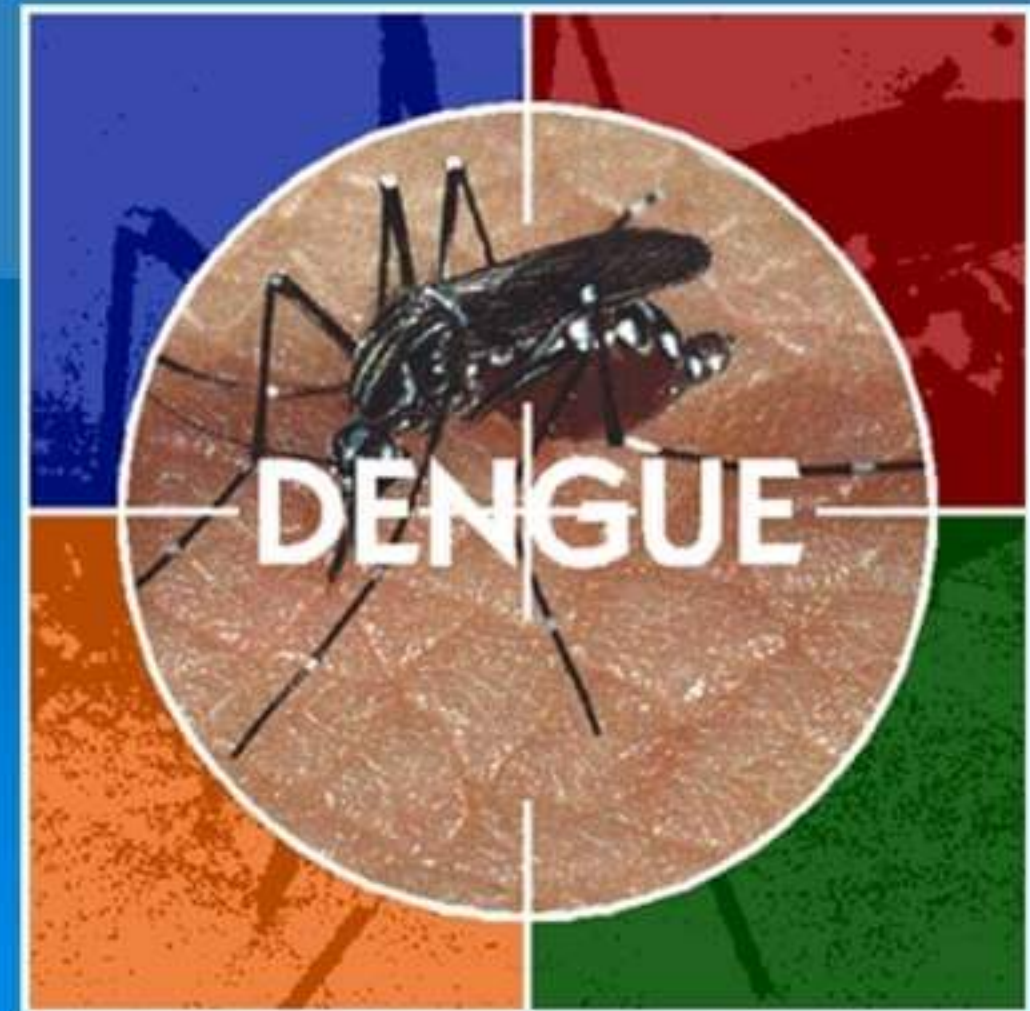


# Dengue Fever



# Dengue Fever

- Dengue virus
- Most prevalent vector-borne viral illness in the world
- Main mosquito vector is *Aedes aegypti*,
- Year round transmission





# Dengue Fever

- WHO says some 2.5 billion people, two fifths of the world's population, are now at risk from dengue and estimates that there may be 50 million cases of dengue infection worldwide every year.
- epidemic in more than 100 countries

# Dengue fever

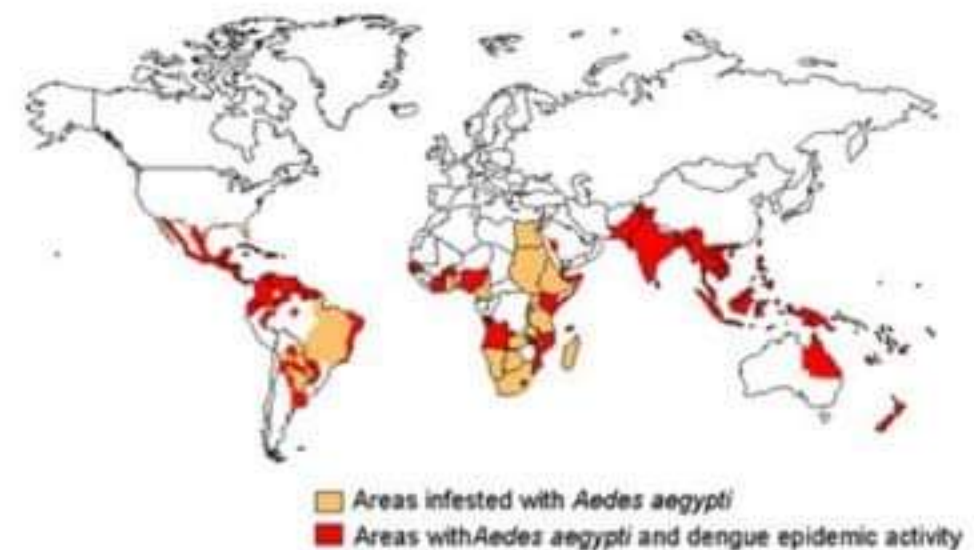
- genus Flavivirus,
- family Flaviviridae
- also known as **breakbone fever**. (*bonecrusher disease*) -Dandy Fever
- Aedes aegypti - rarely the Aedes albopictus mosquito,



# Distribution

- Endemic in more than 100 tropical and subtropical countries
- Pandemic began in Southeast Asia after WW II with subsequent global spread
- Several epidemics since 1980s
- Distribution is comparable to malaria

World Distribution of Dengue - 2005



# Manifestations of dengue virus infection:

ASYMPTOMATIC

SYMPTOMATIC

Undifferentiated  
Fever

Dengue Fever

Without haemorrhagic

With unusual  
haemorrhagic

Dengue  
Haemorrhagic  
Fever

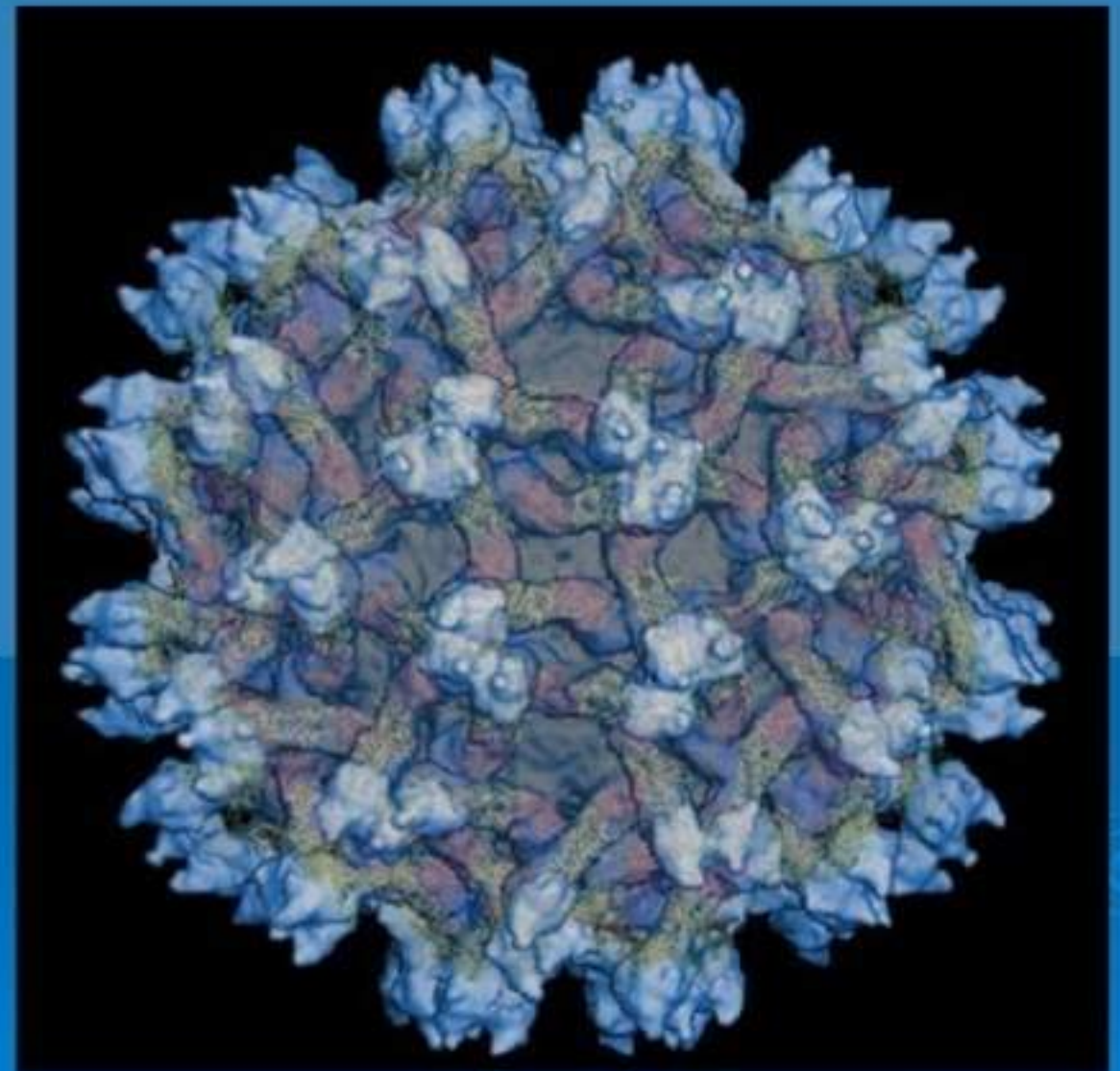
No shock

DSS



# Virology

- Flavivirus family
- Small enveloped viruses containing single stranded positive RNA
- Four distinct viral serotypes (Den-1, Den-2, Den-3, Den-4)





# Dengue Viruses

- Four closely related single-stranded RNA Dengue viruses (DEN-1, DEN-2, DEN-3 and DEN-4)
- Each serotype provides specific lifetime immunity, and short-term cross-immunity (A person can be infected as many as four times, once with each serotype)
- All serotypes can cause severe and fatal disease



# Pathophysiology



- Transmitted by the bite of Aedes mosquito (*Aedes aegypti*)
- Incubation 3-14 days
- Acute illness and viremia 3-7 days
- Recovery or progression to leakage phase



# Dengue Mosquito

- *Aedes aegypti* is the most important dengue mosquito
- It breeds in collections of water close to dwellings
- Common breeding sites are;
  - Domestic water storage containers - tanks, jars, drums, flower vases with water
  - Roof gutters /sun shades
  - Used tyres, discarded tins, cans, pots, yogurt cups, polythene bags, tree axils &
  - Many more places where rain watercollects



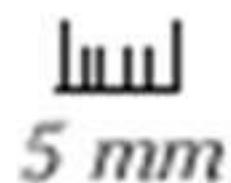




The most common epidemic vector of dengue in the world is the *Aedes aegypti* mosquito. It can be identified by the white bands or scale patterns on its legs and thorax.



They are approximately 5 mm in size:



*Magnified 5 times*

**D**engue mosquitos bite in the early morning and the late afternoon.

# Disease Factors

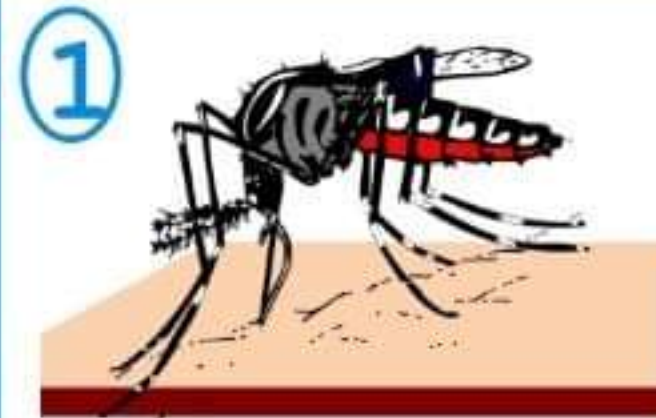
- Dengue-2 serotype most virulent
- Increased severity with secondary infections
- Increased risk in children <15 years and elderly.
- Greatest risk of DHF in infants.
- More severe in females
- Increased mortality with comorbid conditions
- Less common in malnourished children



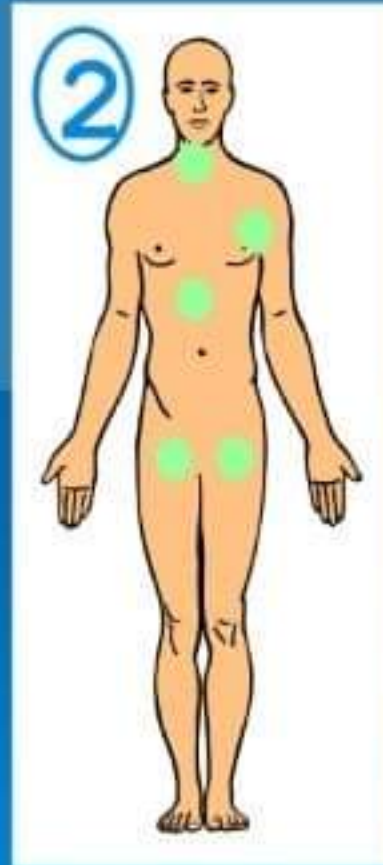
# Replication and Transmission of Dengue Virus (Part 1)

IM  
INTERESTING  
MEDICINE

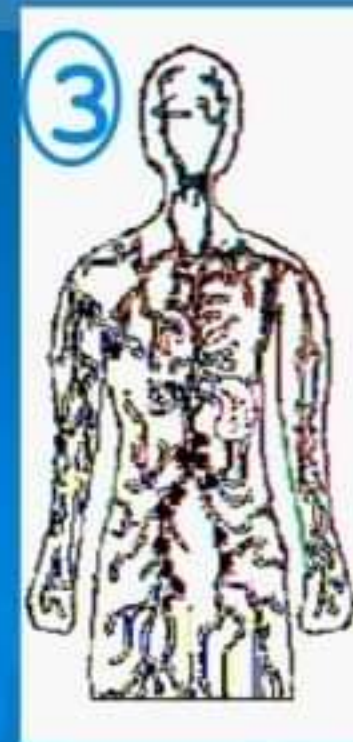
1. Virus transmitted to human in mosquito saliva



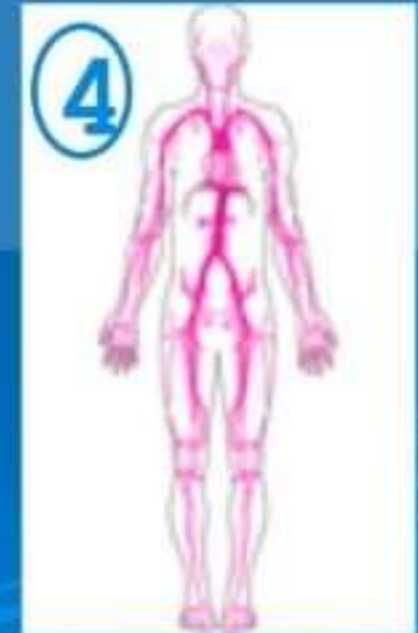
2. Virus replicates in target organs local Lymph nodes, liver



3. Virus infects white blood cells and lymphatic tissues



4. Virus released and circulates in blood

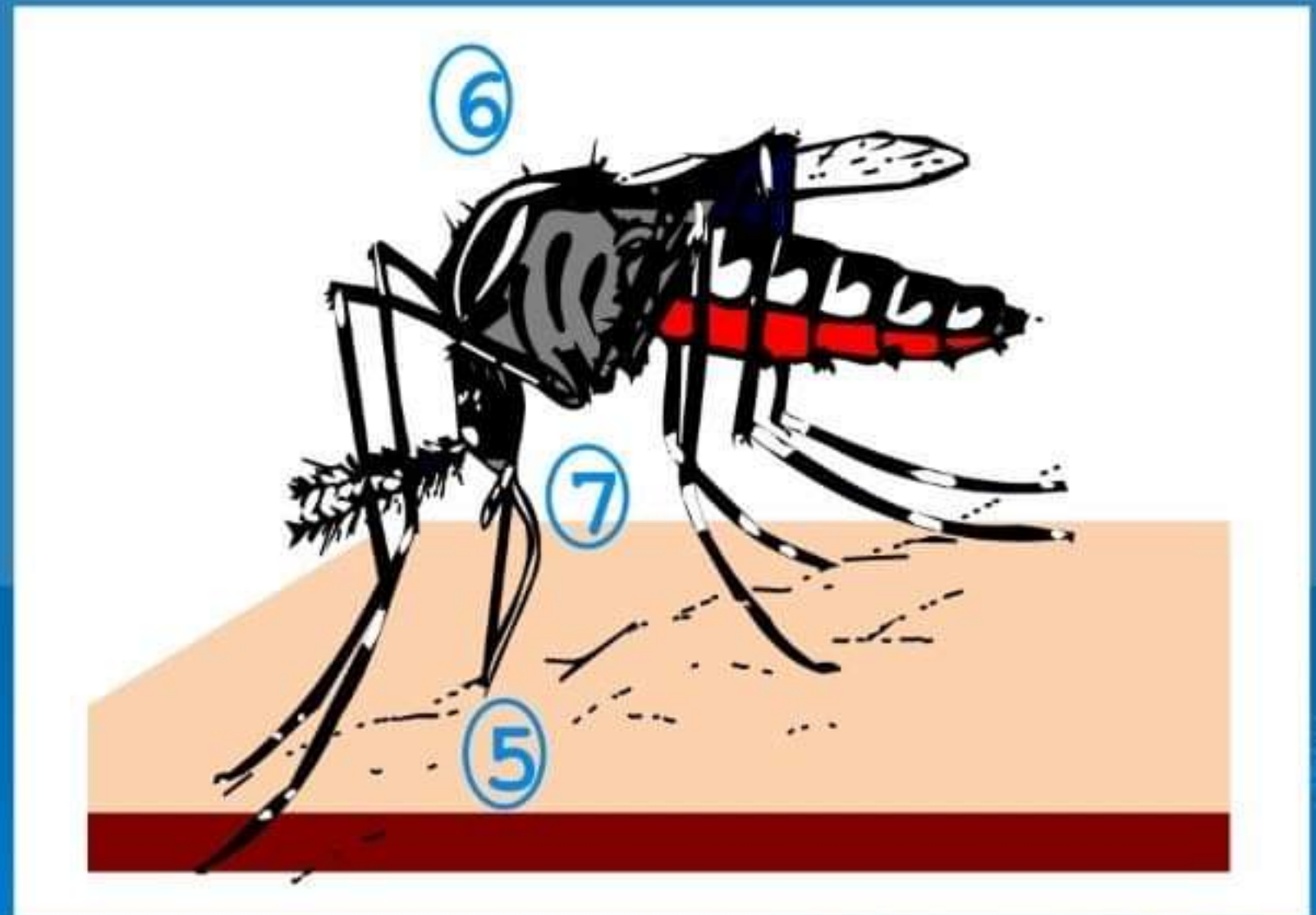




# Replication and Transmission of Dengue Virus (Part 2)

IM  
INTERESTING  
MEDICINE

- 5. Second mosquito ingests virus with blood
- 6. Virus replicates in mosquito midgut and other organs, infects salivary glands
- 7. Virus replicates in salivary glands





# Dengue Clinical Syndromes

- **Undifferentiated fever**
- **Classic dengue fever**
- **Dengue hemorrhagic fever**
- **Dengue shock syndrome**

# 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

- **Fever**
- **Headache**
- **Muscle and joint pain**
- **Nausea/vomiting**
- **Rash**
- **Hemorrhagic manifestations**
- **Retro orbital pain**

# Hemorrhagic Manifestations of Dengue

- **Skin hemorrhages:**  
petechiae, purpura, ecchymoses
- **Gingival bleeding**
- **Nasal bleeding**
- **Gastro-intestinal bleeding:**  
hematemesis, melena,
- **Hematuria**
- **Increased menstrual flow**



# Clinical Case Definition for Dengue Hemorrhagic Fever

## 4 Necessary Criteria:

- **Fever, or recent history of acute fever**
- **Hemorrhagic manifestations**
- **Low platelet count ( $100,000/\text{mm}^3$  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

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



# Four Grades of DHF

- **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**
- **Restlessness or somnolence**



# Unusual Presentations of Severe Dengue Fever

- **Encephalopathy**
- **Hepatic damage**
- **Cardiomyopathy**
- **Severe gastrointestinal hemorrhage**

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

- **Decreased level of consciousness: lethargy, confusion, coma**
- **Seizures**
- **Nuchal rigidity**
- **Paresis**



# Physical Exam



- Nonspecific findings
- Conjunctival injection, pharyngeal erythema, lymphadenopathy, hepatomegaly (20-50%)
- Macular or maculopapular rash (50%)





# Laboratory Findings

- Leukopenia
- Thrombocytopenia ( $<100,000$ )
- Modest liver enzyme elevation (2-5x nml)
- Serology:
  - Acute phase serum IgM (+6-90 days) ELISA
  - Acute and convalescent IgG (99% sens, 96% spec)
  - Hemagglutination inhibition assay (HI) is gold standard. Paired acute and convalescent HI assay, positive if  $>4$  fold titer rise



# tourniquet test

- The tourniquet test is performed by inflating a blood pressure cuff to a point mid-way between the systolic and
- diastolic pressures for five minutes. A test is considered positive when 10 or more petechiae per 2.5 cm<sup>2</sup> (1 inch)
- are observed. In DHF, the test usually gives a definite positive result (i.e. >20 petechiae). The test may be
- negative or mildly positive during the phase of profound shock.



➤ **Dengue is currently classified as an emerging or re-emerging infectious disease**

- 1. Overcrowded population.**
- 2. Unplanned & uncontrolled urbanization.**
- 3. Lack of effective mosquito control.**
- 4. Increased air travel.**
- 5. Decay of public health measures.**



# Treatment

- No specific therapy
- Supportive measures:
  - adequate hydration
  - acetaminophen (if no liver dysfunction)
  - avoid NSAIDs
- DHF or DHF w/ shock:
  - IV fluid resuscitation and hospitalization
  - blood or platelet transfusion as needed



# Treatment

- Treatment with corticosteroids shown not to reduce mortality with severe dengue shock
- 2 studies of 63 and 92 pediatric DHF shock pts treated w/ hydrocortisone 50mg/kg x1 or methylprednisolone 30mg/kg x1 dose vs placebo.
- Study of 95 pediatric DHF shock pts treated with carbazochrome sodium sulfate (AC-17) vs B vitamins for 3 days
- Ribavirin very weak in vitro and in vivo activity against flaviviruses



# Traditional and emerging treatments

- Emerging evidence suggests that mycophenolic acid and ribavirin inhibit dengue replication.
- Brazilian traditional medicine, -cat's claw herb
- Malaysia, -natural medicine. Mas Amirtha and Semalu
- Philippines -tawa-tawa herbs and sweet potato tops juice



# Vaccination

- No current dengue vaccine
- Estimated availability in 5-10 years
- Vaccine development is problematic as the vaccine must provide immunity to all 4 serotypes
- Lack of dengue animal model
- Live attenuated tetravalent vaccines under phase 2 trials
- New approaches include infectious clone DNA and naked DNA vaccines



# Mortality/Morbidity

- Treated DHF/DSS is associated with a 3% mortality rate.
- Untreated DHF/DSS is associated with a 50% mortality rate.



# Differential Diagnoses

- Hepatitis
- Tick-Borne Diseases, Rocky Mountain Spotted Fever
- Malaria
- Yellow Fever
- Meningitis
- Pediatrics, Bacteremia and Sepsis
- Pediatrics, Meningitis and Encephalitis



# Prevention

## Biological:

- Target larval stage of Aedes in large water storage containers
- Larvivorous fish (Gambusia), endotoxin producing bacteria (Bacillus), copepod crustaceans (mesocyclops)

## Chemical:

- Insecticide treatment of water containers
- Space spraying (thermal fogs)



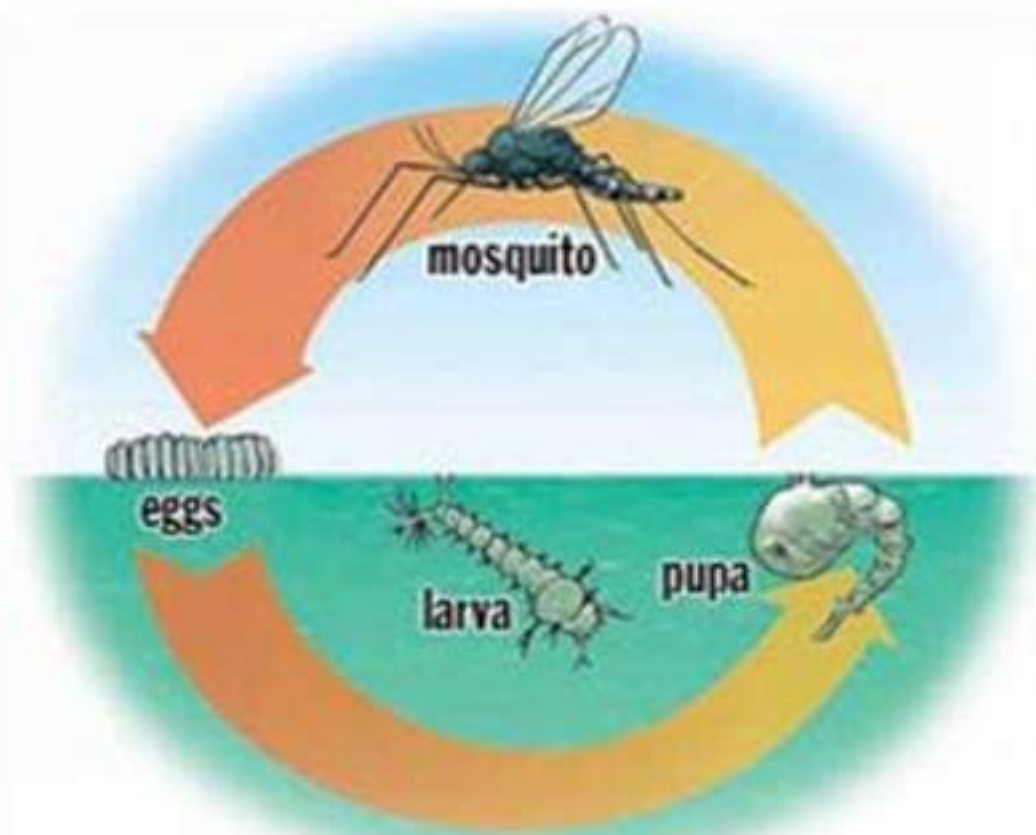
# Public Health

- Major and escalating global public health problem
- Global demographic changes: urbanization and population growth with substandard housing, water, and waste management systems
- Deteriorating public health infrastructure with limited resources resulting in “crisis management” not prevention
- Increased travel
- Lack of effective mosquito control



# Mosquito control:

Options available



"Mosquitoes take about 7 days to complete life cycle.

The first three Stages: eggs, larva and pupa are aquatic.

Therefore, the best way to prevent mosquito breeding is to remove stagnant clear water"



# Common Misconceptions about Dengue Hemorrhagic Fever



- ❑ Dengue + bleeding = DHF
  - ❑ Need 4 WHO criteria & capillary permeability
- ❑ 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
- ❑ DHF is a pediatric disease
  - ❑ All age groups are involved
- ❑ DHF is a problem of low income families
  - ❑ All socioeconomic groups are affected



# Important Instructions for Treatment of DHF

- Ø Cases of DHF should be observed every hour.
- Ø Serial platelet and haematocrit determinations, drop in platelets and rise in haematocrits are essential for early diagnosis of DHF.
- Ø Timely intravenous therapy – isotonic crystalloid solution –  
can prevent shock and/or lessen its severity.
- Ø If the patient's condition becomes worse despite giving 20ml/kg/hr for one hour, replace crystalloid solution with colloid solution such as Dextran or plasma. As soon as improvement occurs replace with crystalloid.



# Important Instructions for Treatment of DHF

- Ø In case of shock, give oxygen.
- Ø For correction of acidosis (sign: deep breathing), use sodium bicarbonate.



# What not to do

- Ø Do not give Aspirin or Brufen for treatment of fever.
- Ø Avoid giving intravenous therapy before there is evidence of haemorrhage and bleeding.
- Ø Avoid giving blood transfusion unless indicated, reduction in haematocrit or severe bleeding.
- Ø Avoid giving steroids. They do not show any benefit.
- Ø Do not use antibiotics
- Ø Do not change the speed of fluid rapidly, i.e. avoid rapidly increasing or rapidly slowing the speed of fluids.
- Ø Insertion of nasogastric tube to determine concealed bleeding or to stop bleeding (by cold lavage) is **not** recommended since it is hazardous.