Dengue: Update management and overview.

Prof. Quazi Tarikul Islam
FCPS, FACP, FRCP(Edin. Glasg.)
Professor of Medicine
Popular Medical College Hospital
Member, RTAG for Dengue, SEARO, WHO
Contents

• New concept of pathophysiology
• Recent diagnostic tools
• New clinical assessment
• Management Triage
• New concept of fluid management
• Progress of vaccine development
Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever

Revised and expanded edition
Dengue and dengue hemorrhagic fever: Key facts (Global)

• Some **2.5 billion** people – two fifths of the world's population in tropical and subtropical countries – are at risk.

• An estimated 50 million dengue infections occur worldwide annually.

• An estimated 500 000 people with DHF require hospitalization each year. A very large proportion (approximately 90%) of them are children aged less than five years, and about 2.5% of those affected die.
Dengue and dengue hemorrhagic fever: Key facts (Global)

- Dengue and DHF is endemic in more than 100 countries in the WHO regions of
  - Africa,
  - Americas,
  - Eastern Mediterranean,
  - South-East Asia and
  - Western Pacific.

- The South-East Asia and Western Pacific regions are the most seriously affected.
Dengue and dengue hemorrhagic fever: Key facts

• Epidemics of dengue are increasing in frequency. Seasonal variation is observed.

• *Aedes (Stegomyia) aegypti* is the primary epidemic vector.

• Primarily an *urban* disease, dengue and DHF are now spreading to rural areas worldwide.

• *Imported cases are common.*

• *Co-circulation of multiple serotypes/genotypes is evident.*
The virus

- The dengue viruses are members of the genus *Flavivirus* and family *Flaviviridae*.
- Among non-structural proteins, envelope glycoprotein, NS1, is of diagnostic and pathological importance, associated with viral haemagglutination and neutralization activity.
- There are four virus serotypes, which are designated as DENV-1, DENV-2, DENV-3 and DENV-4.
- Infection with any one serotype confers lifelong immunity to that virus serotype.
Immunopathogenesis of Dengue Disease
Why study pathogenesis?

• To develop **predictive indicators** or profiles of severe disease.

• To develop **therapeutic interventions**.

• To identify **protective and pathogenic immune correlates**.
Dengue Viral Particle

Structures of Immature Flavivirus Particles

Ying Zhang, Jeroen Corver, Paul R. Chipman, Wei Zhang, Sergei V. Pletnev, Dagmar Sedlak, Timothy S. Baker, James Richard J. Kuhn and Michael G. Rossmann
Tissue Tropism

Many cell types can be infected \textit{in vitro} with DENV: monocytes, epithelial cells, endothelial cells, \textit{hepatocytes}, myocytes.

Evidence of \textit{in vivo} infection: presence of antigen, genome, active replication (negative viral RNA), in tissue samples.
Liver
Kupffer cells
endothelium

Lung
Alveolar macrophages
Vascular macrophages
Endothelium
immunostaining  In situ

Splenic macrophages, lymphocytes

Peripheral blood monocytes, lymphocytes
Virus-Cell Interaction

• Viral entry and replication.
• Activation of the innate immune system.
Activation of the innate immune system by DENV
Lymphocyte
T Cell Roles In Dengue Hemorrhagic Fever
T

CYTOKINES

SHOCK!

PRIMARY INFECTION

SECONDARY INFECTION

Chemokines

Cytokine Tsunami

CYTOKINES

SHOCK!
1. Patients with DHF have higher viral load than patients with DF.

2. Patients with DHF have signs of more intense T cell activation early in the course of the disease than patients with DF.

3. By functional analysis, DHF patients have more pre-existing memory T cells than patients with DF.
4. The responses are characterized by extensive cross-recognition of epitopes of different viruses.

5. Distinct functional responses are associated with specific and cross-reactive recognition of peptide epitopes.

6. Certain genetic markers (HLA) have been identified to predispose individuals to severe disease, other genetic loci appear to provide some protection. These loci regulate how T cells “see” dengue virus.
Soluble NS1 levels by day of illness in DHF and DF

Values are mean ± SEM

† p=0.003, t-test
‡ p=0.02, t-test
preexisting antibodies

Target cells (monocytes, dendritic cells)

Viral products

Immune complexes

complement Activation

Pro-inflammatory cytokine release

Blood vessels

permeability

cytokine release

memory T cells
Viral factors
- viral burden
- virulence ?

Host factors
  Immune

Antibodies
- neutralizing
- ADCC
- enhancing ?

Cellular
- NK cells

Genetics
  HLA, TNF, CD209

Cellular immune activation

Type I IFN response

Viral burden

Pro-inflammatory mediators

Cellular membrane
  Molecules, receptors

Angiogenic mediators

Vascular permeability
Asymptomatic

Viral syndrome

Dengue fever

Symptomatic

1. Prolonged shock: liver failure, renal failure, ... Encephalopathy...
2. Co-morbidities
3. Co-infections
4. True dengue infection - encephalitis

Expanded dengue syndrome (Uncommon)

Plasma leakage

DHF

DSS

1-2
### Natural course of DHF

<table>
<thead>
<tr>
<th>Day 1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **WBC**: 6,000-9,000
- **≤ 5,000**

<table>
<thead>
<tr>
<th>Platelet count</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 50,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hct</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3.5 gm%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 100 mg%</td>
</tr>
</tbody>
</table>

#### Tourniquet Test

**Stop leakage**

- **Plasma leakage**
- **Shock**

**Fluid overload**

**IV fluid: NSS, DAR, DLR**

**Colloid: 10% Dextran, 10% Haes-steril**

**M+5% Deficit**

(- 4,600 ml in adult)
Storage related
Rain-fed
Clinical features of dengue infection

Dengue

- **Systemic**
  - Fever
  - Malaise
  - Headache
  - Muscle/joint pain
  - Rash
  - Fatigue

- **Bleeding diathesis**
  - Thrombocytopenia
  - Tourniquet test
  - Petechiae
  - Coagulopathy
  - Gross bleeding

- **Vascular permeability**
  - Plasma leakage
  - Hemoconcentration
  - Pleural effusion
  - Ascites

- **Hepatic**
  - Elevated transaminases

- **Other (rare)**
  - Encephalopathy
  - Liver failure

**Shock**
### WHO classification of dengue infections and grading of severity of DHF

<table>
<thead>
<tr>
<th>DHF</th>
<th>Grade</th>
<th>Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHF</td>
<td>I</td>
<td>Fever and haemorrhagic manifestation (positive tourniquet test) and evidence of plasma leakage</td>
<td>Thrombocytopenia $&lt;100,000$ cells/mm$^3$; HCT rise $\geq 20%$</td>
</tr>
<tr>
<td>DHF</td>
<td>II</td>
<td>As in Grade I plus spontaneous bleeding.</td>
<td>Thrombocytopenia $&lt;100,000$ cells/mm$^3$; HCT rise $\geq 20%$.</td>
</tr>
<tr>
<td>DHF</td>
<td>III</td>
<td>As in Grade I or II plus circulatory failure (weak pulse, narrow pulse pressure $\leq 20$ mmHg, hypotension, restlessness)</td>
<td>Thrombocytopenia $&lt;100,000$ cells/mm$^3$; HCT rise $\geq 20%$.</td>
</tr>
<tr>
<td>DHF</td>
<td>IV</td>
<td>As in Grade III plus profound shock with undetectable BP and pulse</td>
<td>Thrombocytopenia $&lt;100,000$ cells/mm$^3$; HCT rise $\geq 20%$.</td>
</tr>
</tbody>
</table>
Expanded dengue syndrome (Unusual or atypical manifestations)

• Unusual manifestations are uncommon. But in recent years with the geographical spread of dengue illness and with more involvement of adults, there have been increasing reports of DF and DHF with unusual manifestations.

• These include: neurological, hepatic, renal and other isolated organ involvement.
## Expanded dengue syndrome

<table>
<thead>
<tr>
<th>System</th>
<th>Unusual or atypical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological</td>
<td>Febrile seizures in young children. Encephalopathy. Encephalitis/aseptic meningitis. Intracranial</td>
</tr>
<tr>
<td></td>
<td>haemorrhages/thrombosis. Subdural effusions. Mononeuropathies/polyneuropathies/Guillane-Barre</td>
</tr>
<tr>
<td></td>
<td>Syndrome. Transverse myelitis.</td>
</tr>
<tr>
<td>Gastrointestinal/hepatic</td>
<td>Hepatitis/fulminating hepatic failure. Acalculous cholecystitis. Acute pancreatitis. Hyperplasia of</td>
</tr>
<tr>
<td></td>
<td>Peyer’s patches. Acute parotitis.</td>
</tr>
<tr>
<td>Renal</td>
<td>Acute renal failure. Hemolytic uremic syndrome.</td>
</tr>
</tbody>
</table>
## Expanded dengue syndrome

<table>
<thead>
<tr>
<th>System</th>
<th>Unusual or atypical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Conduction abnormalities.</td>
</tr>
<tr>
<td></td>
<td>Myocarditis.</td>
</tr>
<tr>
<td></td>
<td>Pericarditis.</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Acute respiratory distress syndrome.</td>
</tr>
<tr>
<td></td>
<td>Pulmonary haemorrhage.</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Myositis with raised creatine phosphokinase (CPK).</td>
</tr>
<tr>
<td></td>
<td>Rhabdomyolysis.</td>
</tr>
<tr>
<td>Lymphoreticular/bone marrow</td>
<td>Infection associated haemophagocytic syndrome.</td>
</tr>
<tr>
<td></td>
<td>IAHS or Haemophagocytic lymphohistiocytosis (HLH), idiopathic thrombocytopenic purura (ITP).</td>
</tr>
<tr>
<td></td>
<td>Spontaneous splenic rupture.</td>
</tr>
<tr>
<td></td>
<td>Lymph node infarction.</td>
</tr>
<tr>
<td>Eye</td>
<td>Macular haemorrhage.</td>
</tr>
<tr>
<td></td>
<td>Impaired visual acuity.</td>
</tr>
<tr>
<td></td>
<td>Optic neuritis.</td>
</tr>
<tr>
<td>Others</td>
<td>Post-infectious fatigue syndrome, depression, hallucinations, psychosis, alopecia.</td>
</tr>
</tbody>
</table>
Diagnosis of dengue fever

Acute febrile illness with two or more of the following:

- Headache,
- Retro-orbital pain,
- Myalgia,
- Arthralgia/bone pain,
- Rash,
- Haemorrhagic manifestations,
- Leucopenia (wbc ≤5000 cells/mm3),
- Thrombocytopenia (platelet count <150 000 cells/mm3),
- Rising haematocrit (5 – 10%);
**Diagnosis of dengue fever**

and at least one of following:

- **NS1** (with in 5 days of fever) positive

Supportive serology on single serum sample: titre $\geq 1280$ with haemagglutination inhibition test, comparable IgG titre with enzyme-linked immunosorbent assay, or tasting positive in IgM antibody test,

occurrence at the same location and time as confirmed cases of dengue fever.
Diagnosis of dengue fever

Confirmed diagnosis:

Probable case with at least one of the following:

• Isolation of dengue virus from serum, CSF or autopsy samples.
• Fourfold or greater increase in serum IgG (by haemagglutination inhibition test) or increase in IgM antibody specific to dengue virus.
• Detection of dengue virus or antigen in tissue, serum or cerebrospinal fluid by immunohistochemistry, immunofluorescence or enzyme-linked immunosorbent assay.
• Detection of dengue virus genomic sequences by reverse transcription-polymerase chain reaction. (RT-PCR)
Diagnosis of Dengue haemorrhagic fever

All of following:

- Acute onset of fever of two to seven days duration.
- Haemorrhagic manifestations, shown by any of the following:
  - positive tourniquet test,
  - petechiae, ecchymoses or purpura, or
  - bleeding from mucosa, gastrointestinal tract, injection sites, or other locations.
Diagnosis of Dengue haemorrhagic fever

- Platelet count ≤100,000 cells/mm³
- Objective evidence of plasma leakage due to increased vascular permeability shown by any of the following:
  - Rising haematocrit/haemoconcentration ≥20% from baseline or
  - decrease in convalescence, or
  - evidence of plasma leakage such as pleural effusion, ascites or
  - hypoproteinaemia/albuminaemia.
Diagnosis of Dengue shock syndrome

Criteria for dengue haemorrhagic fever: as above with signs of shock including:

• Tachycardia, cool extremities, delayed capillary refill, weak pulse, lethargy or restlessness, which may be a sign of reduced brain perfusion.

• Pulse pressure ≤20 mmHg with increased diastolic pressure, e.g. 100/80 mmHg.

• Hypotension by age, defined as systolic pressure <80 mmHg for those aged <5 years or 80 to 90 mmHg for older children and adults.
Warning signs

• No clinical improvement or worsening of the situation just before or during the transition to afebrile phase or as the disease progresses.
• Persistent vomiting, not drinking.
• Severe abdominal pain.
• Lethargy and/or restlessness, sudden behavioural changes.
• Bleeding: Epistaxis, black stool, haematemesis, excessive menstrual bleeding, darkcoloured urine (haemoglobinuria) or haematuria.
• Giddiness.
• Pale, cold and clammy hands and feet.
• Less/no urine output for 4–6 hours.
**DENGUE ± WARNING SIGNS**

**Probable dengue**
- live in/travel to dengue endemic area.
- Fever and 2 of the following criteria:
  - Nausea, vomiting
  - Rash
  - Aches and pains
  - Tourniquet test positive
  - Leukopenia
  - Any warning sign

**Laboratory-confirmed dengue**
(important when no sign of plasma leakage)

**Warning signs***
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargement >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*requiring strict observation and medical intervention*

**Severe dengue**
1. Severe plasma leakage
2. Severe haemorrhage
3. Severe organ impairment

**CRITERIA FOR SEVERE DENGUE**
- Severe plasma leakage leading to:
  - Shock (DSS)
  - Fluid accumulation with respiratory distress
- Severe bleeding
  - as evaluated by clinician
- Severe organ involvement
  - Liver: AST or ALT >= 1000
  - CNS: Impaired consciousness
  - Heart and other organs
High-risk patients

- Infants and the elderly,
- Obesity,
- Pregnant women,
- Peptic ulcer disease,
- Women who have menstruation or abnormal vaginal bleeding,
- Haemolytic diseases such as glucose-6-phosphatase dehydrogenase (G-6PD) deficiency, thalassemia and other haemoglobinopathies,
- Congenital heart disease,
- Chronic diseases such as diabetes mellitus, hypertension, asthma, ischaemic heart disease, chronic renal failure, liver cirrhosis,
- Patients on steroid or NSAID treatment, and
- Others.
Updated Management of Dengue
Primary triage

• **History** of the duration of fever and warning signs of high-risk patients to be assessed by a trained nurse or staff, not necessarily medical.

• **Tourniquet test** to be conducted by trained personnel
  - If there is not enough staff, just inflate the pressure to 80 mmHg for >12 years of age and 60 mmHg for children aged 5 to 12 years for five minutes).

• **Vital signs**, including temperature, blood pressure, pulse rate, respiratory rate and peripheral perfusion, to be checked by trained nurse or medical assistant.
Tourniquets test and capillary refill time (CRT)

CRT:
Pressing the nail of the thumb of left hand in right handed person or vice versa till blancing and then release suddenly. The time taken for flushing is the CRT.
Primary triage

• Peripheral perfusion is assessed by palpation of pulse volume, temperature and colour of extremities, and capillary refill time.
• This is mandatory for all patients, particularly so when digital blood pressure monitors and other machines are used.
• Particular attention is to be given to those patients who are afebrile and have tachycardia.
• These patients and those with reduced peripheral perfusion should be referred for immediate medical attention, CBC and blood sugar-level tests at the earliest possible.
Primary triage

• **Recommendations for CBC:**
  - All febrile patients at the first visit to get the baseline HCT, WBC and PLT.
  - All patients with warning signs.
  - All patients with fever >3 days.
  - All patients with circulatory disturbance/shock (these patients should undergo a glucose check).

• **Results of CBC:** If leucopenia and/or thrombocytopenia is present, those with warning signs should be sent for immediate medical consultation.
Primary triage

• **Medical consultation:** Immediate medical consultation is recommended for the following:
  
  • shock.
  
  • patients with warning signs, especially those whose illness lasts for >4 days.
Primary triage

- Decision for observation and treatment:
  - **Shock**: Resuscitation and admission.
  - **Hypoglycemic patients** without leucopenia and/or thrombocytopenia should receive emergency glucose infusion and intravenous glucose containing fluids.
    - Laboratory investigations should be done to determine the likely cause of illness.
    - These patients should be observed for a period of 8–24 hours. Ensure clinical improvement before sending them home, and they should be monitored daily.
  - Those with **warning signs**.
  - **High-risk patients** with leucopenia and thrombocytopenia.
Home care advice (family education) for patients:

- Patient needs to take adequate bed rest.
- Adequate intake of fluids (not plain water) such as milk, fruit juice, isotonic electrolyte solution, oral rehydration solution (ORS) and barley/rice water.
- Beware of overhydration in infants and young children.
- Keep body temperature below 39 °C.
- If the temperature goes beyond 39 °C, give the patient paracetamol.
Home care advice (family education) for patients:

- Paracetamol should be administered in frequencies of not less than six hours.
- The maximum dose for adults is 4 gm/day. Avoid using too much paracetamol, and aspirin or NSAID is not recommended.
- Tepid sponging of forehead, armpits and extremities. A lukewarm shower or bath is recommended for adults.
Primary triage

• **Follow-up visits:**
  • Patients should be aware that the critical period is during the afebrile phase and that follow-up with CBC is essential to detect early danger signs such as leucopenia, thrombocytopenia, and/or haematocrit rise.
  • Daily follow-up is recommended for all patients except those who have resumed normal activities or are normal when the temperature subsides.
Management of DF/DHF cases in hospital observation wards/ on admission
Monitoring of dengue/DHF patients during the critical period (thrombocytopenia around 100K/mm³)

- The critical period of DHF refers to the **period of plasma leakage** which starts around the transition from febrile to afebrile phase.
- Thrombocytopenia is a sensitive indicator of plasma leakage but may also be observed in patients with DF.
- A rising haematocrit of 10% above baseline is an early objective indicator of plasma leakage.
- **Intravenous fluid therapy should be started in patients with poor oral intake or further increase in haematocrit and those with warning signs.**
Parameters that should be monitored:

- **General condition**, appetite, vomiting, bleeding and other signs and symptoms.
- **Peripheral perfusion** can be performed as frequently as is indicated because it is an early indicator of shock and is easy and fast to perform.
- **Vital signs** such as temperature, pulse rate, respiratory rate and blood pressure should be checked at least every 2–4 hours in non-shock patients and 1–2 hours in shock patients.
Parameters that should be monitored:

- **Serial haematocrit** should be performed at least every four to six hours in stable cases and should be more frequent in unstable patients or those with suspected bleeding.
- It should be noted that haematocrit should be done before fluid resuscitation. If this is not possible, then it should be done after the fluid bolus but not during the infusion of the bolus.
- **Urine output** (amount of urine) should be recorded at least every 8 to 12 hours in uncomplicated cases and on an hourly basis in patients with profound/prolonged shock or those with fluid overload.
- During this period the amount of urine output should be about 0.5 ml/kg/h.
Additional laboratory investigations

- Complete blood count (CBC).
- Blood glucose.
- Blood gas analysis, lactate, if available.
- Serum electrolytes and BUN, creatinine.
- Serum calcium.
- Liver function tests.
- Coagulation profile, if available.
- Right lateral decubitus chest radiograph (optional).
- Group and match for fresh whole blood or fresh packed red cells.
- Cardiac enzymes or ECG if indicated, especially in adults.
- Serum amylase and ultrasound if abdominal pain does not resolve with fluid therapy.
- Any other test, if indicated
Intravenous fluid therapy in DHF during the critical period

• Indications for IV fluid:
  • When the patient cannot have adequate oral fluid intake or is vomiting.
  • When HCT continues to rise 10%–20% despite oral rehydration.
  • Impending shock/shock.
The general principles of fluid therapy in DHF

- **Isotonic crystalloid solutions** should be used throughout the critical period except in the very young infants <6 months of age in whom 0.45% sodium chloride may be used.
- **Hyper-oncotic colloid solutions** such as dextran 40 or starch solutions may be used in patients with massive plasma leakage, and those not responding to the minimum volume of crystalloid.
- **Iso-oncotic colloid solutions** such as plasma and hemaccel may not be as effective.
- A volume of about maintenance +5% dehydration should be given to maintain a “just adequate” intravascular volume and circulation.
Duration of intravenous fluid therapy

• The duration of intravenous fluid therapy should not exceed 24 to 48 hours for those with shock.

• However, for those patients who do not have shock, the duration of intravenous fluid therapy may have to be longer but not more than 60 to 72 hours.

• This is because the latter group of patients has just entered the plasma leakage period while shock patients have experienced a longer duration of plasma leakage before intravenous therapy is begun.

• In obese patients, the ideal body weight should be used as a guide to calculate the fluid volume.
## Requirement of fluid based on ideal body weight

<table>
<thead>
<tr>
<th>Ideal body weight (Kgs)</th>
<th>Maintenance (ml)</th>
<th>M +5% deficit (ml)</th>
<th>Ideal body weight (kgs)</th>
<th>Maintenance (ml)</th>
<th>M +5% deficit (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>500</td>
<td>750</td>
<td>35</td>
<td>1800</td>
<td>3550</td>
</tr>
<tr>
<td>10</td>
<td>1000</td>
<td>1500</td>
<td>40</td>
<td>1900</td>
<td>3900</td>
</tr>
<tr>
<td>15</td>
<td>1250</td>
<td>2000</td>
<td>45</td>
<td>2000</td>
<td>4250</td>
</tr>
<tr>
<td>20</td>
<td>1500</td>
<td>2500</td>
<td>50</td>
<td>2100</td>
<td>4600</td>
</tr>
<tr>
<td>25</td>
<td>1600</td>
<td>2850</td>
<td>55</td>
<td>2200</td>
<td>4950</td>
</tr>
<tr>
<td>30</td>
<td>1700</td>
<td>3200</td>
<td>60</td>
<td>2300</td>
<td>5300</td>
</tr>
</tbody>
</table>
Management of DHF grade I, II (non-shock cases)

- In general, the fluid allowance (oral + IV) is about maintenance (for one day) + 5% deficit (oral and IV fluid together), to be administered over 48 hours.
- For example, in a child weighing 20 kg, the deficit of 5% is 50 ml/kg x 20 = 1000 ml.
- The maintenance is 1500 ml for one day.
- Hence, the total of M + 5% is 2500 ml
- This volume is to be administered over 48 hours in non-shock patients.
**IV Adjust non-shock grade I, II**

Name..........................BW........Kg  
M...........CC/Day =.......cc/hr,M+5%.................CC/Day=.......cc/hr

<table>
<thead>
<tr>
<th>Shock time</th>
<th>Hct</th>
<th>Platelets</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Rate of IV fluid for children (Rate for adults)**

<table>
<thead>
<tr>
<th>Type</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hct (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine (mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rate of IV replacement

- The rate of IV replacement should be adjusted according to the rate of plasma loss, guided by the clinical condition, vital signs, urine output and haematocrit levels.
Indication of Platelet Transfusion

• Platelet transfusion is not recommended for thrombocytopenia (no prophylaxis platelet transfusion).

• It may be considered in adults with underlying hypertension and very severe thrombocytopenia (less than 10 000 cell/mm3).
Management of patients with warning signs

• It is important to verify if the warning signs are due to dengue shock syndrome or other causes such as acute gastroenteritis, vasovagal reflex, hypoglycemia, etc.

• The presence of thrombocytopenia with evidence of plasma leakage such as rising haemotocrit and pleural effusion differentiates DHF/DSS from other causes.

• Blood glucose level and other laboratory tests may be indicated to find the causes.

• For other causes, IV fluids and supportive and symptomatic treatment should be given while these patients are under observation in hospital. They might need ICU support. They can be sent home within 8 to 24 hours if they show rapid recovery and are not in the critical period (i.e. when their platelet count is >100 000 cells/mm3).
MANAGEMENT OF DHF Grade I & II

Patients should be observed for at least 3 days after fall in temperature for

PURPURA ON THE SKIN
MANAGEMENT OF DHF Grade I & II

SUB CONJUNCTIVAL HAEMORRHAGE
MANAGEMENT OF DHF Grade I & II

SUB CUTENOUS BLEEDING
Management of shock: DHF Grade 3

- DSS is hypovolemic shock caused by plasma leakage and characterized by increased systemic vascular resistance, manifested by narrowed pulse pressure (systolic pressure is maintained with increased diastolic pressure, e.g. 100/90 mmHg).

- When *hypotension* is present, one should suspect that severe *bleeding, and often concealed gastrointestinal bleeding*, may have occurred in addition to the plasma leakage.
Management of shock: DHF Grade 3

- It should be noted that the fluid resuscitation of DSS is different from other types of shock such as septic shock.
- Most cases of DSS will respond to 10 ml/kg in children or 300–500 ml in adults over one hour or by bolus, if necessary.
- However, before reducing the rate of IV replacement, the clinical condition, vital signs, urine output and haematocrit levels should be checked to ensure clinical improvement.
Rate of infusion in DSS case

IV Adjust on shock grade III, IV

| Hour | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  | 17  | 18  | 19  | 20  | 21  | 22  | 23  | 24  |
|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Time |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Type IV Intake |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Urine (ml.) |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Hct (%) |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
Management of prolonged/profound shock: DHF Grade 4

- The initial fluid resuscitation in Grade 4 DHF is more vigorous.
- Even mild hypotension should be treated aggressively.
- **10 ml/kg of bolus fluid should be given as fast as possible, ideally within 10 to 15 minutes.**
- When the blood pressure is restored, further intravenous fluid may be given as in Grade 3.
Management of prolonged/profound shock: DHF Grade 4

- **If shock is not reversible after the first 10 ml/ kg, a repeat bolus of 10 ml/kg and laboratory results should be pursued and corrected as soon as possible.**

- Urgent blood transfusion should be considered as the next step (after reviewing the prerescuscitation HCT) and followed up by closer monitoring, e.g. continuous bladder catheterization, central venous catheterization or arterial lines.
Management of prolonged/profound shock: DHF Grade 4

• It should be noted that restoring the blood pressure is critical for survival and if this cannot be achieved quickly then the **prognosis is extremely grave.**

• Inotropes may be used to support the blood pressure, if volume replacement has been considered to be adequate such as in high central venous pressure (CVP), or cardiomegaly, or in documented poor cardiac contractility.
Management of prolonged/profound shock: DHF Grade 4

- If blood pressure is restored after fluid resuscitation with or without blood transfusion, and organ impairment is present, the patient has to be managed appropriately with special supportive treatment.
- Examples of organ support are peritoneal dialysis, continuous renal replacement therapy and mechanical ventilation.
- If intravenous access cannot be obtained urgently, try oral electrolyte solution if the patient is conscious or the intraosseous route if otherwise. The intraosseous access is life-saving and should be attempted after 2–5 minutes or after two failed attempts at peripheral venous access or after the oral route fails.
Management of severe haemorrhage

• If the source of bleeding is identified, attempts should be made to stop the bleeding if possible.

• Urgent blood transfusion is life-saving and should not be delayed till the HCT drops to low levels.

• If blood loss can be quantified, this should be replaced. However, if this cannot be quantified, aliquots of 10 ml/kg of fresh whole blood or 5 ml/kg of freshly packed red cells should be transfused and response evaluated. The patient may require one or more aliquot.
Management of severe haemorrhage

• In gastrointestinal bleeding, H-2 antagonists and proton pump inhibitors have been used, but there has been no proper study to show its efficacy.

• There is no evidence to support the use of blood components such as platelet concentrates, fresh frozen plasma or cryoprecipitate. Its use could contribute to fluid overload.

• Recombinant Factor VII might be helpful in some patients without organ failure, but it is very expensive and generally not available.
Management of high-risk patients
(In Special Situations)

- **Obese patients** have less respiratory reserves and care should be taken to avoid excessive intravenous fluid infusions.

- **Infants** also have less respiratory reserves and are more susceptible to liver impairment and electrolyte imbalance. Infants should, therefore, be evaluated more frequently for oral fluid intake and urine output.

- Intravenous insulin is usually required to control the blood sugar levels in dengue patients with **diabetes mellitus**. Non-glucose containing crystalloids should be used.
Management of high-risk patients

- **Pregnant women** with dengue should be admitted early to intensely monitor disease progress. Joint care among obstetrics, medicine and paediatrics specialities is essential. Families may have to be counselled in some severe situations. Amount and rate of IV fluid for pregnant women should be similar to those for non-pregnant woman using pre-pregnant weight for calculation.

- Patients with **hypertension** may be on anti-hypertensive therapy that masks the cardiovascular response in shock. A blood pressure that is perceived to be normal may in fact be low for these patients.
Management of high-risk patients

• **Anti-coagulant therapy** may have to be stopped temporarily during the critical period.

• **Haemolytic diseases and haemoglobinopathies:** These patients are at risk of haemolysis and will require blood transfusion. Caution should accompany hyperhydration and alkalinization therapy, which can cause fluid overload and hypocalcemia.
Management of high-risk patients

• **Congenital and ischaemic heart diseases:** Fluid therapy should be more cautious as they may have less cardiac reserves.

• **Patients on steroid therapy,** continued steroid treatment is recommended but the route may be changed.
Management of convalescence

• Convalescence can be recognized by the improvement in clinical parameters, appetite and general well-being.

• Haemodynamic state such as good peripheral perfusion and stable vital signs should be observed.

• Decrease of HCT to baseline or below and diuresis are usually observed.

• Intravenous fluid should be discontinued.
Management of convalescence

• In those patients with massive effusion and ascites, hypervolemia may occur and diuretic therapy may be necessary to prevent pulmonary oedema.
• Hypokalemia may be present due to stress and diuresis and should be corrected with potassium-rich fruits or supplements.
• Bradycardia is commonly found and requires intense monitoring for possible rare complications such as heart block or ventricular premature contraction (VPC).
• Convalescence rash is found in 20%–30% of patients.
CONVALESCENT CONFLUENT PETECHIAE RASH
Signs of recovery

- Stable pulse, blood pressure and breathing rate.
- Normal temperature.
- No evidence of external or internal bleeding.
- Return of appetite.
- No vomiting, no abdominal pain.
- Good urinary output.
- Stable haematocrit at baseline level.
- Convalescent confluent petechiae rash or itching, especially on the extremities.
Criteria for discharging patients

- Absence of fever for at least 24 hours without the use of anti-fever therapy.
- Return of appetite.
- Visible clinical improvement.
- Satisfactory urine output.
- A minimum of 2–3 days have elapsed after recovery from shock.
- No respiratory distress from pleural effusion and no ascites.
- Platelet count of more than 50,000/mm³. If not, patients can be recommended to avoid traumatic activities for at least 1–2 weeks for platelet count to become normal. In most uncomplicated cases, platelet rises to normal within 3–5 days.
Management of complications

- Detection of fluid overload in patients
- Management of fluid overload
- Management of encephalopathy
Referral to Tertiary Care Hospital

- Infants <1 year old.
- Obese patients.
- Pregnant women.
- Profound/prolonged shock.
- Significant bleeding.
- Repeated shock 2–3 times during treatment.
- Patients who seem not to respond to conventional fluid therapy.
- Patients who continue to have rising haematocrit and no colloidal solution is available.
- Patients with known underlying diseases such as Diabetes mellitus (DM), hypertension, heart disease or haemolytic disease.
- Patients with signs and symptoms of fluid overload.
- Patient with isolated/multiple organ involvement.
- Patients with neurological manifestations such as change of consciousness, semi-coma, coma, convulsion, etc.
Prospects of Dengue Vaccine
Burden of dengue in disability-adjusted life years (DALY)

- Estimated global burden (from 2001–2003) was 264 DALY per million per year (DALY/M/yr) for the 2 billion people living at risk of dengue
  
- Estimate for SE Asia (from 2004) was 420 DALY/M/yr
  
  - Comparable to meningitis, twice the burden of hepatitis, one third the burden of HIV/AIDS

- Estimated burden for Puerto Rico (from 1984–1994) was 658 DALY/M/yr
  
  - Comparable to meningitis, hepatitis, malaria, tuberculosis

---

Estimated direct costs of dengue in eight countries in Asia and the Americas, 2005

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of cases</th>
<th>Cost/case in US$</th>
<th>Cost in millions of US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>84,000</td>
<td>599</td>
<td>47.8 million</td>
</tr>
<tr>
<td>Malaysia</td>
<td>31,000</td>
<td>234</td>
<td>38.2 million</td>
</tr>
<tr>
<td>Cambodia</td>
<td>11,000</td>
<td>265</td>
<td>2.8 million</td>
</tr>
<tr>
<td>Venezuela</td>
<td>44,000</td>
<td>231</td>
<td>10.2 million</td>
</tr>
<tr>
<td>Panama</td>
<td>2000</td>
<td>536</td>
<td>0.9 million</td>
</tr>
<tr>
<td>Guatemala</td>
<td>8000</td>
<td>144</td>
<td>1.2 million</td>
</tr>
<tr>
<td>El Salvador</td>
<td>11,000</td>
<td>156</td>
<td>1.7 million</td>
</tr>
<tr>
<td>Brazil</td>
<td>387,000</td>
<td>351</td>
<td>135.2 million</td>
</tr>
</tbody>
</table>

### Under Reported Dengue Cases

<table>
<thead>
<tr>
<th>Cohort study</th>
<th>Total</th>
<th>Inpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand*</td>
<td>8.7 fold</td>
<td>2.6 fold</td>
</tr>
<tr>
<td>Cambodia</td>
<td>9.1 fold</td>
<td>1.4 fold</td>
</tr>
</tbody>
</table>

* Ratchaburi, Kamphaeng Phet
Thailand, a frontrunner of Dengue Vaccine Since 1993

Mahidol University signed Collaboration Agreement and License Agreement with PMsv, France
January 6, 1993
The Ideal Dengue Vaccine

- Must be safe and no significant reactogenicity after each vaccination
- Must be tetravalent and effective against all 4DENV serotypes
- Provide lifelong protection and
- Long term no vaccine enhanced DHF severe disease, ADE.

# Dengue vaccines in clinical development

<table>
<thead>
<tr>
<th>Developer</th>
<th>Preclinical</th>
<th>Clinical Evaluation Phase</th>
<th>Licensure estimated</th>
</tr>
</thead>
<tbody>
<tr>
<td>sanofi pasteur</td>
<td></td>
<td></td>
<td>2014/15</td>
</tr>
<tr>
<td>NIH</td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Biological E (India)</td>
<td>?</td>
<td>2014?</td>
<td>2017</td>
</tr>
<tr>
<td>Butantan (Brazil)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panacea (India)</td>
<td>2012</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Vabiotech (Vietnam)</td>
<td>2013?</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Inviragen</td>
<td></td>
<td></td>
<td>2014</td>
</tr>
<tr>
<td>Merck</td>
<td></td>
<td>2013</td>
<td>2018</td>
</tr>
</tbody>
</table>
Genus *Flavivirus*

Japanese Encephalitis Virus, Yellow Fever Virus, West Nile Virus, Chikungunya virus

- **enveloped** (+)ss RNA virus.
- **structural proteins** C, prM/M and E.
- **non-structural proteins** NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5.
- **four serotypes** DENV 1, 2, 3 and 4.
Healthy Children Aged 2 to 14 years in Asia 10,278 subjects will receive 3 vaccinations at 0, 6 and 12 months

Vaccine : Placebo = 2 : 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Study vaccine</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>CYD dengue vaccine</td>
<td>6,852</td>
</tr>
<tr>
<td>Group 2</td>
<td>Placebo (NaCl 0.9%)</td>
<td>3,426</td>
</tr>
<tr>
<td></td>
<td><strong>Total (All subjects)</strong></td>
<td><strong>10,278</strong></td>
</tr>
</tbody>
</table>

Phase III, multi-center, observer-blind, randomized, placebo-controlled
Study Centers

- 10,278 subjects
- Approximately 11 sites in 5 countries (approximately 2 to 3 sites in each country)
  - Kamphaeng Phet
  - Rachaburi- Banpong, Potharam

Subjects 1,000-2,000
Primary Objective

To assess the **efficacy** of CYD dengue vaccine after 3 vaccinations at 0, 6, and 12 months

- preventing symptomatic virologically-confirmed dengue cases, regardless of the severity, due to any of the four serotypes in children aged 2 to 14 years at the time of inclusion.
Objectives for Vaccine Introduction

Public Sector

• Reduce suffering
• Meet the demands of the people
• Increase economic development
• Increase capacity for vaccine introduction
• Generate more funding for health

Private Sector

• Reduce suffering
• Meet the demands of the people
• Increase economic development
• Increase capacity for vaccine introduction
• Make a return on investment
Take Home Message
Dos or Don’ts:

1. Do not give aspirin or any NSAIDs for the treatment of any fever.
2. Cases of DHF should be observe hourly.
3. Avoid giving I/V therapy before there is evidence of hemorrhage or bleeding. ORT with ORS or its equivalent is recommended for patients with moderate dehydration caused by vomiting & high temperature.
4. Avoid giving blood transfusion unless indicated, reduction in hematocrit or severe bleeding.
Dos or Don’ts:

4. Avoid giving steroid as these will complicate the situation and there is no sound evidenced based indication.

5. Food should be given according to appetite. But fresh fruit juice should be given frequently. Avoid commercially available juices due to preservatives.

6. Don’t use antibiotics as these don’t help.

7. Don’t change the speed of fluid rapidly.

8. In case of infant & children if there is febrile convulsion and or history of so appropriate standard measures should be taken.
Thank you