DENGUE:
A GLOBAL THREAT

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DENGUE: A GLOBAL THREAT

• Global epidemiology
• Case classification
• Prevention
DENGUE

The most important arthropod-borne viral disease of humans
Dengue cases reported to WHO

WHO: Global Strategy for Dengue Prevention and Control 2012-2020
The greatest dengue burden is in the Asia-Pacific region

- 75% of the global dengue burden is in the Asia-Pacific region
- Indonesia, Thailand and Viet Nam have the greatest number of reported cases
Dengue incidence is under-reported.

- The case definition is not universally applied.
- There is limited access to dengue diagnostics.
- Misdiagnosis
  - Similarity to other febrile illnesses.
- Surveillance and reporting systems are not well established in many countries.
- There is a lack of knowledge about major regions theoretically at risk.
  - China, sub-Saharan Africa, India

Epidemic Dengue Haemorrhagic Fever in Asia

1950-1969

1970-1979

1980+
When DHF emerges endemically in Asia, the Americas are relatively protected.
Average dengue incidence per 100,000 by country in the Americas, 1980–2010

Dengue and *Aedes aegypti* in Africa. The 34 countries in a dark colour indicate those in which dengue has been reported, including dengue reported only in travellers, and the presence of *Aedes aegypti* mosquitoes. Light-coloured area indicate the 13 countries in which dengue has not been reported but where *Aedes aegypti* mosquitoes are present. White indicates five countries for which data are not available.

(Emerg Infect Dis. 2011 August; 17(8): 1349–1354.)
From dengue risk to burden

- Pair probability of occurrence with cohort studies to infer inapparent (n=54) and apparent (n=39) incidence per pixel
- Then pair with population surfaces for 2010 to sum up global totals
- Consistent global estimates for BMGF, GAVI and surfaces for GBD2013
WHY IS DENGUE SUCH A BIG PROBLEM TODAY?

- Complacency
- Population Growth
- Unplanned Urbanization
  - Deterioration of Cities
- Changing Lifestyles
- Modern Transportation
- Lack of Effective Mosquito Control
  - Infrastructure
  - Lack of Professionals
- Climate Change?
DENGUE

The most important arthropod-borne viral disease of humans
2009 WHO
Revised Dengue Classification

Dengue Case Classification by Severity
Dengue Transmission Cycle

1. Bites dengue infected person
2. Mosquito ingests blood with dengue virus. Takes 8-10 days for dengue virus to incubate.
3. Dengue infected mosquito bites another person
4. That person gets dengue 4-13 days later
Clinical Spectrum of DENV Infection

DHF/Severe Dengue
Hospitalized DF
Non-hospitalized DF
Inapparent DENV Infection

Field’s Virology, 4th Ed. Chapter 9: Pathogenesis of Viral Infections, Kenneth L. Tyler and Neal Nathanson
Acute dengue virus infection

Days of defervescence

-8  -6  -4  -2  0  2  4  6

Diagnostic Requirement

Manifestations:
Shock
Hemorrhage
Encephalitis
Liver injury

Anti-dengue Ig

Mosquito bite
Fever
Viremia

Days after infection

0  2  4  6  8  10  12  14  16
Thaithumyanon P, Thisyakorn U, Deerojanawong J, Innis BL

Dengue infection during parturition complicated in severe hemorrhage and vertical transmission.

2009 WHO revised dengue classification

Dengue case classification by severity

Dengue ± warning signs

- With warning signs

- Without

Severe dengue

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

Criteria for 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
    - Leucopenia
    - 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 ≥2cm
  - Laboratory: Increase in HCT concurrent with rapid decrease in platelet count

- Criteria for severe dengue
  1. Severe plasma leakage leading to:
     - Shock (DSS)
     - Fluid accumulation with respiratory distress
  2. Severe bleeding
     as evaluated by clinician
  3. Severe organ involvement
     - Liver: AST or ALT ≥1000
     - CNS: Impaired consciousness
     - Heart and other organs
Major pathophysiologic changes in DHF

- Leakage of plasma
- Abnormal haemostasis
BLEEDING PRECAUTIONS
Mitrakul C, Thisyakorn U. Haemostatic studies in DHF

- Vasculopathy
- Coagulopathy
- Platelet abnormalities

Reports of dengue patients with unusual manifestations

- 1976 Wuler, Indonesia
  Saguansermsri, Thailand
  Tin U, Burma
- 1978 Sumarmo, Indonesia
- 1981 Kho, Indonesia
- 1987 Nimmannitya & Thisyakorn, Thailand
- 1988 George, Malaysia
Thisyakorn U, Thisyakorn C. DHF: Unusual manifestations and problem in management

The unusual manifestations include encephalopathy, encephalitis and fulminant hepatitis.
Thisyakorn U, Thisyakorn C, Limpitikul W, Nisalak A. Dengue infection with CNS manifestations

Neurological manifestations of dengue including alteration of consciousness, seizures, pyramidal tract signs, meningeal signs and headache. CSF showed lymphocytic pleocytosis in 1/5 while presence of IgM in few patients.
Solomon T, et al. Neurological manifestations of dengue infection

In dengue endemic areas patients with encephalitis and encephalopathy should be investigated for this infection, whether or not they have other features of the disease.

Hepatic functions in dengue patients

Hepatocellular injury manifested by hepatomegaly, elevation of ALT and coagulopathy are common in DHF and even in DF, though hepatomegaly is absent.

Innis BL, et al. Acute liver failure is one important cause of fatal dengue infection.

Liver injury is either a direct effect of virus replication in the liver or a consequence of host responses to infection.

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurological</strong></td>
<td>Febrile seizures in young children. Encephalopathy.</td>
</tr>
<tr>
<td></td>
<td>Encephalitis/aseptic meningitis.</td>
</tr>
<tr>
<td></td>
<td>Intracranial haemorrhages/thrombosis.</td>
</tr>
<tr>
<td></td>
<td>Subdural effusions.</td>
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<tr>
<td></td>
<td>Mononeuropathies/polyneuropathies/Guillane-Barre Syndrome.</td>
</tr>
<tr>
<td></td>
<td>Transverse myelitis.</td>
</tr>
<tr>
<td><strong>Gastrointestinal/Hepatic</strong></td>
<td>Hepatitis/fulminant hepatic failure.</td>
</tr>
<tr>
<td></td>
<td>Acalculous cholecystitis.</td>
</tr>
<tr>
<td></td>
<td>Acute pancreatitis.</td>
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<tr>
<td></td>
<td>Hyperplasia of Peyer’s patches.</td>
</tr>
<tr>
<td></td>
<td>Acute parotitis.</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>Acute renal failure.</td>
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<tr>
<td></td>
<td>Hemolytic uremic syndrome.</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>Conduction abnormalities.</td>
</tr>
<tr>
<td></td>
<td>Myocarditis.</td>
</tr>
<tr>
<td></td>
<td>Pericarditis.</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td>Acute respiratory distress syndrome.</td>
</tr>
<tr>
<td></td>
<td>Pulmonary haemorrhage.</td>
</tr>
</tbody>
</table>

Dengue: Unusual or Atypical Manifestations (1/2)
## Dengue: Unusual or Atypical Manifestations (2/2)

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td>Myositis with raised creatine phosphokinase (CPK). Rhabdomyolysis.</td>
</tr>
<tr>
<td><strong>Lymphoreticular/Bone marrow</strong></td>
<td>Infection associated haemophagocytic syndrome (IAHS) or Haemophagocytic lymphohistiocytosis (HLH). Idiopathic thrombocytopenic purpura (ITP). Spontaneous splenic rupture. Lymph node infarction.</td>
</tr>
<tr>
<td><strong>Eye</strong></td>
<td>Macular haemorrhage. Impaired visual acuity. Optic neuritis.</td>
</tr>
</tbody>
</table>

Co-infection in dengue patients

Co-infection can modify clinical presentations of dengue disease and result in missed or delayed diagnosis and treatment and possible misinterpretation as unusual manifestations.

Concurrent Infections:

- Malaria + dengue
- Malaria + dengue + leptospirosis
- Malaria + dengue + leptospirosis + hepatitis E
- Dengue + Kawasaki syndrome
- Dengue + etc.
## Dengue & Kawasaki Disease

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Kawasaki Disease</th>
<th>Dengue</th>
<th>Ref</th>
</tr>
</thead>
</table>
Clinical course

day 6  day 8
Clinical course

day 6  IVIG  ASA, echocardiogram
Clinical course
2009 WHO revised dengue classification

Dengue case classification by severity

**Dengue ± warning signs**

- **Without**
- **with warning signs**

**Severe dengue**

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

Criteria for 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
    - Leucopenia
    - Any warning sign
- **Laboratory confirmed dengue**
  (important when no sign of plasma leakage)

Criteria for severe dengue

1. Severe plasma leakage leading to:
   - Shock (DSS)
   - Fluid accumulation with respiratory distress
2. Severe bleeding
   - as evaluated by clinician
3. Severe organ involvement
   - Liver: AST or ALT $\geq$ 1000
   - CNS: Impaired consciousness
   - Heart and other organs

*Warning signs*:

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargement $\geq$ 2 cm
- Laboratory: Increase in HCT concurrent with rapid decrease in platelet count

* Requiring strict observation and medical intervention
2009 WHO
Revised Dengue Classification

Dengue Case Classification by Severity
Successful treatment of DHF depends on early recognition and careful monitoring of the development of shock.
DENGUE

Prevention and Control
Dengue: Prevention and Control

Combat vector mosquitoes through:

• preventing mosquitoes from accessing egg-laying habitats by environmental management and modification.
• disposing of solid waste properly and removing artificial man-made habitats.
• covering, emptying and cleaning of domestic water storage containers on a weekly basis.
• applying appropriate insecticides to water storage outdoor containers.
• using of personal household protection such as window screens, long-sleeved clothes, insecticide treated materials, coils and vaporizers.
• improving community participation and mobilisation for sustained vector control.
• applying insecticides as space spraying during outbreaks as one of the emergency vector control measures.
• active monitoring and surveillance of vectors should be carried out to determine effectiveness of control interventions.

(WHO: Fact sheet No 117, November 2012)
Potential breeding habitats (indicated in dotted circle) of *Ae. aegypti* and *Ae. albopictus* in an indoor situation.
Potential breeding habitats of *Ae. aegypti* and *Ae. albopictus* in an outdoor situation

Global Distribution of *Aedes aegypti* and *Aedes albopictus*

DON'T MAKE DR USA WORRY!
CONTROVERSIES IN DENGUE PATHOGENESIS

- The 1997 WHO case definition is inadequate
- DHF is not significantly associated with second dengue infections
- DHF is caused by virulent viruses
- DHF results from an abnormal T cell response
- DHF results from dengue infection-induced autoimmunity
- DHF results from DENV-infected endothelial cells
Dengue Vaccine

The complexity of developing a dengue vaccine development

• Need for a tetravalent vaccine with not just one but four immunogens that will give a balanced immune response whereby a protective long-lasting immunity is induced against all four viruses simultaneously (balancing viral interference, immunogenicity, and reactogenicity).

• Lack of immune correlate of protection since the mechanism of protective immunity against DEN infection is only partially understood. It is assumed that neutralizing antibodies are the main effector of protection against DEN infection.

• Lack of a suitable animal model that recapitulates human disease and can be used to evaluate candidate vaccines.

• Potential immunopathogenesis, including antibody-dependent enhancement implementation.

• Need for long-term follow-up.

• Need for testing in both Asia and the Americas.

• Ideally, can be tested against all four DEN serotypes.

• The exact location, timing and serotype/genotype composition of dengue epidemics varies from year to year and is somewhat unpredictable.
Dengue Vaccines: Latest Developments and Future Directions

- Live attenuated virus
- Chimeric virus
- Inactivated virus
- Subunit
- DNA
- Vectored
- Recombinant E proteins
- VLP based

# Vaccine candidates in clinic

## DEPARTMENTS

<table>
<thead>
<tr>
<th>DEVELOPERS</th>
<th>PRECLINICAL</th>
<th>PHASE I</th>
<th>PHASE II</th>
<th>PHASE III</th>
</tr>
</thead>
<tbody>
<tr>
<td>SANOFI PASTEUR</td>
<td></td>
<td></td>
<td></td>
<td>Live attenuated chimeric tetravalent</td>
</tr>
<tr>
<td>TAKEDA (INVIRAGEN)</td>
<td></td>
<td></td>
<td></td>
<td>Live attenuated tetravalent</td>
</tr>
<tr>
<td>NIH/BUTANTAN (Brazil)</td>
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<td></td>
<td></td>
<td>Live attenuated tetravalent</td>
</tr>
<tr>
<td>MERCK</td>
<td></td>
<td></td>
<td>Recombinant envelope protein</td>
<td></td>
</tr>
<tr>
<td>GSK / FIOCRUZ</td>
<td></td>
<td></td>
<td></td>
<td>Inactivated</td>
</tr>
</tbody>
</table>

*Modified from Consolidated Points to Consider for Dengue Vaccines Introduction in Endemic Countries, DVI, March 2013*
Generation of prM-E Chimeric Viruses

Backbone: DENV-2 PDK-53, YFV vaccine, or 3’utr Δ30

Replacement

DENV-1
DENV-2
DENV-3
DENV-4
1st ADVASC Meeting Report

The ASEAN Dengue Vaccination Advocacy Steering Committee (ADVASC) is a newly formed scientific forum dedicated to dengue vaccine advocacy. The committee consists of medical experts including virologists, paediatricians, physicians and experts in the fields of infectious diseases, tropical medicine and immunisation. The first meeting of ADVASC was held on 18 December 2011 and served to define the objectives of ADVASC in relation to the introduction of a dengue vaccine in South-east Asia.

The mosquito-borne dengue virus is a potential threat to almost half of the world's population, with an estimated 60 million people infected annually. Around 500,000 of those infected each year develop dengue haemorrhagic fever (DHF), a severe form of the disease that can lead to dengue shock syndrome and death. DHF is a leading cause of hospitalisation and places a large economic burden on affected countries. South-east Asia and the Western Pacific carry the majority of the global burden, with over 70% of the population at risk of dengue infection living in those regions. The incidence of dengue fever has been rising dramatically, facilitated by increased urbanisation and travel.

Current efforts to halt the spread of dengue focus on mosquito control and reducing virus transmission; however, such efforts alone are not sufficiently effective. A vaccine that protects against the virus would therefore be of tremendous benefit in the fight against dengue. Vaccines against dengue are in development, with the lead candidates currently undergoing Phase III clinical trials. Estimates suggest that the vaccine will be available for the global market by 2015. Early preparation for vaccine introduction is essential to maximise the benefits of the vaccine.

ADVASC aims to assist the introduction of the dengue vaccine in South-east Asia. This initial meeting provided an opportunity to develop and clarify the group's identity, objectives and activities. In the first session of the meeting, nine presentations were given by the attendees to provide country-specific background information on the current dengue situation across South-east Asia, as detailed in the following table.

Table 1: ADVASC Meeting Presentations

<table>
<thead>
<tr>
<th>Presenter</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Usa Thaysrirum</td>
<td>Dengue in the Asia-Pacific region</td>
</tr>
<tr>
<td>Professor Usa Thaysrirum</td>
<td>Dengue surveillance in Thailand</td>
</tr>
<tr>
<td>Dr. Maria Rosario Cagpeing</td>
<td>The Global Dengue vCV Initiative</td>
</tr>
<tr>
<td>Dr. Maria Rosario Cagpeing</td>
<td>Dengue vaccination programmes in the Philippines</td>
</tr>
<tr>
<td>Dr. Daniel Koh</td>
<td>Dengue in Singapore</td>
</tr>
</tbody>
</table>

57% of global burden is in Asia-Pacific region. Need preparation in advance of vaccine release to ensure rapid introduction.

Dengue surveillance system in place since 1988. Reporting mandatory, usually within 24 hours. Reports are public.

vCV aims to simplify and extend burden of dengue; provide guidance to facilitating introduction and advocacy for funding.

Safety and immunogenicity of candidate vaccine in subjects aged 2-45 years, including follow-up.

High success rate for immunisation for childhood diseases. Good vaccine acceptance and coverage.
OBJECTIVES

• Identifying & making practical recommendations on:
  - Improved surveillance and case diagnostics
  - Select initial groups for vaccination
  - Address program feasibility
  - Prepare and implement risk management plan

• Communicating recommendations to all stakeholders

• Collaborating with other relevant dengue initiatives

Thisyakorn U. Vaccine 2012; 30: 5587-8
Letter to the Editor

ADVASC—New regional initiative supporting transition from dengue vaccine to vaccination in Southeast Asia

Keywords:
Advisory
Asian
Dengue
Vaccination

Dear Editor,

I am pleased to announce the formation of a new scientific forum dedicated to dengue vaccine advocacy in Southeast Asia. The ASEAN Member States Dengue Vaccination Advocacy Steering Committee (ADVASC) aims to disseminate information and make recommendations on dengue vaccine introduction strategies in Southeast Asia.

ADVASC members (Table 1) include virologists, paediatricians, physicians and experts across the fields of infectious disease, tropical medicine and immunisation. Countries represented include Indonesia, the Philippines, Malaysia, Singapore and Thailand. ADVASC recognises the value of partnerships with other groups working on dengue and vaccine introduction in the region, and intends to work wherever possible with the World Health Organization (WHO), the Dengue Vaccine Initiative (DVI) and the Dengue Vaccine to Vaccination Initiative (Dengue V2V) [1].

The objectives of ADVASC were agreed at the inaugural Steering Committee meeting held in Bangkok on 16 December 2011 (Box 1). Presentations at the meeting addressed topics of dengue epidemiology – documenting the increasing prevalence of the disease across the ASEAN region and at the individual country level – and dengue infection in adults, which is often misdiagnosed due to the perception of dengue as a paediatric disease.

Dengue is a mosquito-borne viral disease found throughout equatorial regions and is a potential threat to almost half of the world’s population [2]. Many factors have contributed to a recent dramatic rise in dengue fever cases, including increased urbanisation and travel [3]. Recent studies estimate that 50–100 million people are infected per year, of whom about 500,000 develop dengue haemorrhagic fever (DHF) – a severe form of the disease and 22,000 die [4].

More than 70% of the population at risk for dengue worldwide (around 1.8 billion people) live in the regions of Southeast Asia and the Western Pacific that bear nearly 75% of the current global dengue burden [5].

There is currently no specific antiviral treatment for dengue and preventing the disease through vector control methods alone is problematic. Vaccines for dengue are in development, with the lead candidate currently in Phase III clinical trials and estimated to be available by 2015 [6].

Box 1: Objectives of ADVASC

1. Identifying opportunities and making practical recommendations about how to:
   a. Improve surveillance and laboratory capacity for dengue disease confirmation, including:
      i. Documenting and standardising existing systems and coverage
      ii. Standardising case confirmation and diagnostics
   b. Select initial target groups for vaccination
   c. Address programme feasibility by improving existing infrastructure (cold chain, pharmacovigilance, vaccination compliance monitoring, and vaccine supply and distribution logistics)
   d. Prepare and implement a risk management plan

2. Communicating recommendations to:
   a. National and local government bodies
   b. International, regional, and local medical and academic societies
   c. Other stakeholders including WHO (Southeast Asia and Western Pacific Regional Offices)
   d. The public/media

3. Collaborating with other relevant dengue initiatives including V2V and DVI

Table 1

<table>
<thead>
<tr>
<th>ADVASC members</th>
<th>Chair</th>
<th>Thailand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Lila Thanlawn</td>
<td>Chulalongkorn University, Thailand</td>
<td></td>
</tr>
<tr>
<td>Dr. Maria Robelita Lepel undes</td>
<td>Research Institute for Tropical Medicine, the Philippines</td>
<td></td>
</tr>
<tr>
<td>Dr. Daniel Koh</td>
<td>Yong Loo Lin School of Medicine, Singapore</td>
<td></td>
</tr>
<tr>
<td>Dr. Zulaidill Ismail</td>
<td>KTP Selangor Specialist Hospital, Malaysia</td>
<td></td>
</tr>
<tr>
<td>Professor Tine Pong Tanlalwien</td>
<td>Chulalongkorn University, Thailand</td>
<td></td>
</tr>
<tr>
<td>Dr. Satire Yohen</td>
<td>Mahidol University, Thailand</td>
<td></td>
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<tr>
<td>Professor Sri Reiki Hasmyegor</td>
<td>Dr. Cipto Mangunkusumo Hospital, Indonesia</td>
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</table>

Early preparation for vaccine introduction will ensure that the vaccine can reach those who need it as early as possible. In 2012, ADVASC intends to focus on understanding dengue surveillance systems in Southeast Asia, making recommendations on regional standardisation and identifying gaps in diagnostic capabilities and case classification. Robust surveillance of dengue will allow valid assessment of vaccine impact and aid control of the disease.

Financial disclosure

ADVASC is supported by an unrestricted educational grant from Sanofi Pasteur.
Recommendations from ADVA

Standardizing the monitoring & reporting of dengue in the ASEAN region
Recommendations from ADVA I/V
Case definition & classification

• Reconciled and harmonized WHO 1997, WHO 2009 and WHO 2011-SEARO guidelines for simplified surveillance and meeting key diagnostic criteria

• Information on DHF, DSS is preserved in order to compare with historical data
Recommendations from ADVA II/V

Data collection & analysis

• Data should be collected at all levels and reported

• Vaccination status should be linked to existing surveillance systems

• Promote regional networks
Recommendations from ADVA III/V

Laboratory testing

• Choice of diagnostic tests
• Results of all tests should be linked to surveillance system
• If testing of all cases is not possible, sentinel sites and representative sampling of cases
• Quality control by a central reference laboratory
Recommendations from ADVA IV/V Research

• Continue to strengthen the evidence base through research
• Continue research and development
• Assess existing surveillance system to ensure efficiency and sustainability
Recommendations from ADVA V/V Advocacy

- Continue to raise visibility of dengue and dengue vaccination
- Encourage rapid sharing information from early adopter countries
- Plan an awareness campaign
- Explore initiatives and build partnerships to ensure sustainable, long-term financing for dengue prevention and control
Goal:
To reduce the burden of dengue

Objectives:
- To reduce dengue mortality by at least 50% by 2020*
- To reduce dengue morbidity by at least 25% by 2020*
- To estimate the true burden of the disease by 2015

* The year 2010 is used as the baseline.

Technical elements:
1. Diagnosis and case management
2. Integrated surveillance and outbreak preparedness
3. Sustainable vector control
4. Future vaccine implementation
5. Basic operational and implementation research

Enabling factors for effective implementation of the global strategy:
- Advocacy and resource mobilization
- Partnership, coordination and collaboration
- Communication to achieve behavioural outcomes
- Capacity building
- Monitoring and evaluation
DENGUE

Prevention and Control
DENGUE: A GLOBAL THREAT

- Global epidemiology
- Case classification
- Prevention
CONCLUSION

• The human and economic cost of dengue are significant and likely to be even higher than estimated

• Disease prevention is a key to public health