DENGUE:
A GLOBAL THREAT

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Dengue Disease: Global Threat

30-fold increase in last decades

- Over 2.5 billion people now at risk
  - >40% of the world's population
- Dengue is the most common disease transmitted by a mosquito
- Now a major public health problem in many tropical and subtropical regions:
  - 100–200++ million infections / year
  - >100 tropical and subtropical countries
  - ~ 20,000 deaths annually
- Factors leading to increase include:
  1. Population growth and urbanization
  2. Inadequate water, sewer & waste management systems
  3. Rise in global commerce & tourism
  4. Global warming
  5. Changes in public health policy

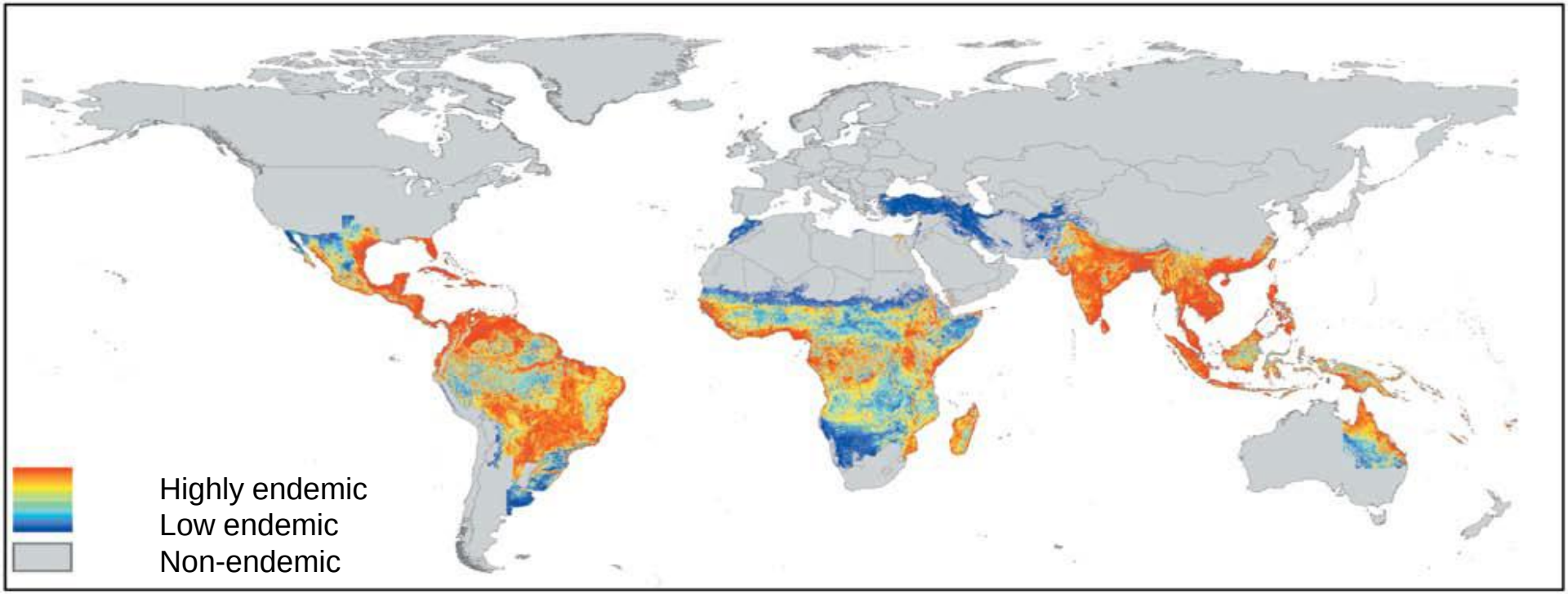
Source: தகவலுழவன்

www.who.int/mediacentre/factsheets/fs117/en/

Undurraga *PLoS Negl Trop Dis* 2013

Gubler *Expert Rev Vaccines* 2011

Worldwide Threat of Dengue



Specific WHO Objective:

By 2020, reduce mortality and morbidity from dengue by at least 50% and 25% respectively

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.

Suaya et al. 2006. WP3.2 from http://apps.who.int/tdr/svc/publications/tdr-research-publications/swg-report-dengue

GLOBAL DISTRIBUTION & DENGUE BURDEN

The accurate estimation of dengue burden will help to guide improvements in disease control strategies and in their economic evaluation.

Nature 2013; 496: 504-7

Acknowledgements

nature

LETTER

doi:10.1038/nature12060

The global distribution and burden of dengue

Samir Bhatt[1], Peter W. Gething[1], Oliver J. Brady[1,2], Jane P. Messina[1], Andrew W. Farlow[1], Catherine L. Moyes[1], John M. Drake[1,3], John S. Brownstein[4], Anne G. Hoen[5], Osman Sankoh[6,7,8], Monica F. Myers[1], Dylan B. George[9], Thomas Jaenisch[10], G. R. William Wint[1,11], Cameron P. Simmons[12,13], Thomas W. Scott[9,14], Jeremy J. Farrar[12,13,15] & Simon I. Hay[1,9]

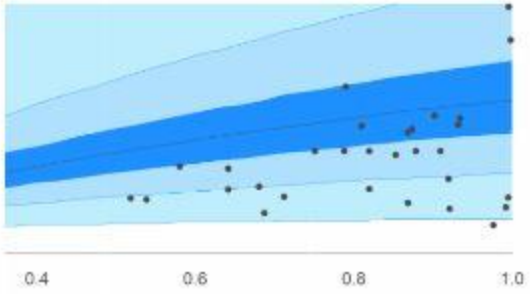
- Bhatt *et al.* (2013). *Nature*, **496**(7446): 504-507. http://www.nature.com/nature/journal/vaop/ncurrent/full/nature12060.html
- The International Research Consortium on Dengue Risk Assessment, Management and Surveillance (IDAMS: http://www.idams.eu) is funded by the European Commission Seventh Framework Programme
- Green open-access with European PubMed Central ID: PMC3651993

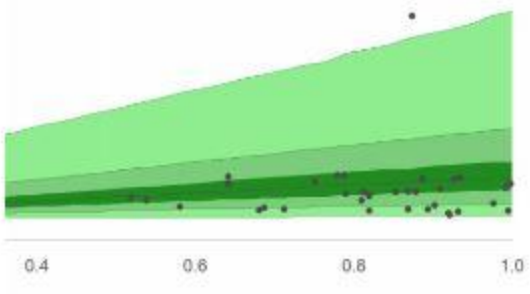
GLOBAL DISTRIBUTION & DENGUE BURDEN

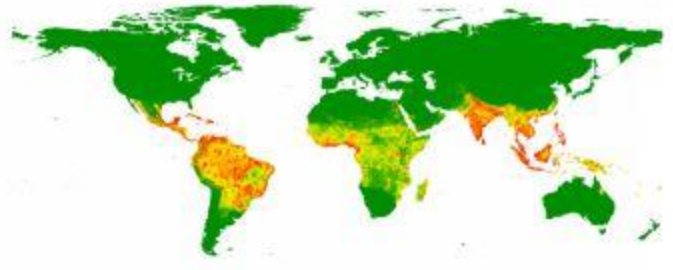
- An exhaustive assembly of known records of dengue occurrence worldwide
- Use an advance in disease modelling approaches to map the global distribution of dengue risk
- Pair the resulting risk map with detailed longitudinal information from dengue cohort studies and population surfaces to infer the public health burden of dengue

Nature 2013; 496: 504-7

From dengue risk to burden







	Apparent		Inapparent	
	Millions	(credible interval)	Millions	(credible interval)
Africa	15.7	(10.5 - 22.4)	48.4	(34.3 - 65.2)
Asia	66.8	(47.0 – 94.4)	204.4	(151.8 – 273.0)
Americas	13.3	(9.5 - 18.5)	40.5	(30.5 – 53.3)
Oceania	0.2	(0.1 - 0.3)	0.6	(0.4 - 0.8)
Global	**96.0**	**(67.1 - 135.6)**	**293.9**	**(217.0 – 392.3)**
Tropics	71.8	(50.9 - 100.1)	219.8	(16.4 - 29.0)
Not-tropics	23.4	(15.7 - 34.4)	71.7	(51.1 - 99.0)

- 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

GLOBAL DISTRIBUTION & DENGUE BURDEN

Dengue infection is more than three times the dengue burden estimate of the World Health Organization

Nature 2013; 496: 504-7

GLOBAL SPREAD
OF
DENGUE VIRUS SEROTYPES

MAPPING THE 70 YEAR HISTORY

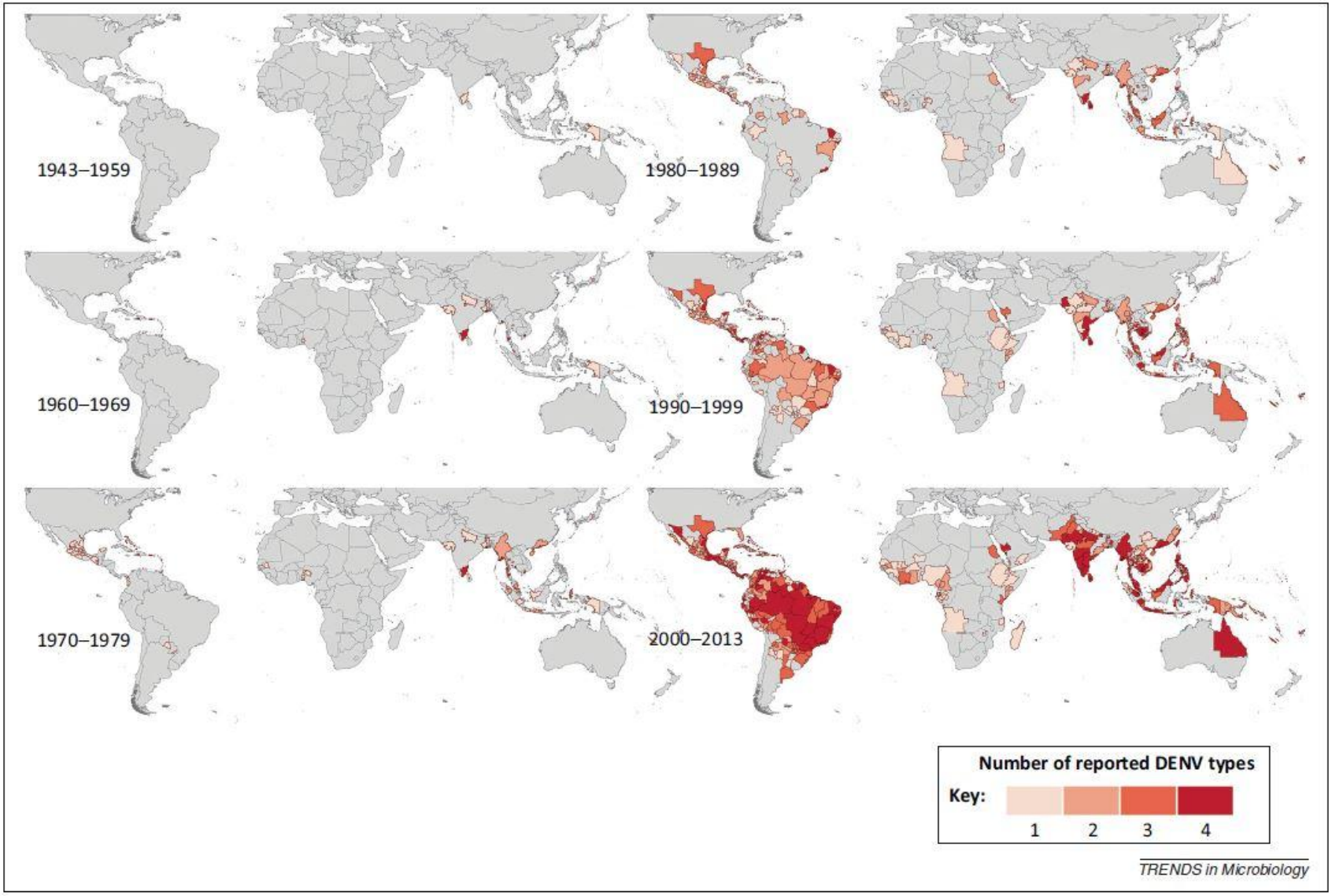


Figure 5. DENV Co-circulation. Cumulative number of DENV types reported by decade since 1943.

Global spread of dengue virus types: mapping the 70 year history

- Worldwide expansion of the types
- The expansion of disease hyperendemicity
- The establishment of an increasingly important infectious disease of global health significance

Trends Microbiol 2014; 22: 138-46.

ECONOMIC & DISEASE BURDEN OF DENGUE in SOUTHEAST ASIA

- Dengue poses a substantial economic and disease burden in SEA with a DALY burden per million inhabitants in the region
- The burden is higher than that of 17 other conditions, including Japanese encephalitis, upper respiratory infections, and hepatitis B

PLOS Neglected Tropical Diseases 2013; 7: e2055.

DENGUE

The most important arthropod-borne viral disease of humans

Is dengue eclipsing malaria as a global health threat?

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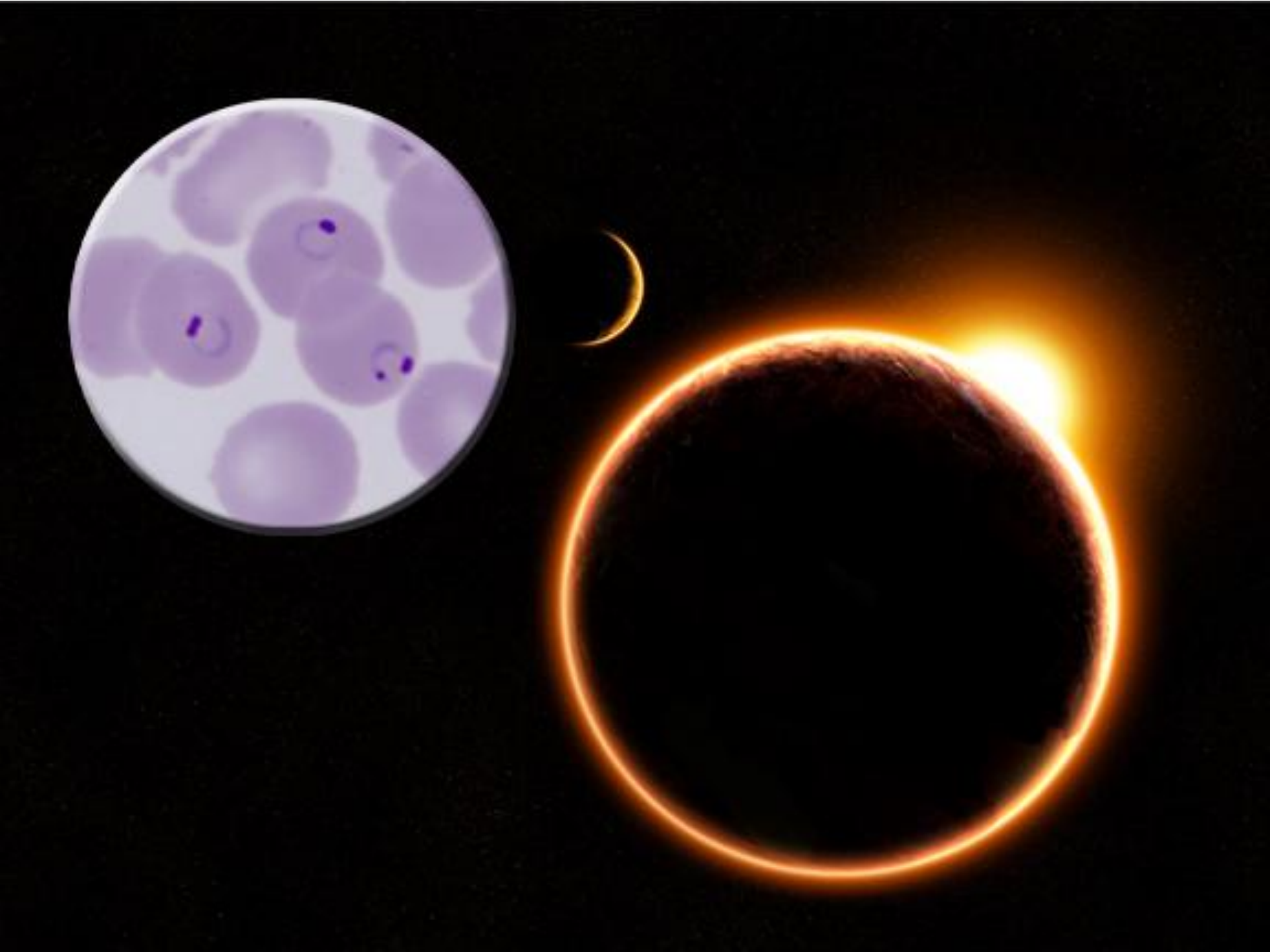
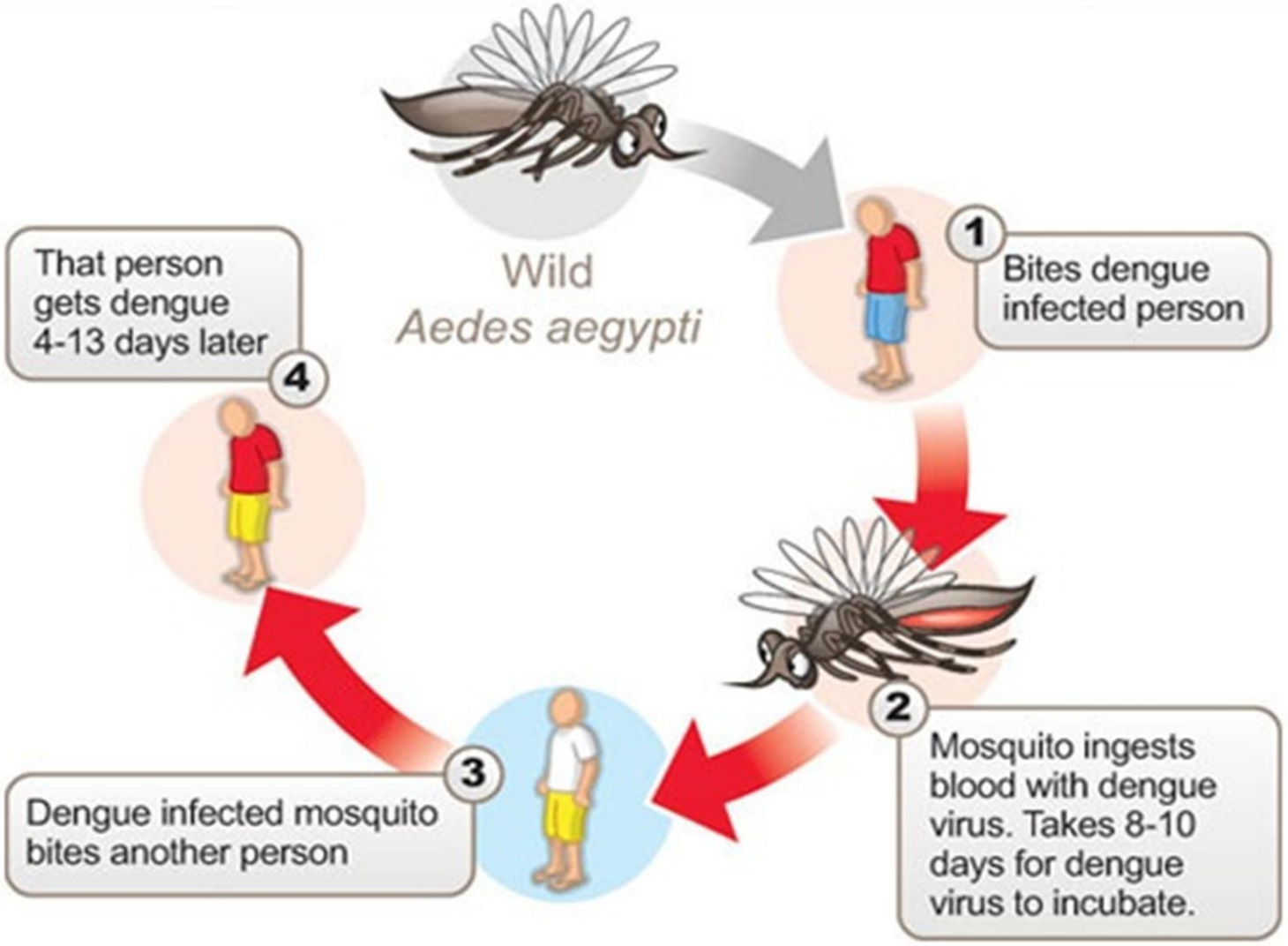
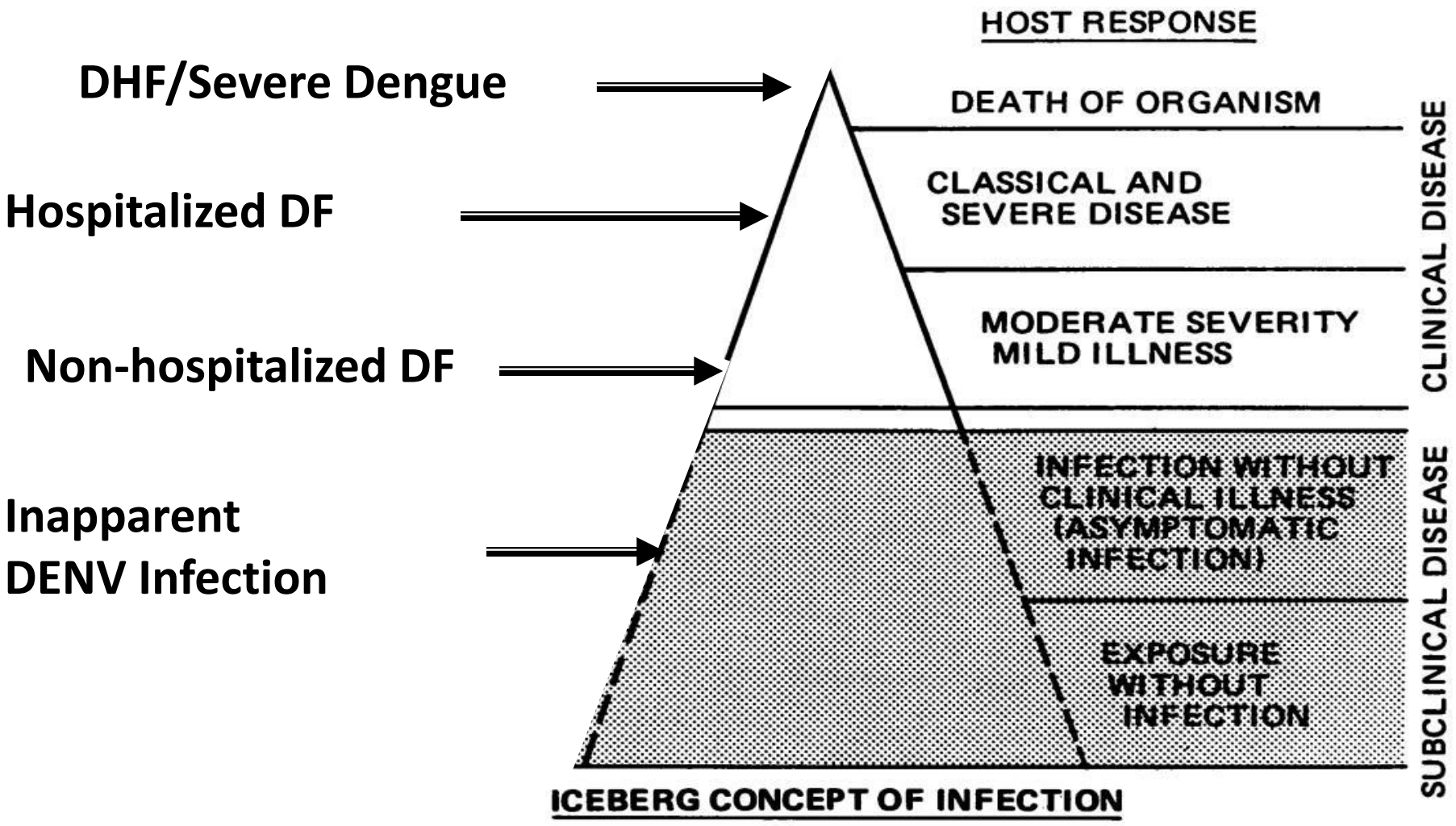



malaria
DENGUE

Dengue Transmission Cycle



Clinical Spectrum of DENV Infection



Field's Virology, 4th Ed. Chapter 9: Pathogenesis of Viral Infections, Kenneth L. Tyler and Neal Nathanson

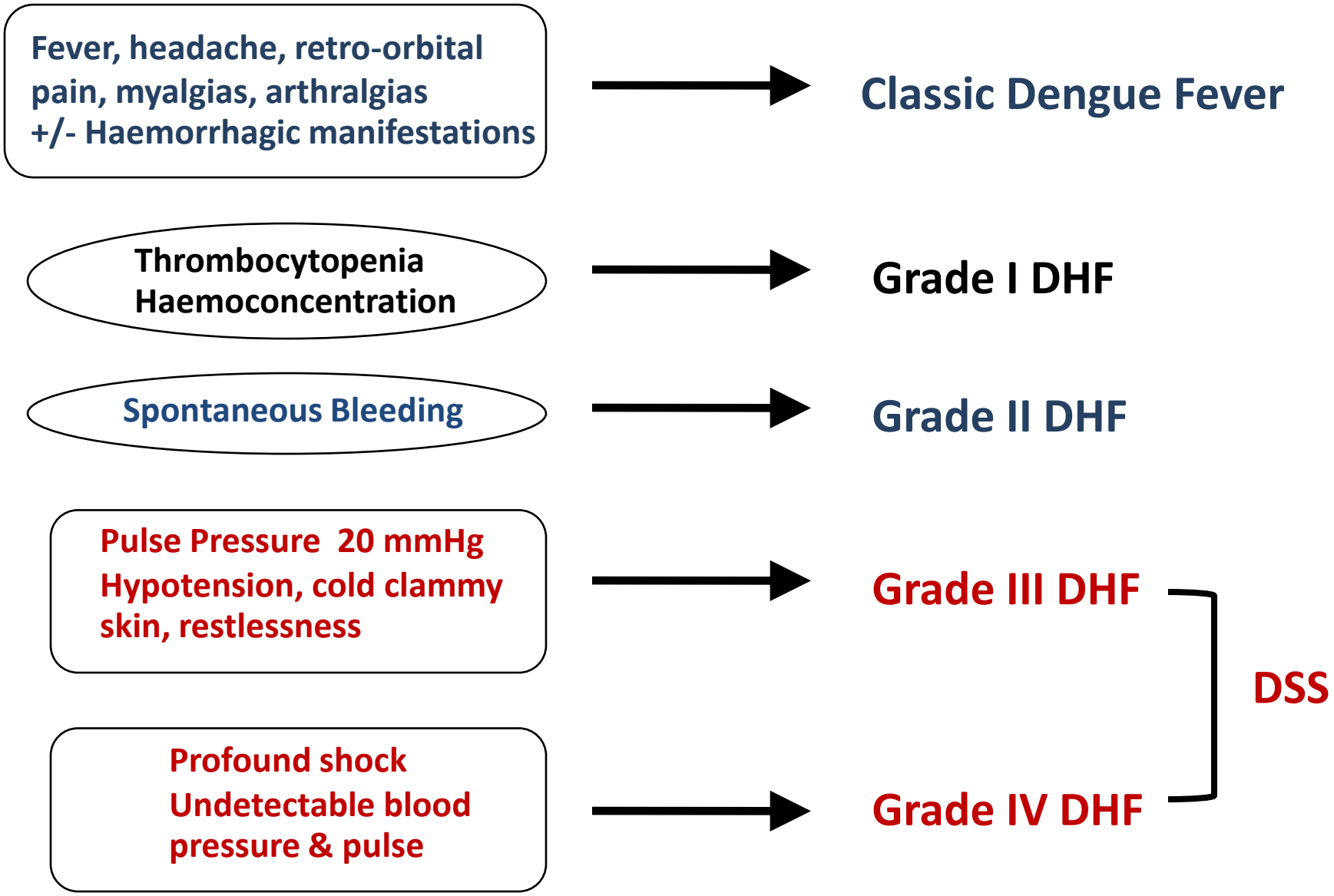
Major pathophysiologic changes in DHF

- Leakage of plasma
- Abnormal hemostasis

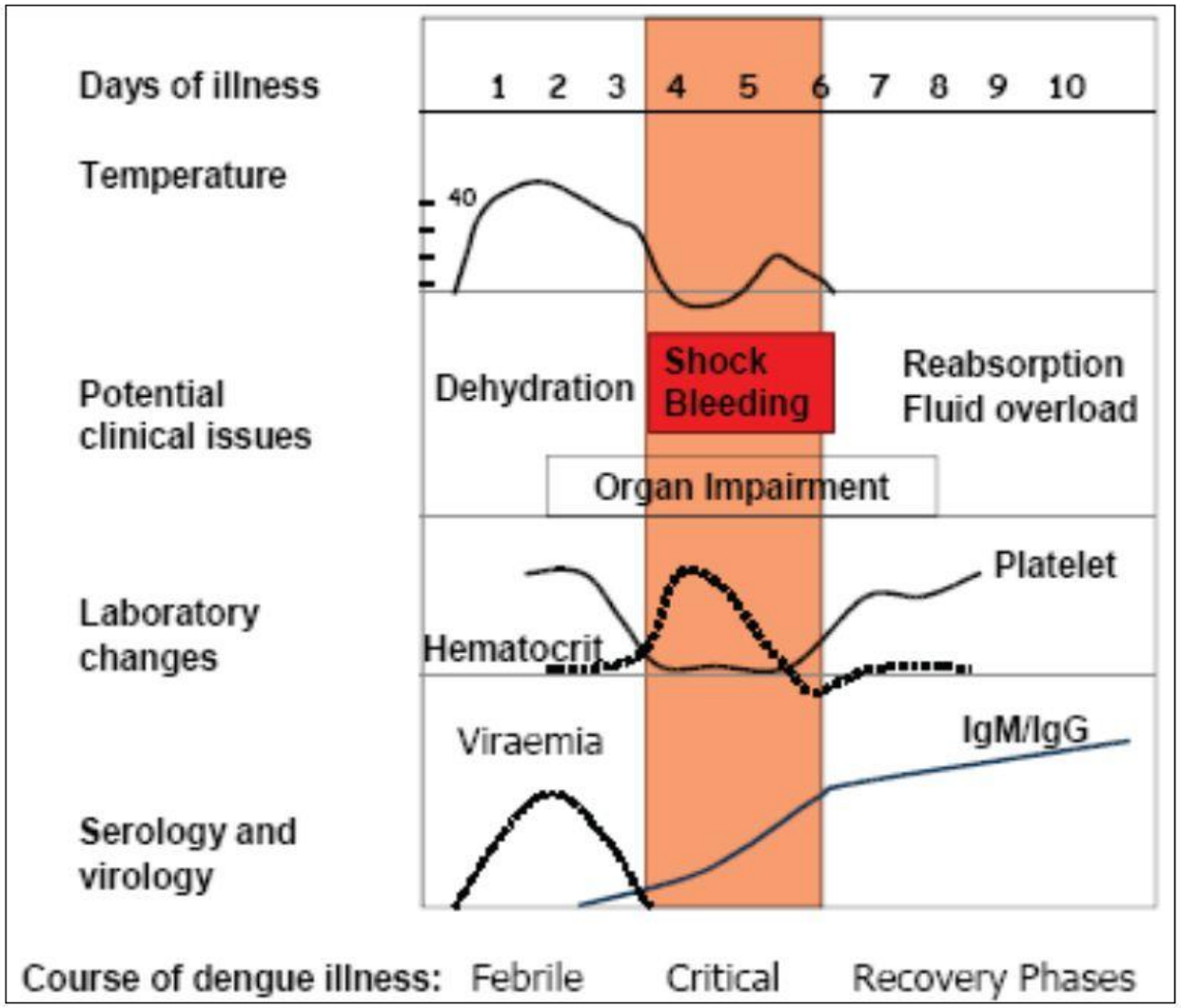
1997 WHO classification of dengue infection

Severity	Platelet	Plasma leakage
DF	variable	absent
DHF grade I	< 100,000	present
grade II	< 100,000	present
DHF grade III	< 100,000	present
grade IV	< 100,000	present

1997 WHO dengue classification



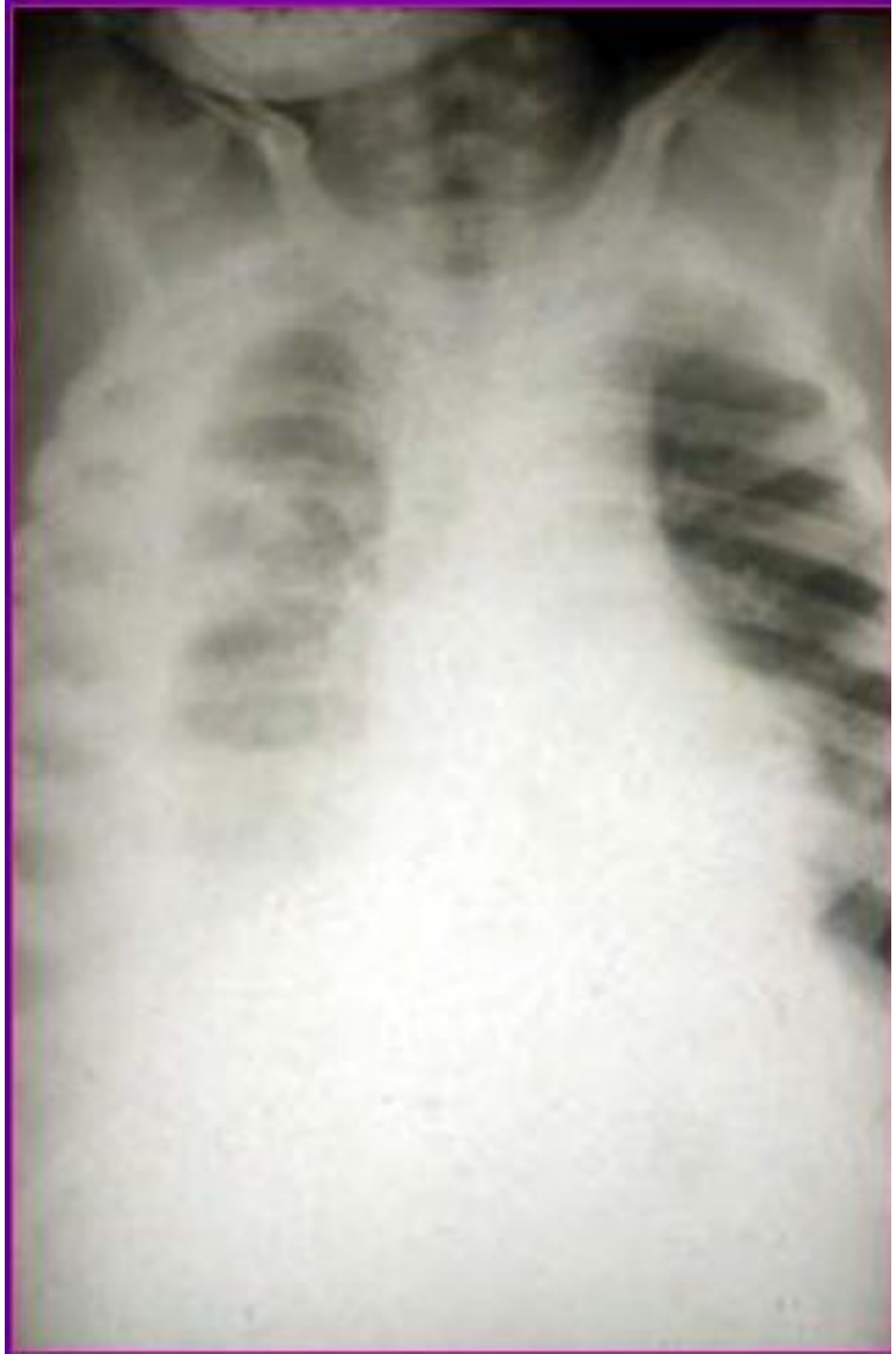
The course of dengue illness



IgM = immunoglobulin M; IgG = immunoglobulin G. Temperature is given in degrees Celsius (°C)
Source: adapted from Yip, 1980 (2) by authors.

Major pathophysiologic changes in DHF

- Leakage of plasma
- Abnormal hemostasis



BLEEDING PRECAUTIONS

Mitrakul C, Thisyakorn U. Haemostatic studies in DHF

- Vasculopathy
- Coagulopathy
- Platelet abnormalities

Proceedings of 1st International Congress of Tropical Pediatrics. Nov 8-12, 1989, Bangkok, Thailand: 215-7.

HEMOSTATIC STUDIES IN DENGUE PATIENTS

- **Laboratory evidences of DIC are demonstrated in all degrees of severity**
- **Only in severe dengue is profound DIC aggravated, leading to uncontrolled bleeding and death**
- **Plasma von Willebrand factor antigen is the best indicator of progression to severe dengue in a study to determine the extent of the activation of endothelial cells and the hemostatic system in correlation with severe dengue**

Sosothikul D, et al. Southeast Asian J Trop Med Pub Health 2015 (Suppl1); 46: S43-5.

Thaithumyanon P, Thisyakorn U, Deerojanawong J, Innis BL

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

Clin Infect Dis 1994; 18: 248-9

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

JAMA.SEA 1994; 10: 102-3.

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.

Southeast Asian J Trop Med Pub Hlth 1999; 30: 504-9

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.

Lancet 2000; 355: 1053-9.

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.

J Med Assoc Thai 2002; 85: S298-301.

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.

Southeast Asian J Trop Med Pub Hlth 1990; 21: 695-6.

Dengue: Unusual or Atypical Manifestations(1/2)

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

Dengue: Unusual or Atypical Manifestations(2/2)

Organ system	Manifestation
Musculoskeletal	Myositis with raised creatine phosphokinase (CPK). Rhabdomyolysis.
Lymphoreticular/ Bone marrow	Infection associated haemophagocytic syndrome (IAHS) or Haemophagocytic lymphohistiocytosis (HLH). Idiopathic thrombocytopenic purpura (ITP). Spontaneous splenic rupture. Lymph node infarction.
Eye	Macular haemorrhage. Impaired visual acuity. Optic neuritis.
Others	Post-infectious fatigue syndrome. Depression. Hallucinations. Psychosis. Alopecia.

Source: Gulati S, Maheshwari A. Atypical manifestations of dengue. *Trop Med Int Health. 2007;12:1087–95.*

2009 WHO
Revised Dengue Classification

Dengue Case Classification
by
Severity

2009 WHO revised dengue classification

Dengue case classification by severity

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

** Requiring strict observation and medical intervention*

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

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.

Thisyakorn U. Pediatr Infect Dis J 1998; 17: 81-2.

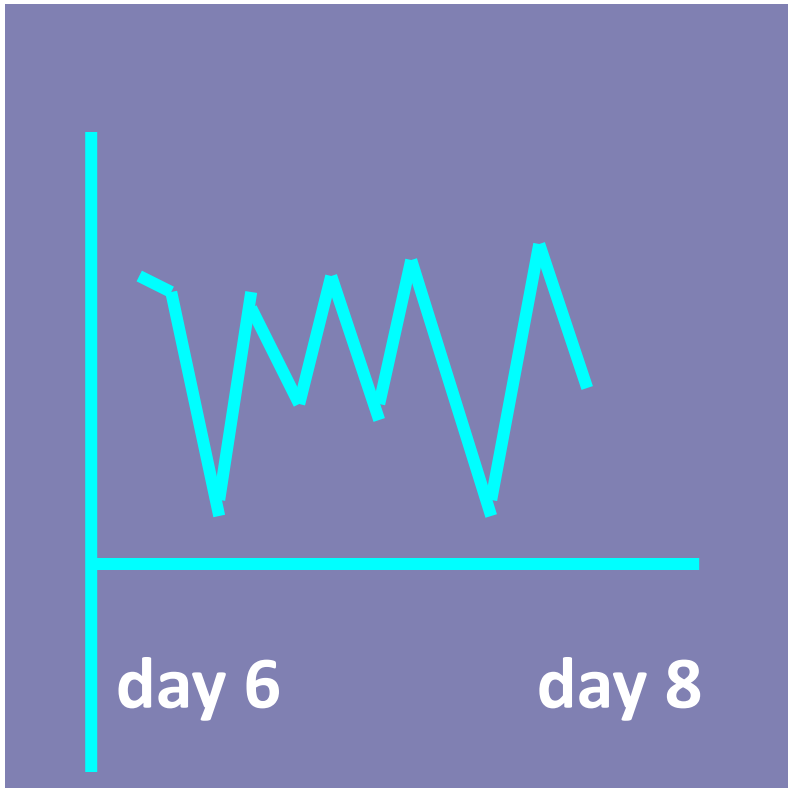
Concurrent Infections

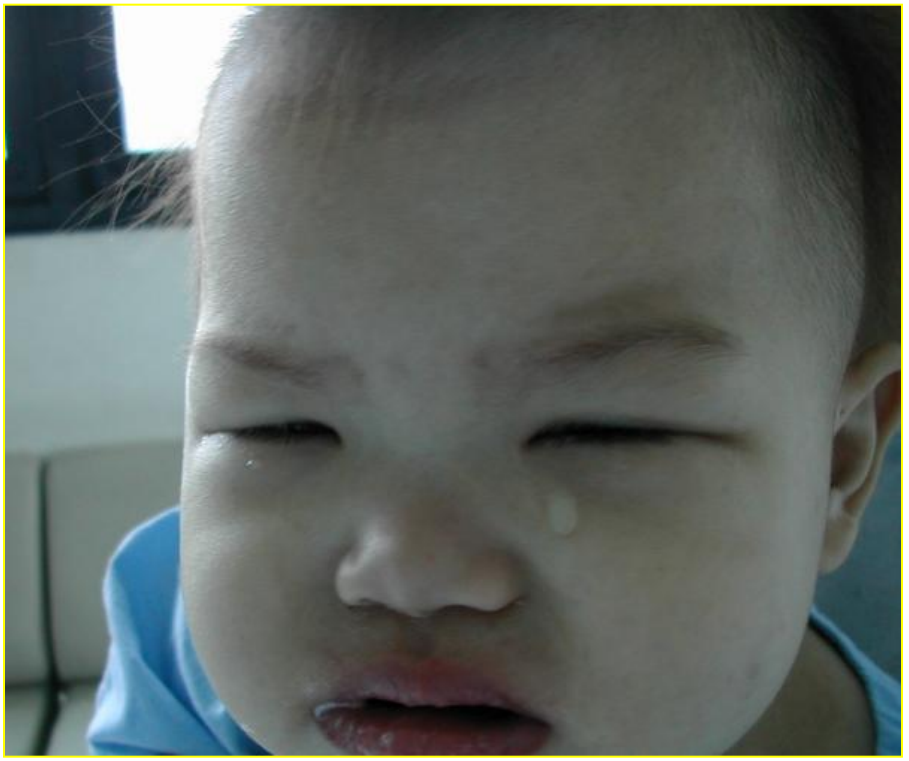
- Malaria + dengue
- Malaria + dengue + leptospirosis
- Malaria + dengue + leptospirosis + hepatitis E
- Dengue + Kawasaki syndrome
- Dengue + etc.

Dengue & Kawasaki disease

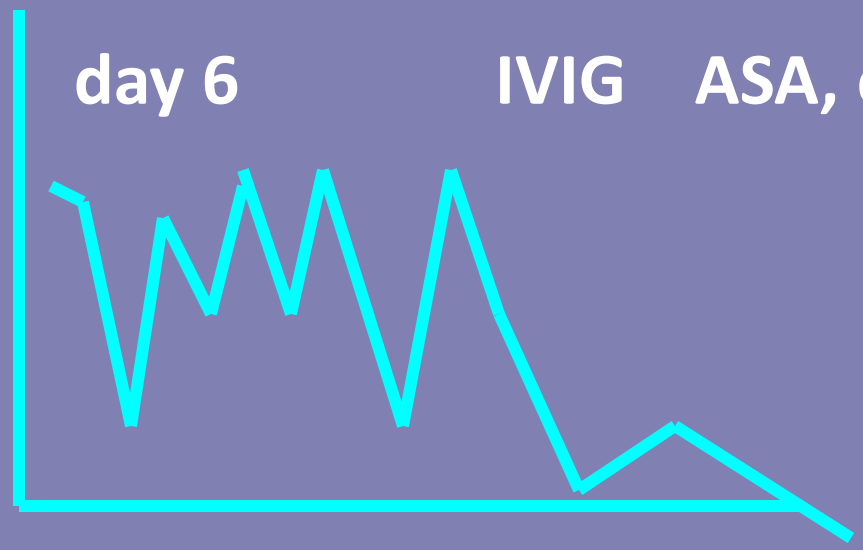
No.	Sex	Age (yr)	Kawasaki Disease	Dengue	Ref
1	M	10	Atypical	DHF III	Sopontammarak S, et al. SEA J Trop Med Public Health 2000;31:190
2	M	2 4/12	Classic	Dengue infection	Toumeux P, et al. Arch Pediatr 2002; 9: 218
3	F	11/12	Classic	DHFII	Mekmullica J, et al. J Med Assoc Thai 2005; 88:436-9.

Clinical course

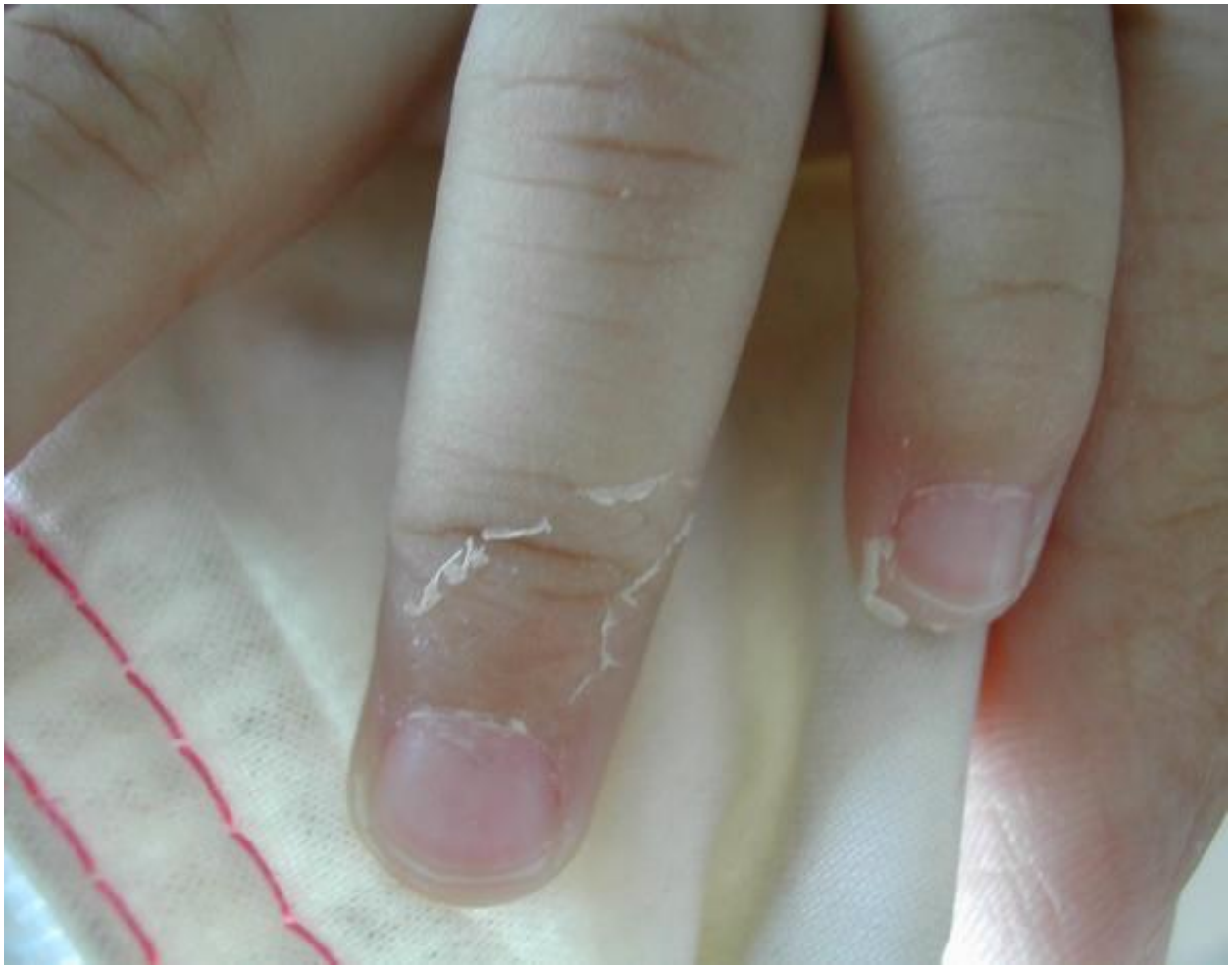




Clinical course



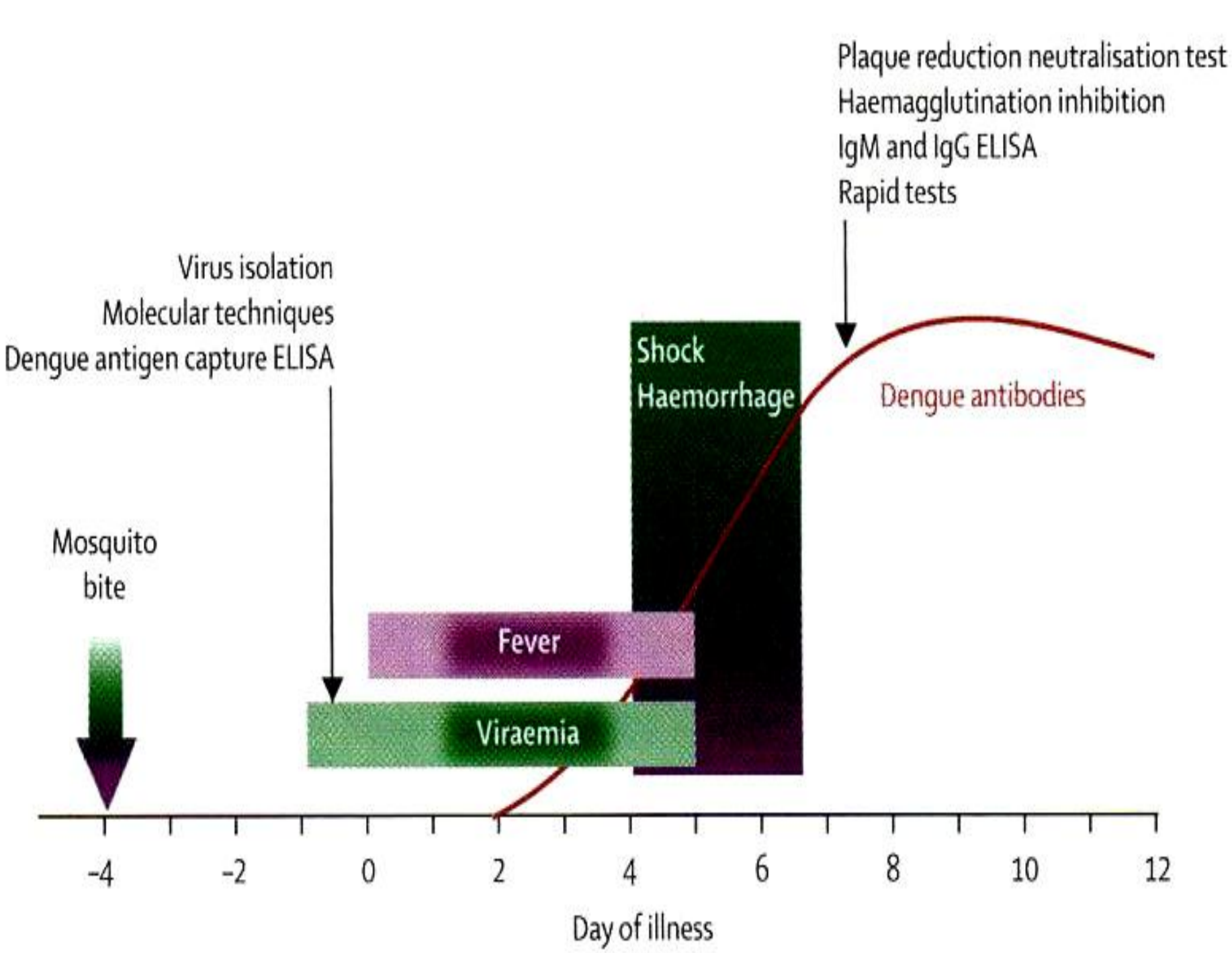
Clinical course



Dr. Kawasaki







Plaque reduction neutralisation test
Haemagglutination inhibition
IgM and IgG ELISA
Rapid tests
Virus isolation
Molecular techniques
Dengue antigen capture ELISA
Shock
Haemorrhage
Dengue antibodies
Mosquito
bite
Fever
Viraemia
-4
-2
0
2
4
6
8
10
12
Day of illness

Thisyakorn U, Thisyakorn C. Diseases caused by arboviruses

Successful treatment of DHF depends on early recognition and careful monitoring of the development of shock.

Med J Aust 1994; 160: 22-6.

HEMODYNAMIC PROFILES OF PATIENTS WITH DHF DURING TOXIC STAGE: AN ECHOCARDIOGRAPHIC STUDY

- **The mechanisms of decreased cardiac output during toxic stage of DHF is complex**
- **Decreased preload is accompanied by decreased left ventricular performance, and possibly a subnormal heart rate response in some patients**

Khongphatthanayothin A, et al. Intensive Care Med 2003; 29: 570-4.

MYOCARDIAL DEPRESSION IN DHF : PREVALENCE AND CLINICAL DESCRIPTION

- **Transient myocardial depression is not uncommon in patients with DSS.**
- **Cardiac dysfunction in children with DSS may contribute to the clinical severity and the degree of fluid overload in these patients.**

Khongphatthanayothin A, et al. Pediatr Crit Care Med 2007; 8: 524-9.

Initial fluid resuscitation for children with DSS

There is no difference between crystalloids and colloids regarding initial fluid resuscitation in moderate DSS.

No significant evidence to support colloids as the fluid for initial resuscitation in serious DSS.

Any type of colloids is not significantly different from one another.

The decision in choosing appropriate type of fluid depends on the physician's judgment.

Permpalung N, et al. Asian Biomedicine 2009; 3: 579-88.

CONTROVERSIES IN DENGUE PATHOGENESIS

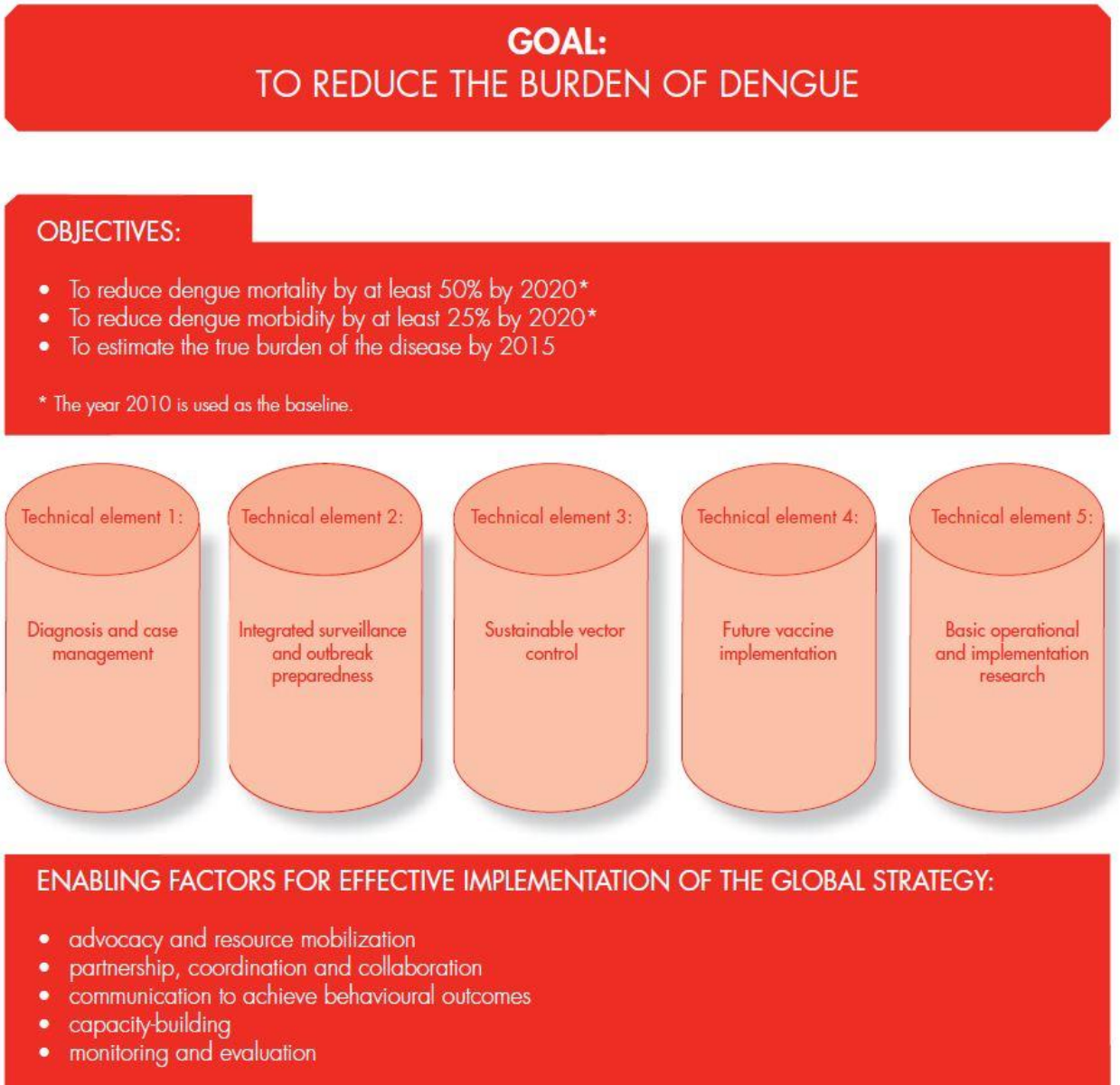
- The 1997 WHO case definition is inadequate
- DHF is not significantly associated with second dengue infections
- DHF is caused by virulent viruses
- DHF results from an abnormal T cell response
- DHF results from dengue infection-induced autoimmunity
- DHF results from DENV-infected endothelial cells

Pediatrics and International Child health 2012; 32: S5-9.

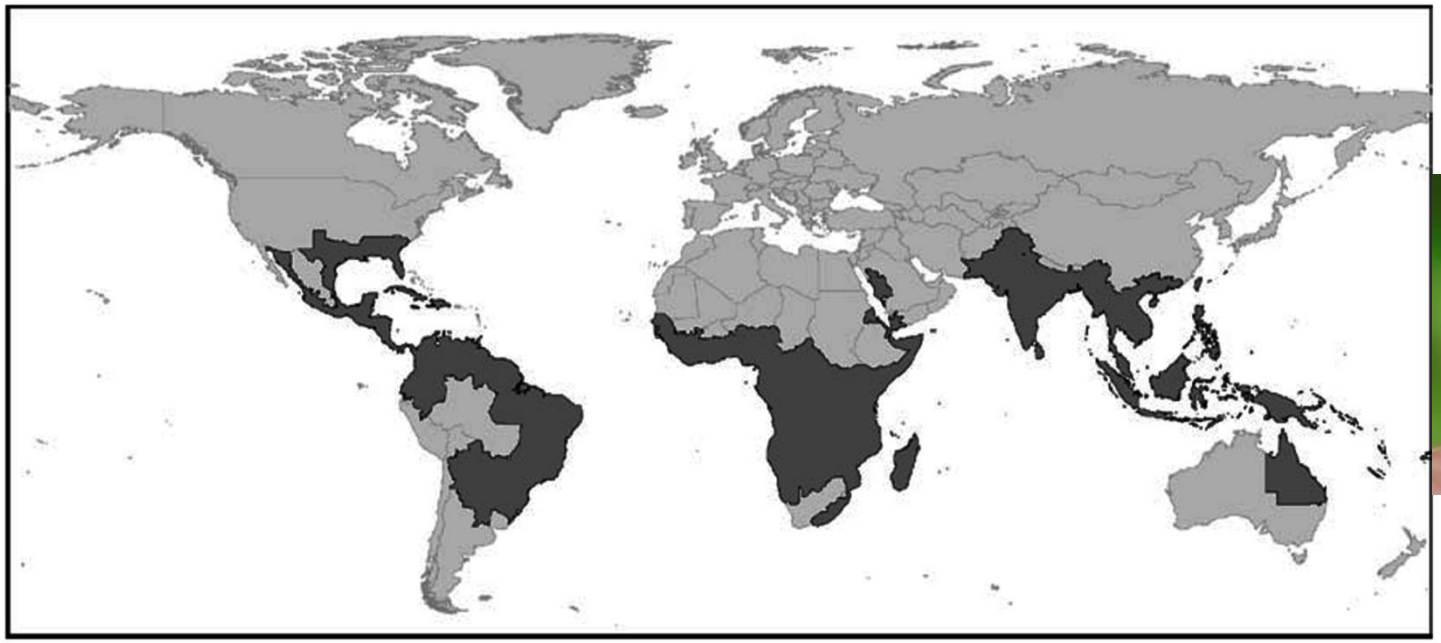
DENGUE

Prevention and Control

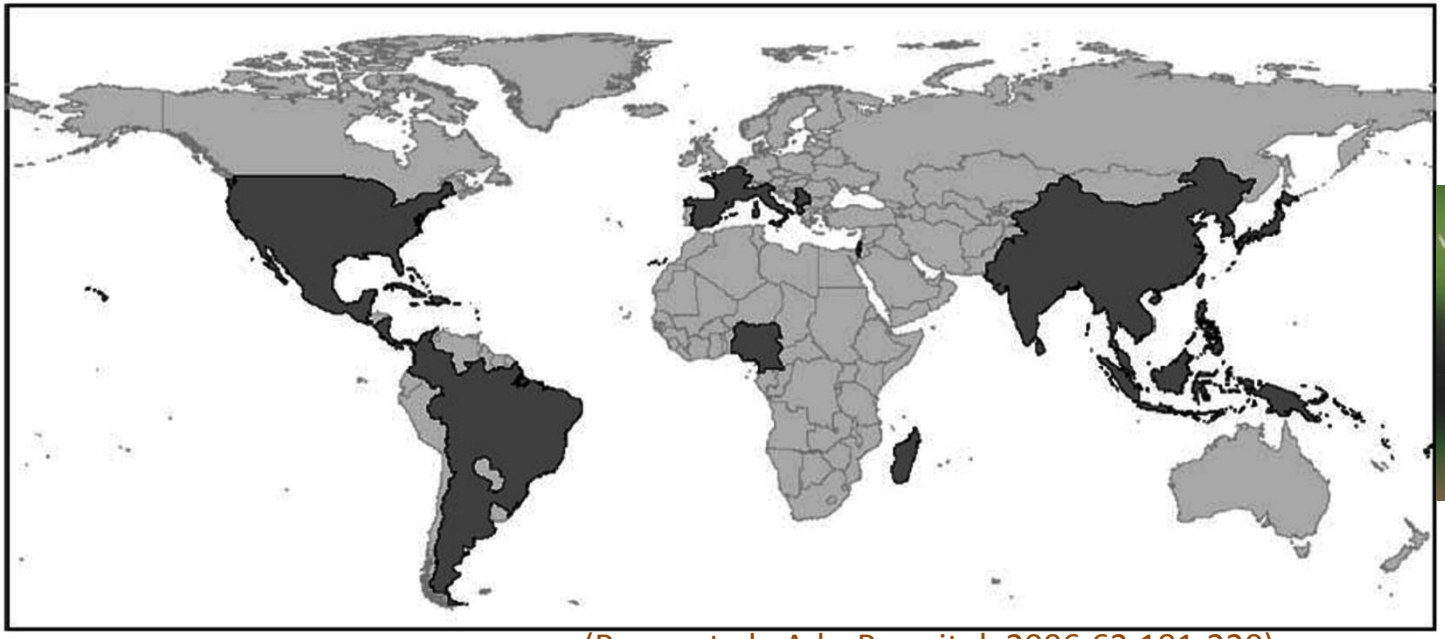
Global strategy for dengue prevention & control, 2012-2020



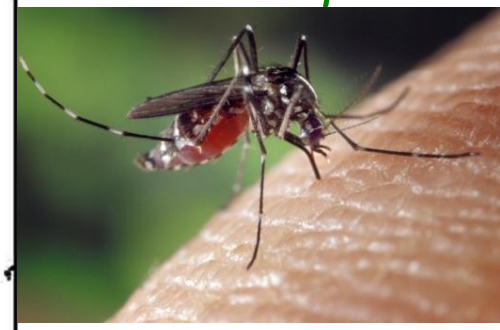
Global Distribution of *Aedes aegypti* and *Aedes albopictus*



Aedes aegypti



Aedes albopictus



(Roger et al., Adv. Parasitol. 2006;62:181-220)

INTEGRATED VECTOR MANAGEMENT

- **Advocacy, social mobilization and legislation**
- **Collaboration within the health sector and with other sectors**
- **Integrated approach to disease control**
- **Evidence-based decision-making**
- **Capacity-building**

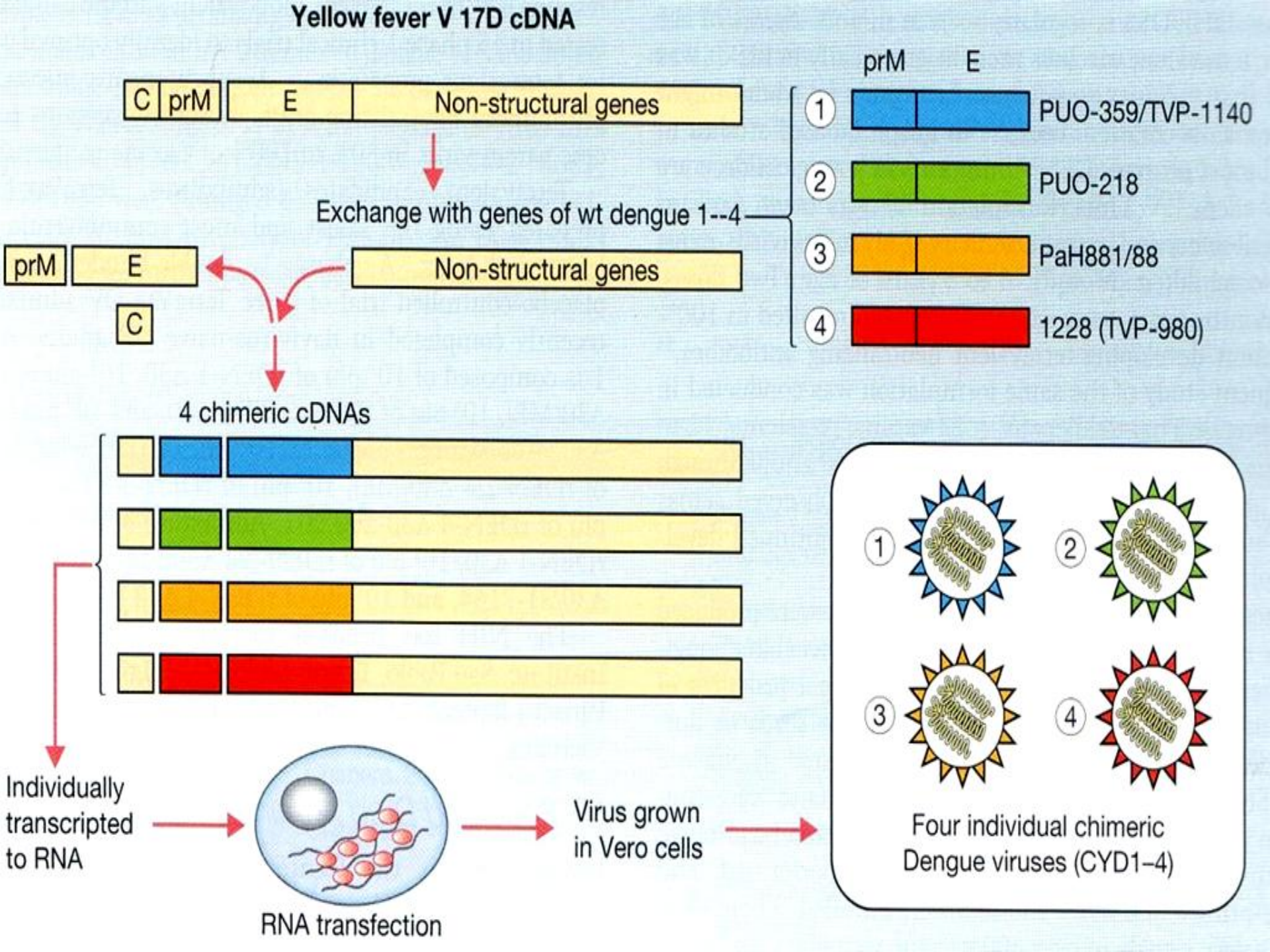
Accessible at http://apps.who.int/tdr/svc/publications/training-guideline publications/dengue-diagnosis-treatment; 2009 [accessed 04.07.11].

Dengue Vaccines:
Latest Developments and Future Directions

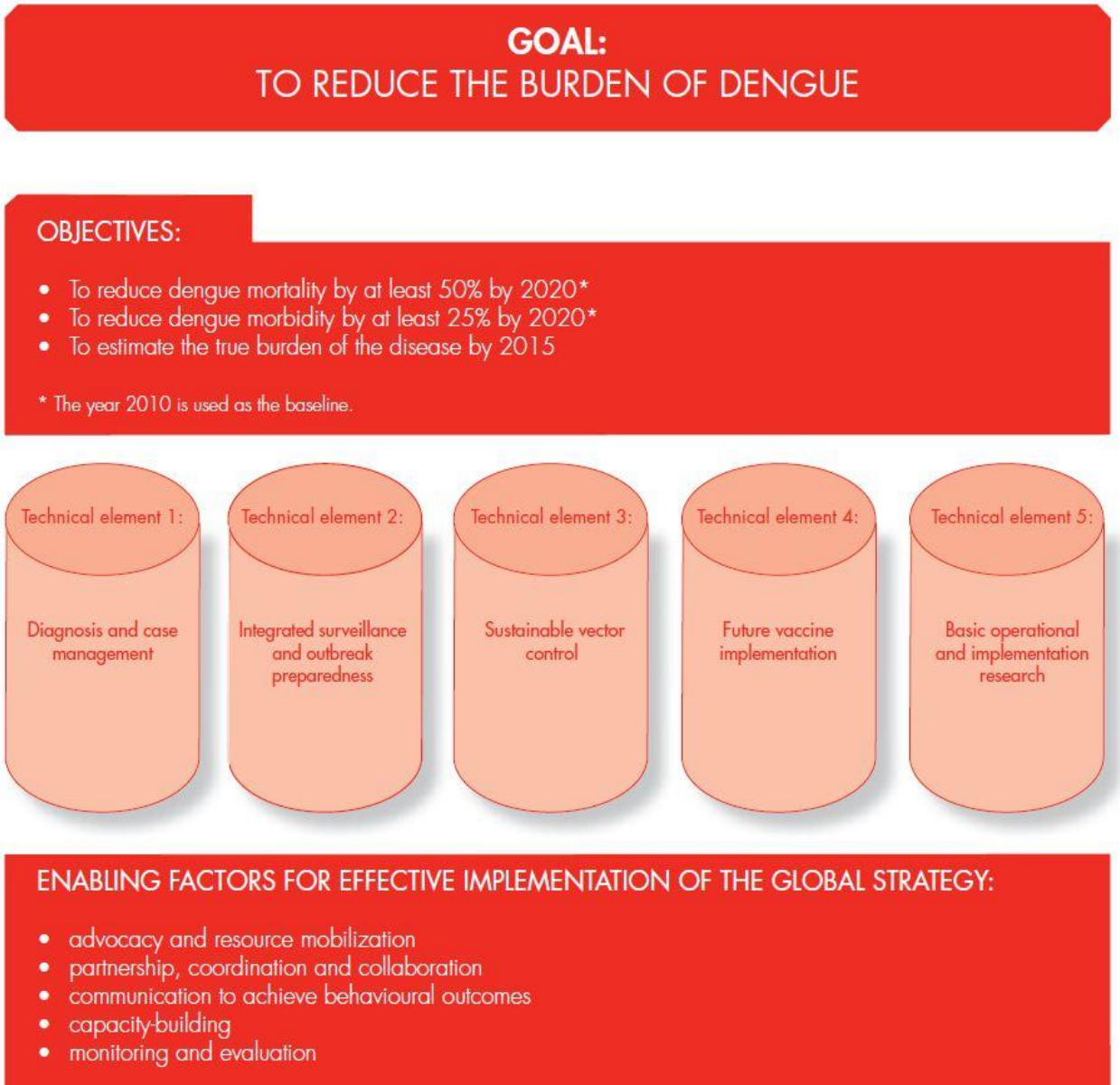
- Live attenuated virus
- Chimeric virus
- Inactivated virus
- Subunit
- DNA
- Vectored
- Recombinant E proteins
- VLP based

Thisyakorn U, Thisyakorn C. Ther Adv Vaccines 2014; 2: 3-9. Doi: 10.1177/2051013613507862

Tetravalent Dengue Vaccines in Clinical Trial Pipeline


Yellow fever V 17D cDNA
C
prM
E
Non-structural genes
Exchange with genes of wt dengue 1--4
prM
E
C
Non-structural genes
prM
E
1
PUO-359/TVP-1140
2
PUO-218
3
PaH881/88
4
1228 (TVP-980)
4 chimeric cDNAs
Individually transcripted to RNA
RNA transfection
Virus grown in Vero cells
1
2
3
4
Four individual chimeric Dengue viruses (CYD1–4)

Global strategy for dengue prevention & control, 2012-2020



ADVA
ASEAN Dengue Vaccination Advocacy

1st ADVASC Meeting Report

Attendees at the 1st ADVASC Meeting in Bangkok. L–R: (back row) Jeremy Beet, Dr Sutee Yoksan, Dr Zulkifli Ismail, Dr Daniel Goh, Professor Tanpong Tantawichien, (front row) Dr Maria Rosario Capeding, Professor Usa Thisyakorn, Anh Wartel-Tram.

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 disease, tropical medicine and immunisation. The first meeting of ADVASC was held on 16 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 50 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.[1] 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 75% 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 candidate currently undergoing Phase III clinical trials. Estimates suggest that the vaccine will be available for the global market by 2015.[2] 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

Professor Usa Thisyakorn	*Dengue in the Asia-Pacific region* 75% of global burden is in Asia-Pacific region. Need preparation in advance of vaccine release to ensure rapid introduction.
Professor Usa Thisyakorn	*Dengue surveillance in Thailand* Dengue surveillance system in place since 1958, reporting mandatory, usually within 24 hours. Reports are public.
Dr Maria Rosario Capeding	*The Global Dengue v2V Initiative* v2V aims to establish and document burden of dengue, raise awareness of vaccination benefits, provide guidance in relation to introduction and advocate for funding.
Dr Maria Rosario Capeding	*Dengue and vaccination programmes in the Philippines* Safety and immunogenicity of tetravalent vaccine in subjects aged 2–45 years, including follow-up. Immunogenicity and safety in healthy toddlers 12–15 months. Efficacy and safety in healthy children 2–14 years. First scientific symposium 12 Aug 2011, positive media response.
Dr Daniel Goh	*Dengue in Singapore* High success rate for immunisation for childhood diseases. Good vaccine acceptance and coverage. Infrastructure for implementation in place, but some concerns over new vaccine. National Environment Agency (NEA) currently undertakes mosquito control.

ADVA
ASEAN Dengue Vaccination Advocacy

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

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Letter to the Editor

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

Keywords:
Advocacy
ASEAN
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
ADVASC members.

Professor Usa Thisyakorn (Chair)	Chulalongkorn University, Thailand
Dr Maria Rosario Capeding	Research Institute for Tropical Medicine, the Philippines
Dr Daniel Goh	Yong Loo Lin School of Medicine, Singapore
Dr Zulkifli Ismail	KPJ Selangor Specialist Hospital, Malaysia
Professor Terapong Tantawichien	Chulalongkorn University, Thailand
Dr Sutee Yoksan	Mahidol University, Thailand
Professor Sri Rezeki Hadinegoro	Dr Cipto Mangunkusumo Hospital, Indonesia

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.

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ADVA
ASEAN Dengue Vaccination Advisory
1st ADVA Workshop
Bangkok
Thailand
22–23 September 2012
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Recommendations from ADVA

Standardizing the monitoring & reporting of dengue in the ASEAN region

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

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