DENGUE

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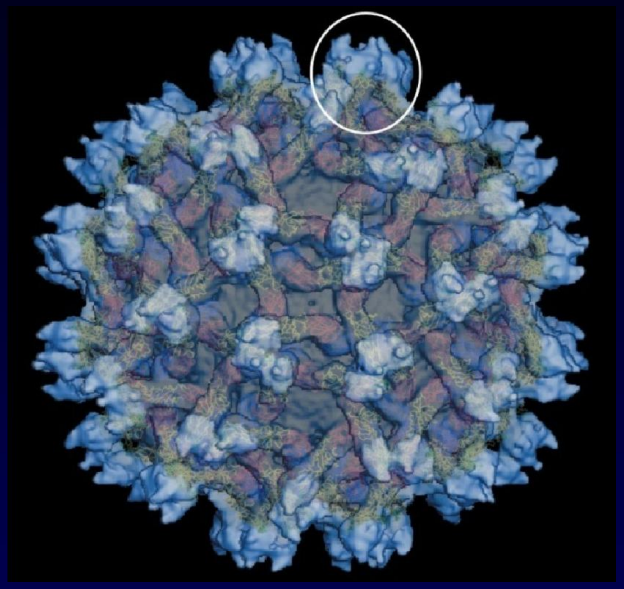
8th Danish Paediatric Infectious Diseases Symposium

2-3 October 2015

Comwell Klarskovgaard, Korsør

CHILDREN'S HOSPITAL 1
HO CHI MINH CITY



Rossman et al.

Dengue is self-limited, systemic viral infection transmitted between humans by mosquitoes.

*** Dengue virus- single-stranded positive-sense RNA viruses; 4 serotypes**

(DEN-1, DEN-2,DEN-3, DEN-4)

•Mosquitoes:

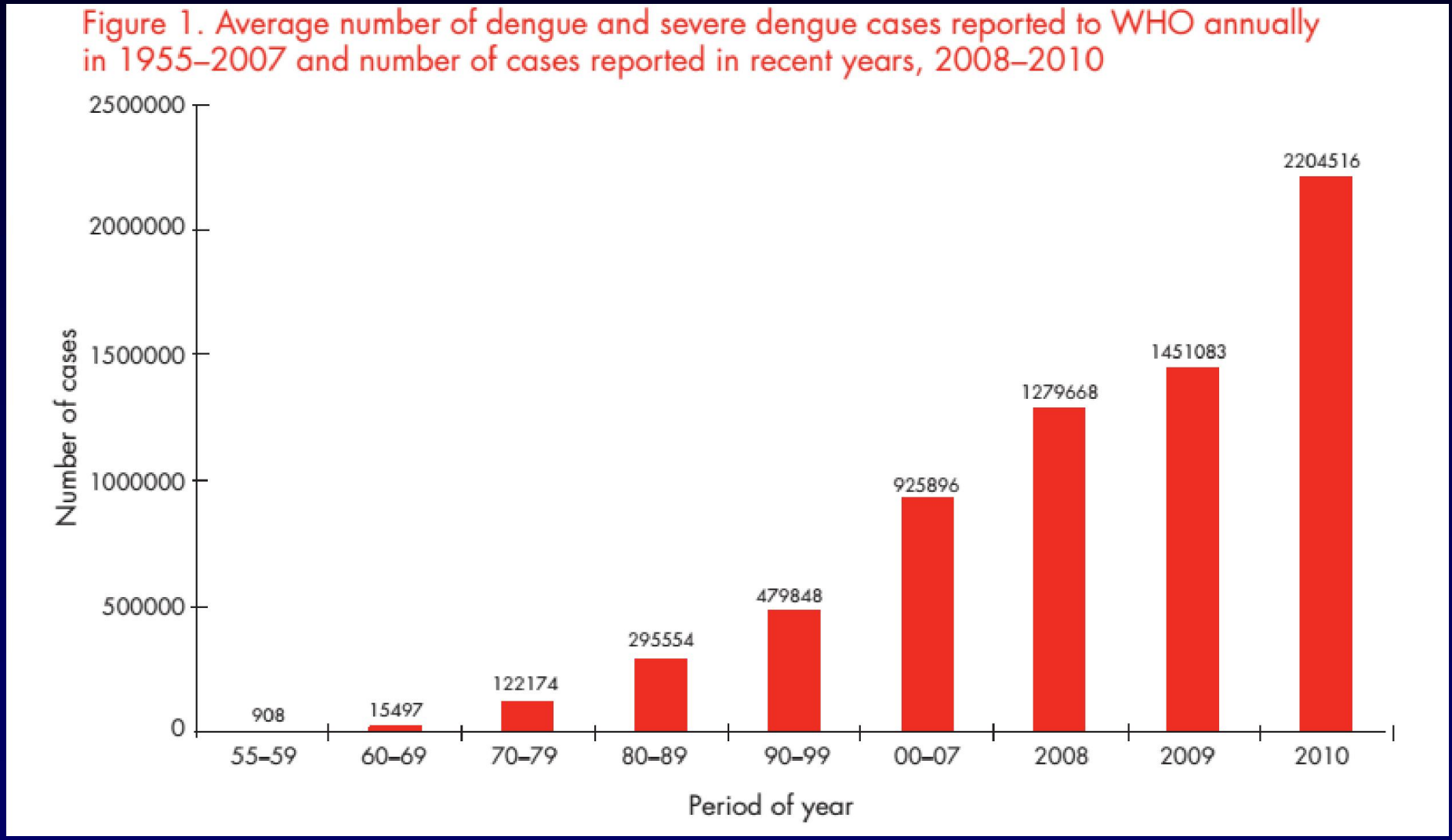
Aedes- aegypti, A.albopictus

Case-fatality rate <1- 5%

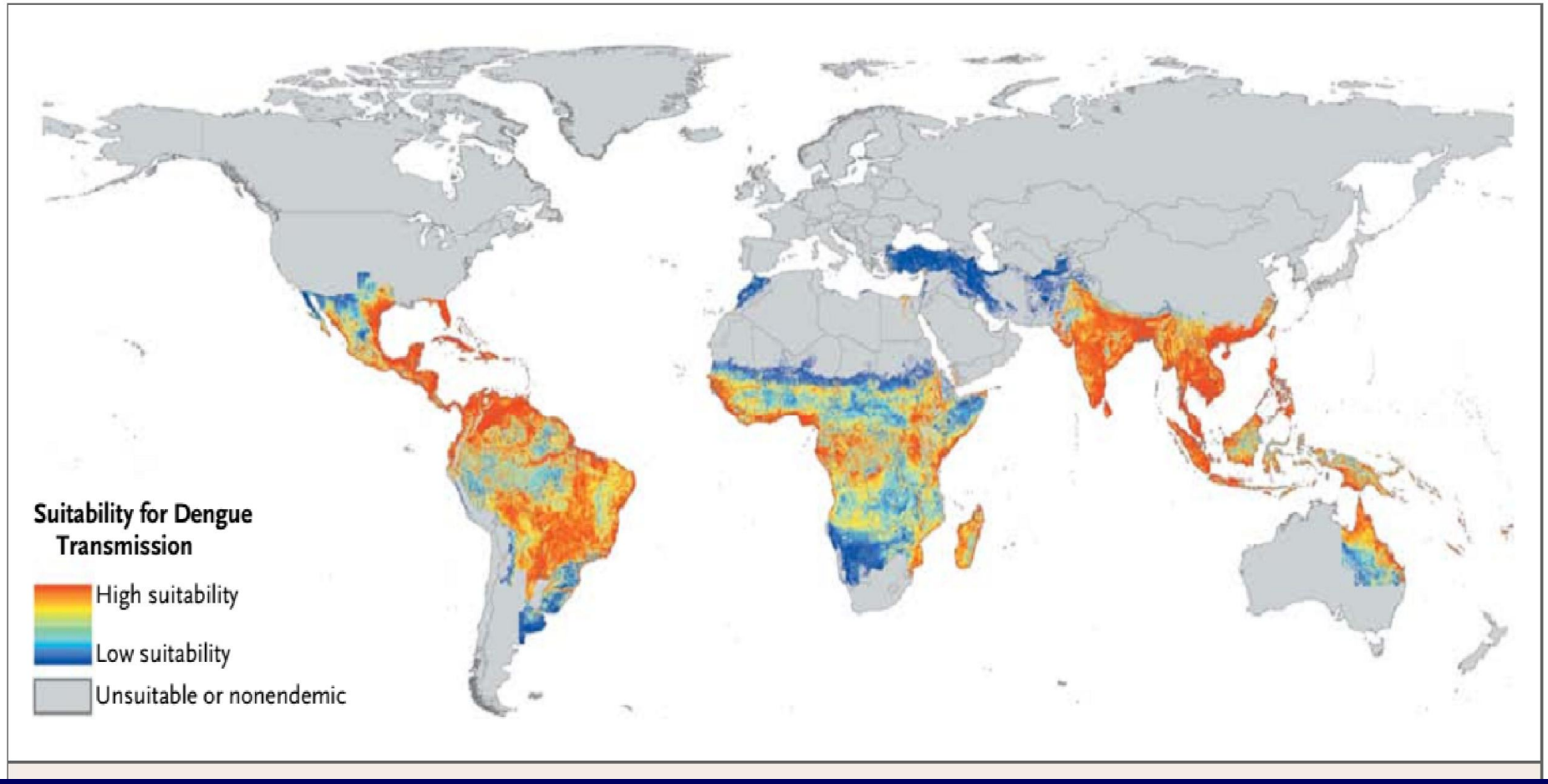
1. **Epidemiology**
2. **Clinical manifestations & Diagnosis**
3. **Management of Dengue**
4. **Prevention**
5. **How can Case-fatality rate of Dengue be reduced?**

1. Epidemiology

Dengue is a serious public health problem worldwide (50 million infections/year across 100 countries)



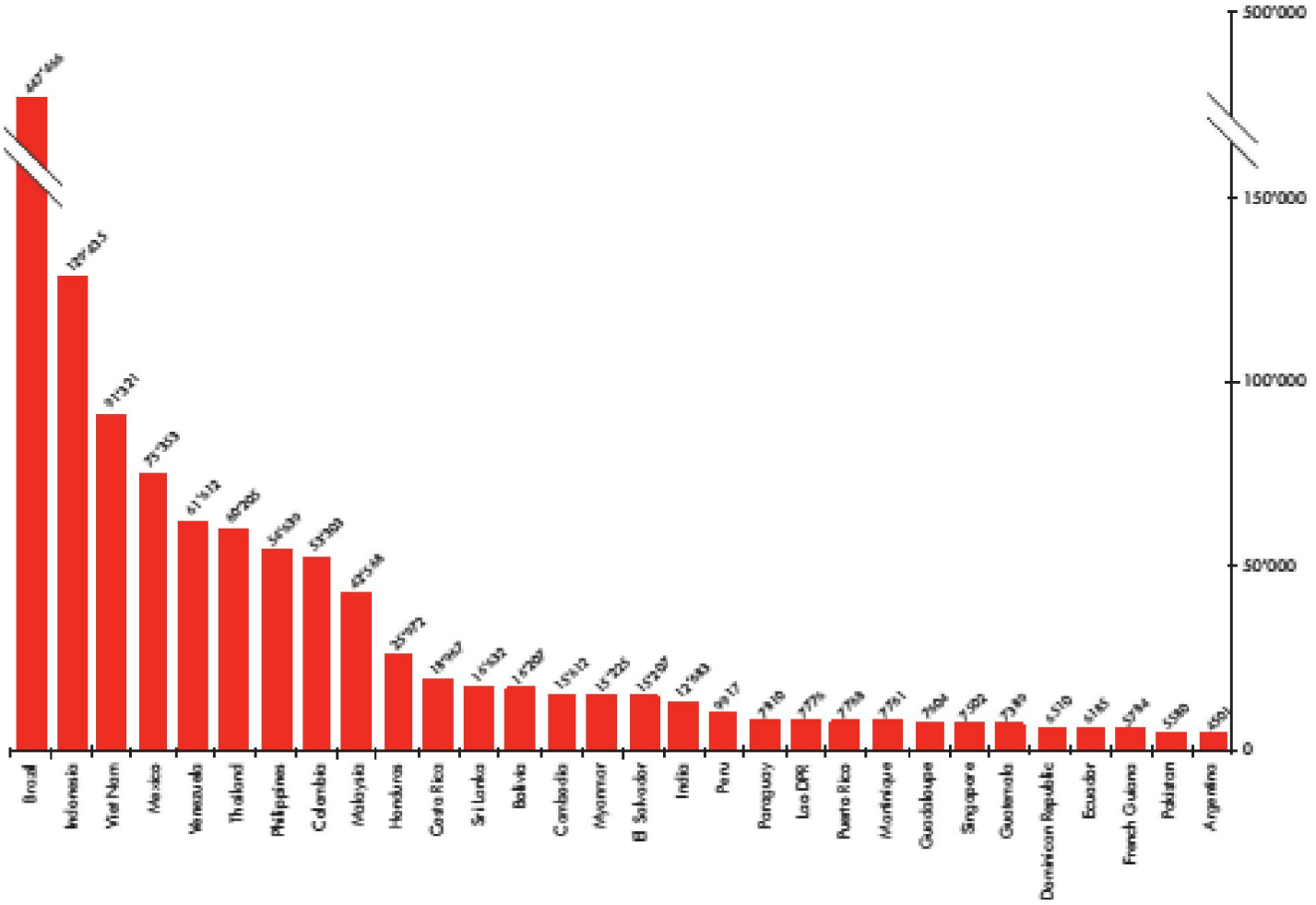
Global Dengue Risk



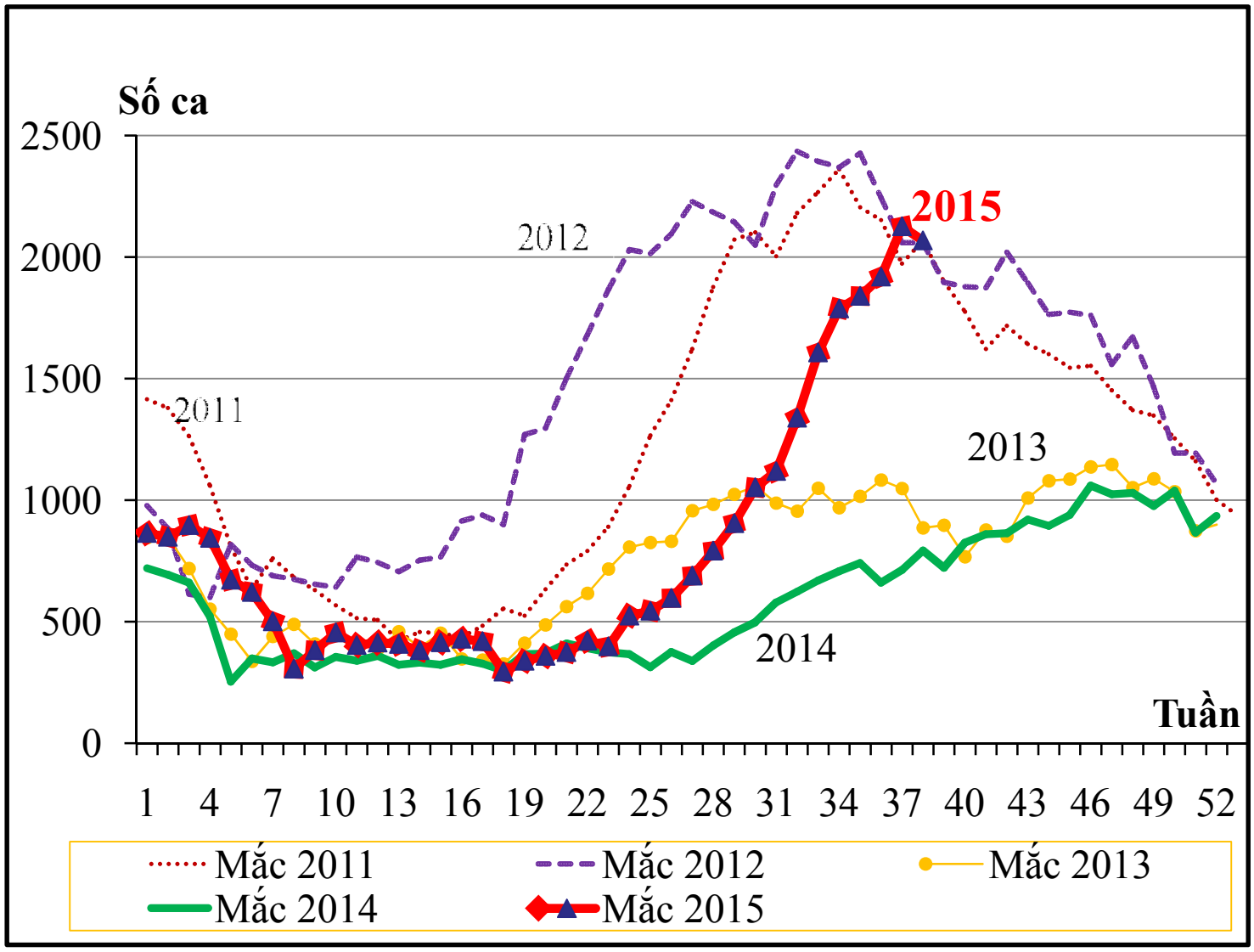
(Simons CP et al. 2012. N Engl J Med 366:1423-32.)

The 30 most highly dengue endemic countries (WHO 2012)

Figure 3. Average number of dengue cases in 30 most highly endemic countries/territories as reported to WHO, 2004–2010



Dengue in Vietnam (1Jan-20 Sept: 40,000 reported cases, 25 deaths) [National Dengue Control Program, 2015]



PHILIPPINES

Philippines

From 1 January to 1 August 2015, there were 48,872 suspected cases of dengue, including 162 deaths, reported in Philippines. This is 4.03% higher compared with the same reporting period in 2014 (n=46,980) (Figure 3).

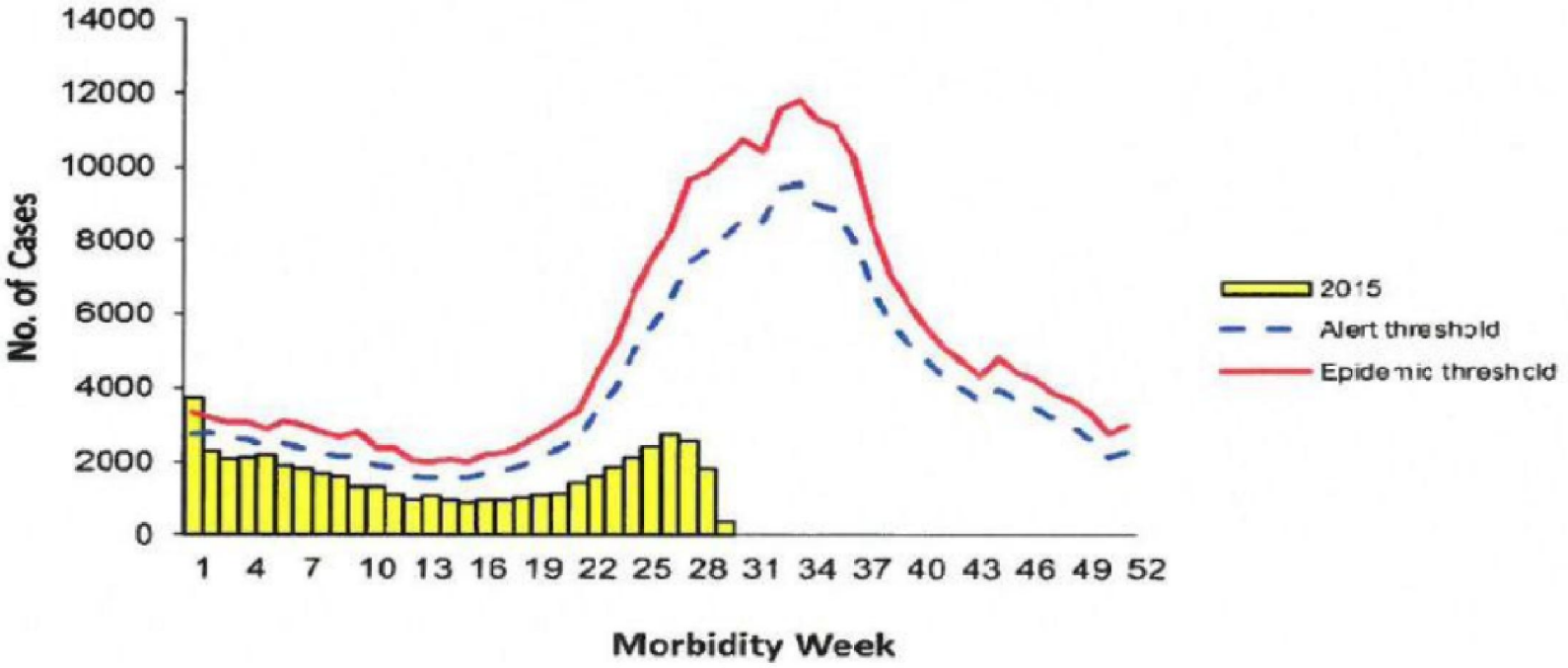


Figure 3: Number of dengue cases per morbidity week in 2015, Department of Health National Epidemiology Centre, Philippines

(WHO, Western Pacific Region, Dengue Situation Update 2015, No. 472)

MALAYSIA

Malaysia

As of 15 August 2015, there were 75,795 cases of dengue with 212 deaths reported in Malaysia for 2015. This is 26.8% higher compared with the same reporting period of 2014 (n=59,790) (Figure 2). From 9 to 15 August 2015, there were 2,532 cases of dengue reported, 2% lower than the number of cases reported in the previous week (n=2,583).

Figure 2: Number of dengue cases per week 2014-2015, Department of Health, Malaysia

(WHO, Western Pacific Region, Dengue Situation Update 2015, No. 472)

SINGAPORE

Singapore

As of 15 August 2015, there were 5,868 cases of dengue reported in Singapore for 2015. From 9 August to 15 August 2015, 221 dengue cases were reported, 5 cases fewer than the previous week, and lower than the same reporting period in 2013 and 2014.(Figure 4).

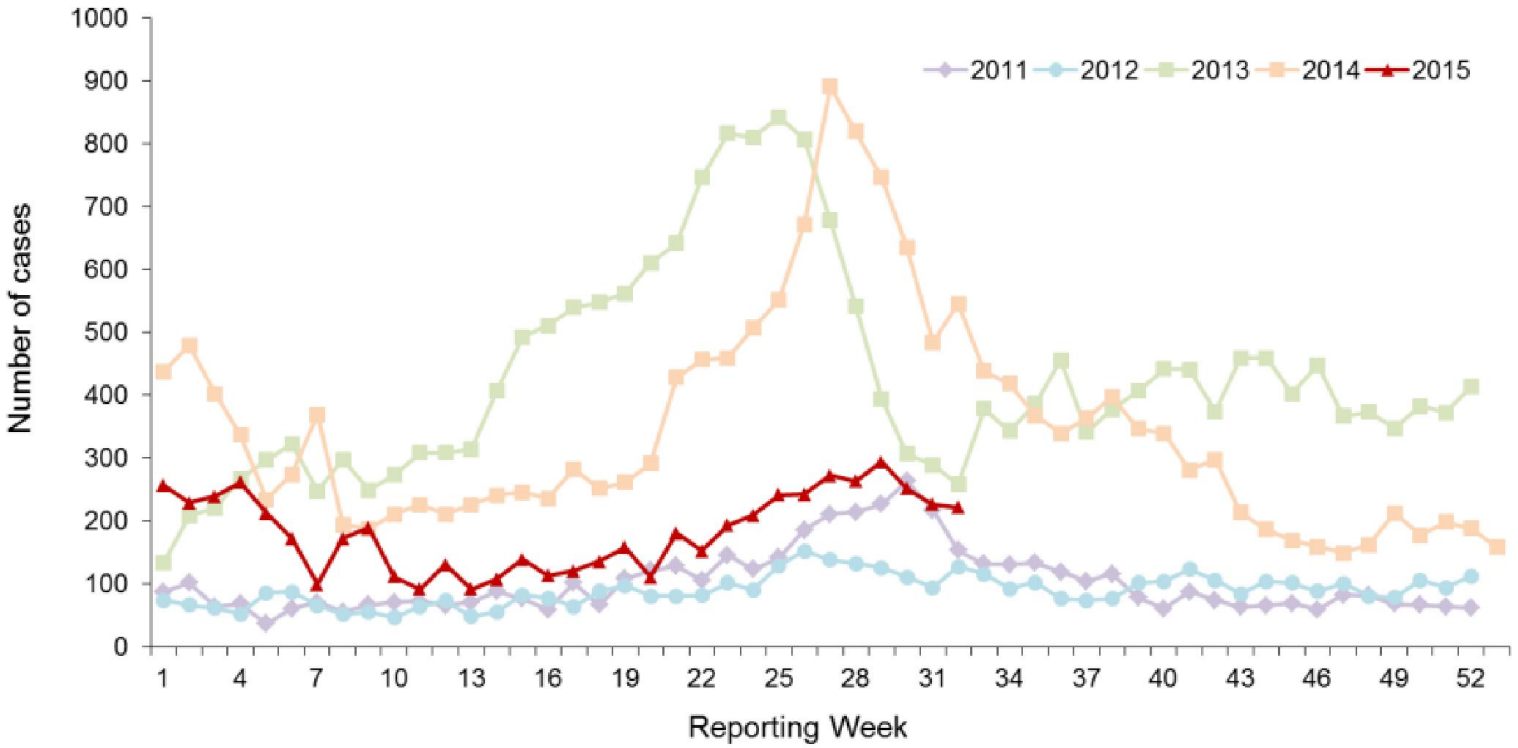


Figure 4: Number of dengue cases per week 2011-2015, Communicable Diseases Division, Ministry of Health Singapore

(WHO, Western Pacific Region, Dengue Situation Update 2015, No. 472)

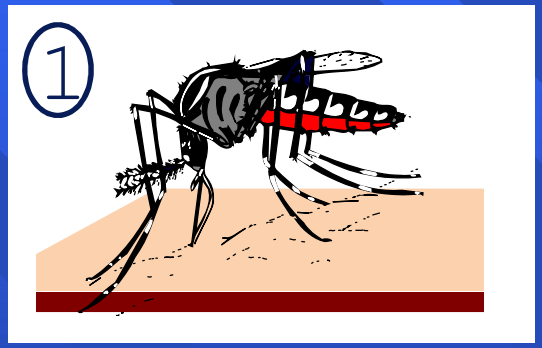
Replication and Transmission of Dengue Virus (p.1)

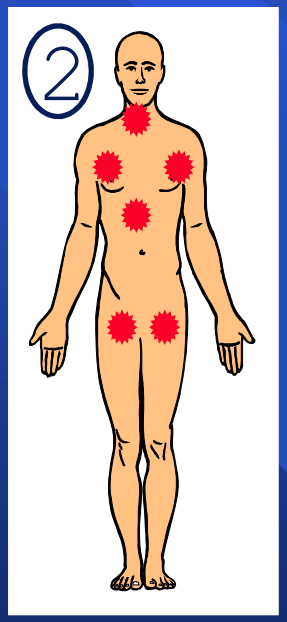
1. Virus transmitted to human in mosquito saliva

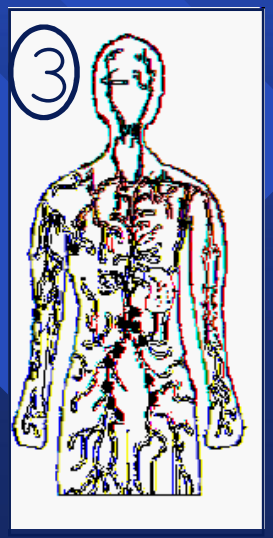
2. Virus replicates in target organs

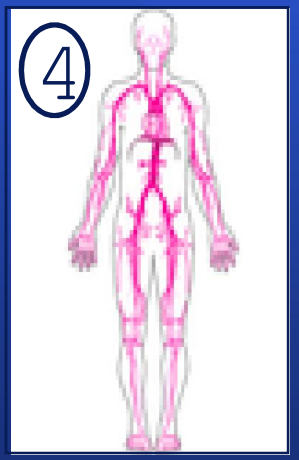
3. Virus infects white blood cells and lymphatic tissues

4. Virus released and circulates in blood









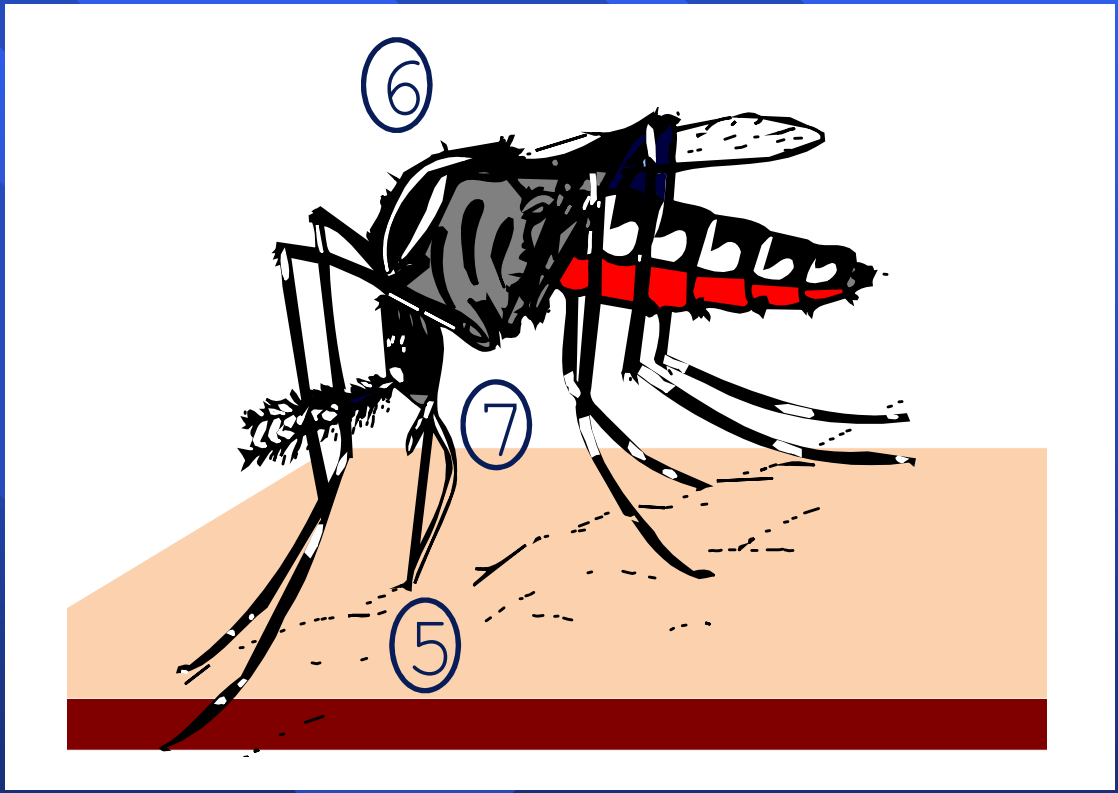
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Replication and Transmission of Dengue Virus (P.2)

5. Second mosquito ingests virus with blood

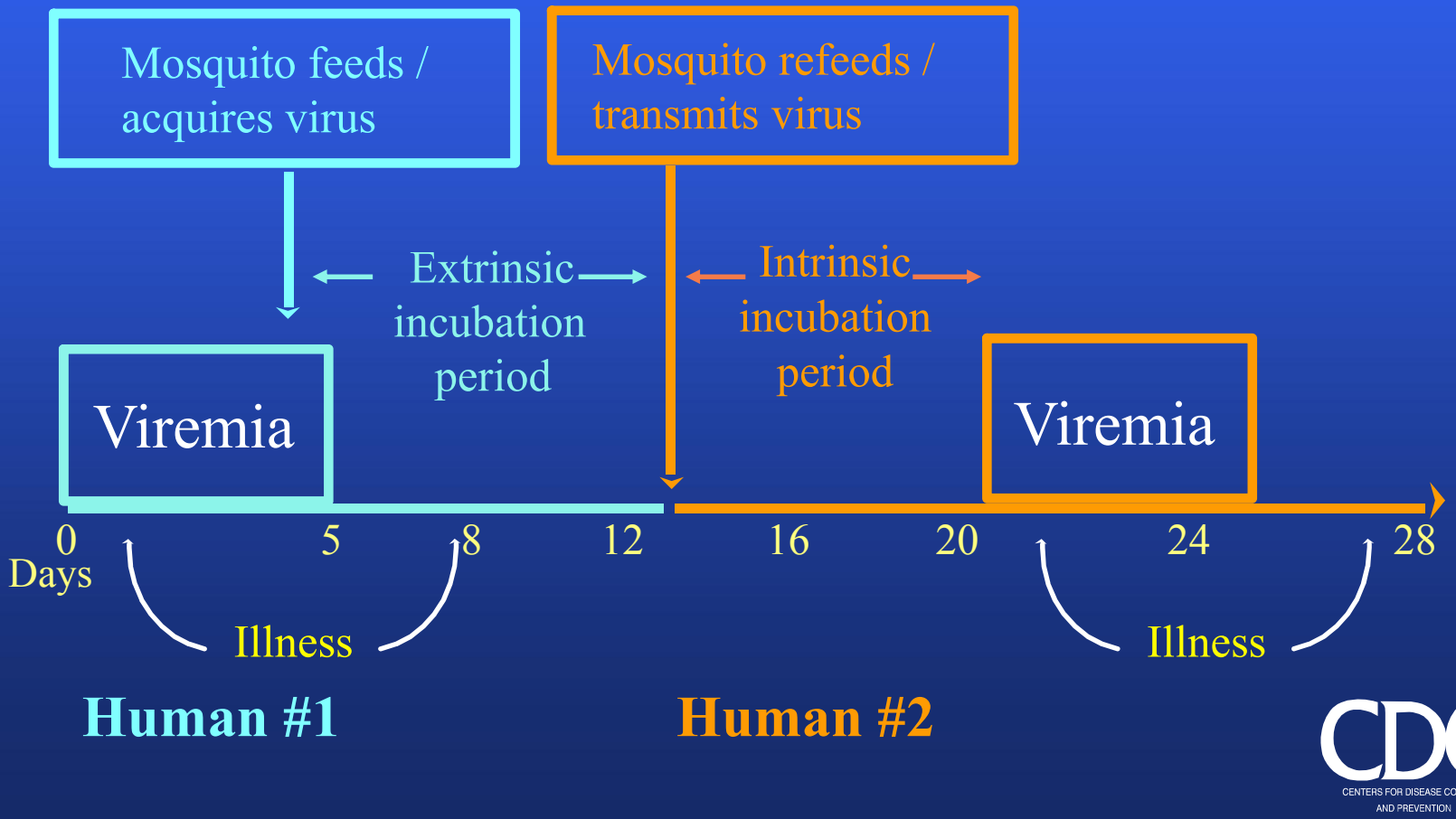
6. Virus replicates in mosquito midgut and other organs, infects salivary glands

7. Virus replicates in salivary glands

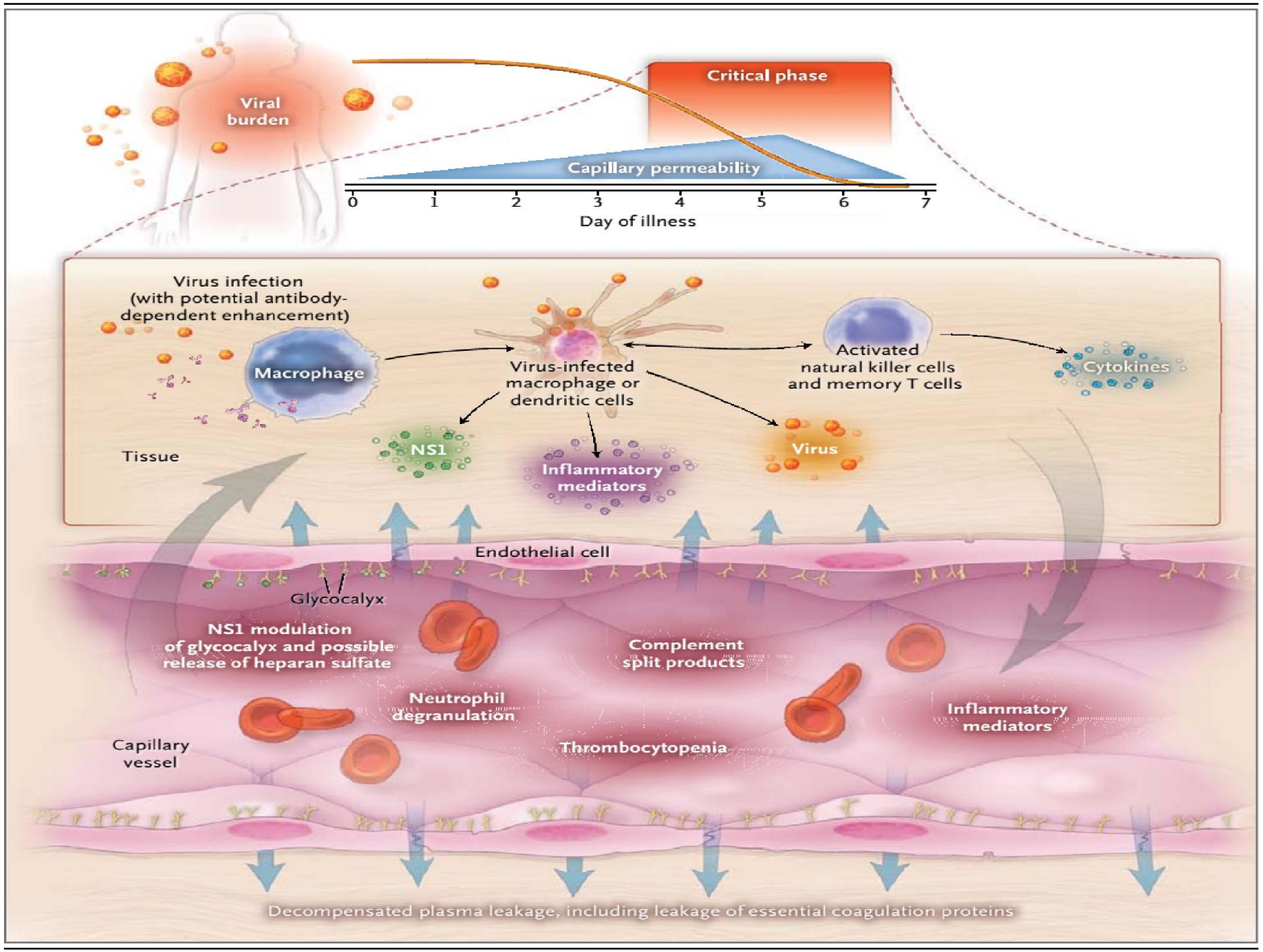


CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

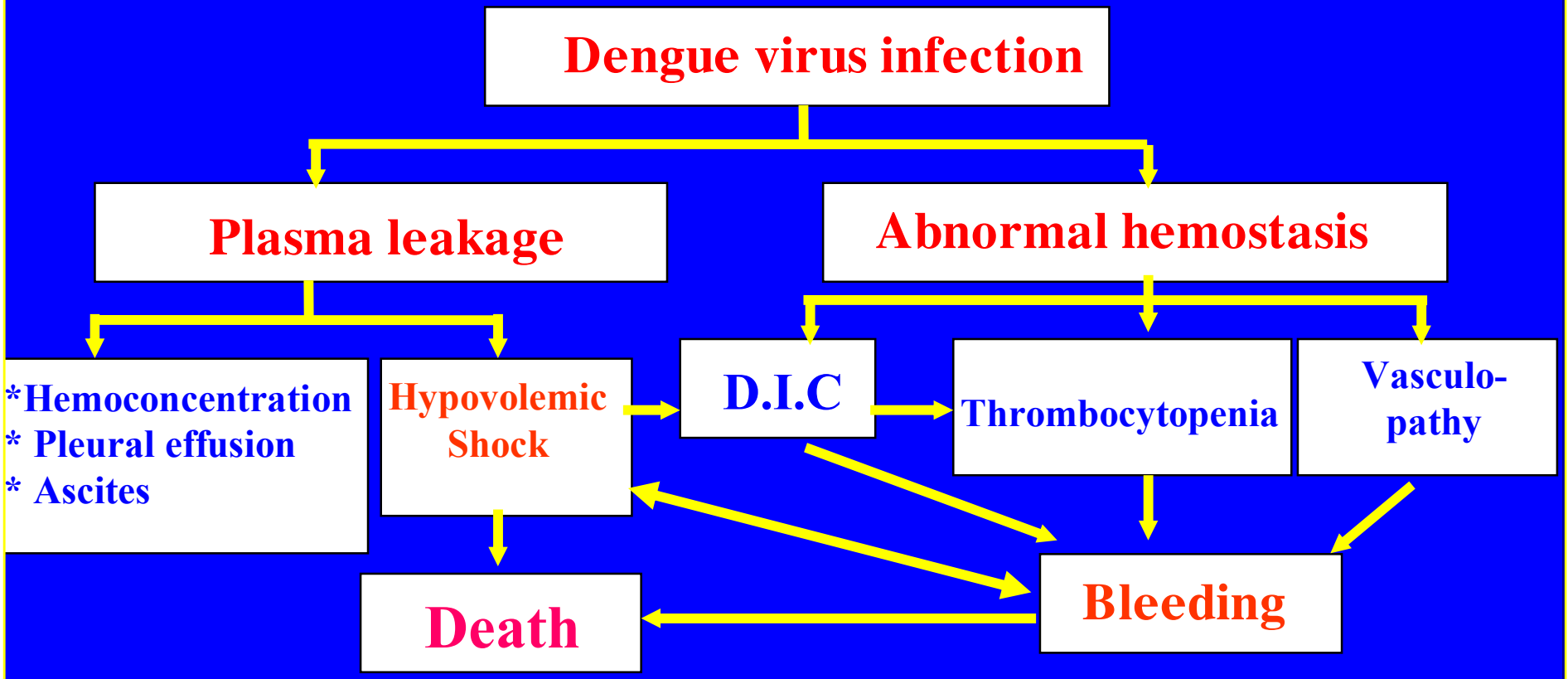
Transmission of Dengue Virus by *Aedes aegypti*



CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION



Immunopathogenesis of Dengue (***Simmons CP et al.(2012). N Engl J Med 366;15, 1423-1432)***

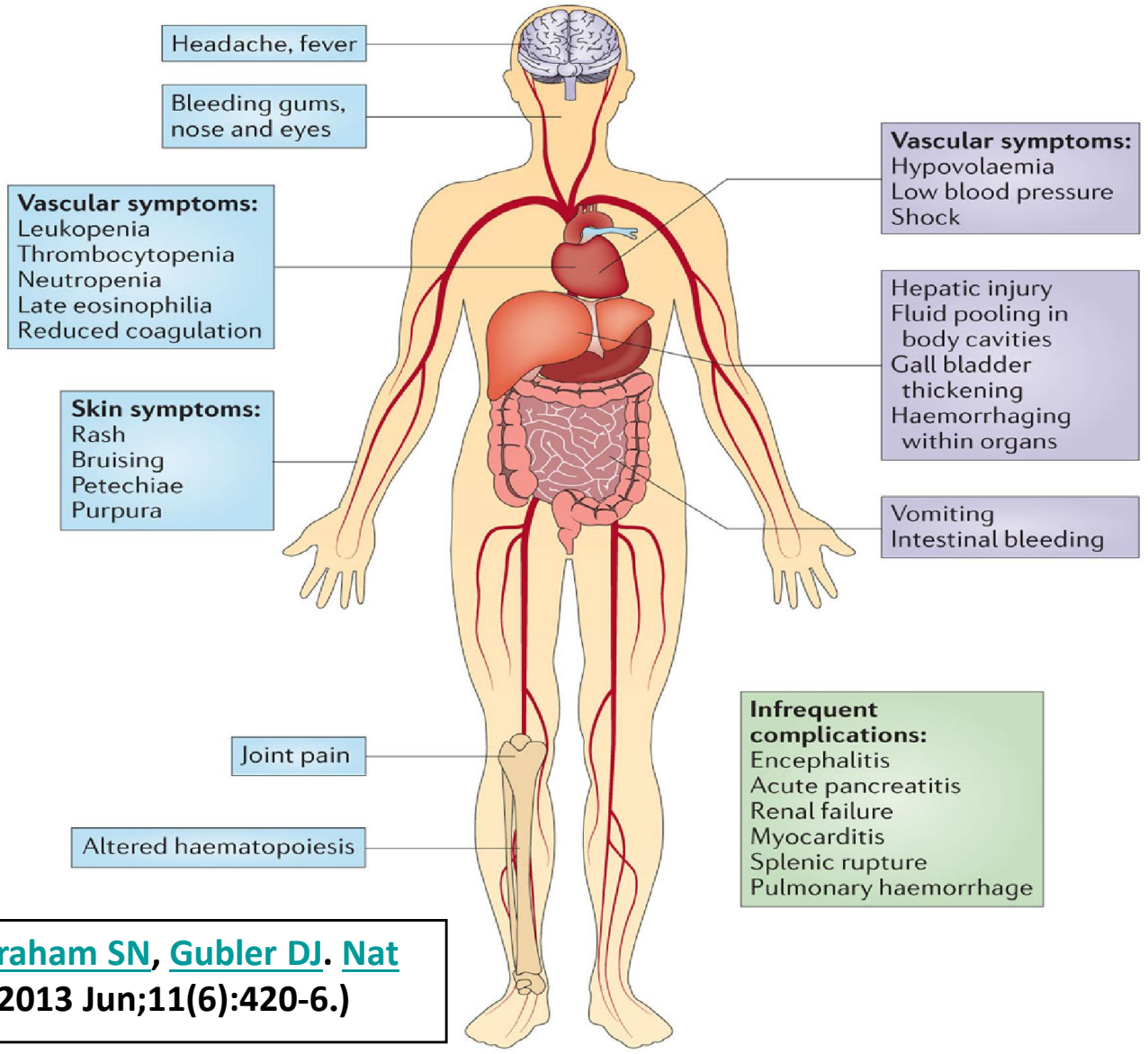


The correlation between pathophysiology and clinical manifestations of DHF

(Hung and Thanh, 2002)

2. Clinical manifestations & Diagnosis

CLINICAL MANIFESTATIONS



(St John AL, Abraham SN, Gubler DJ. Nat Rev Microbiol. 2013 Jun;11(6):420-6.)

Nature Reviews | Microbiology

MAIN CLINICAL PATTERNS OF DENGUE (WHO 1997)

Plasma leakage

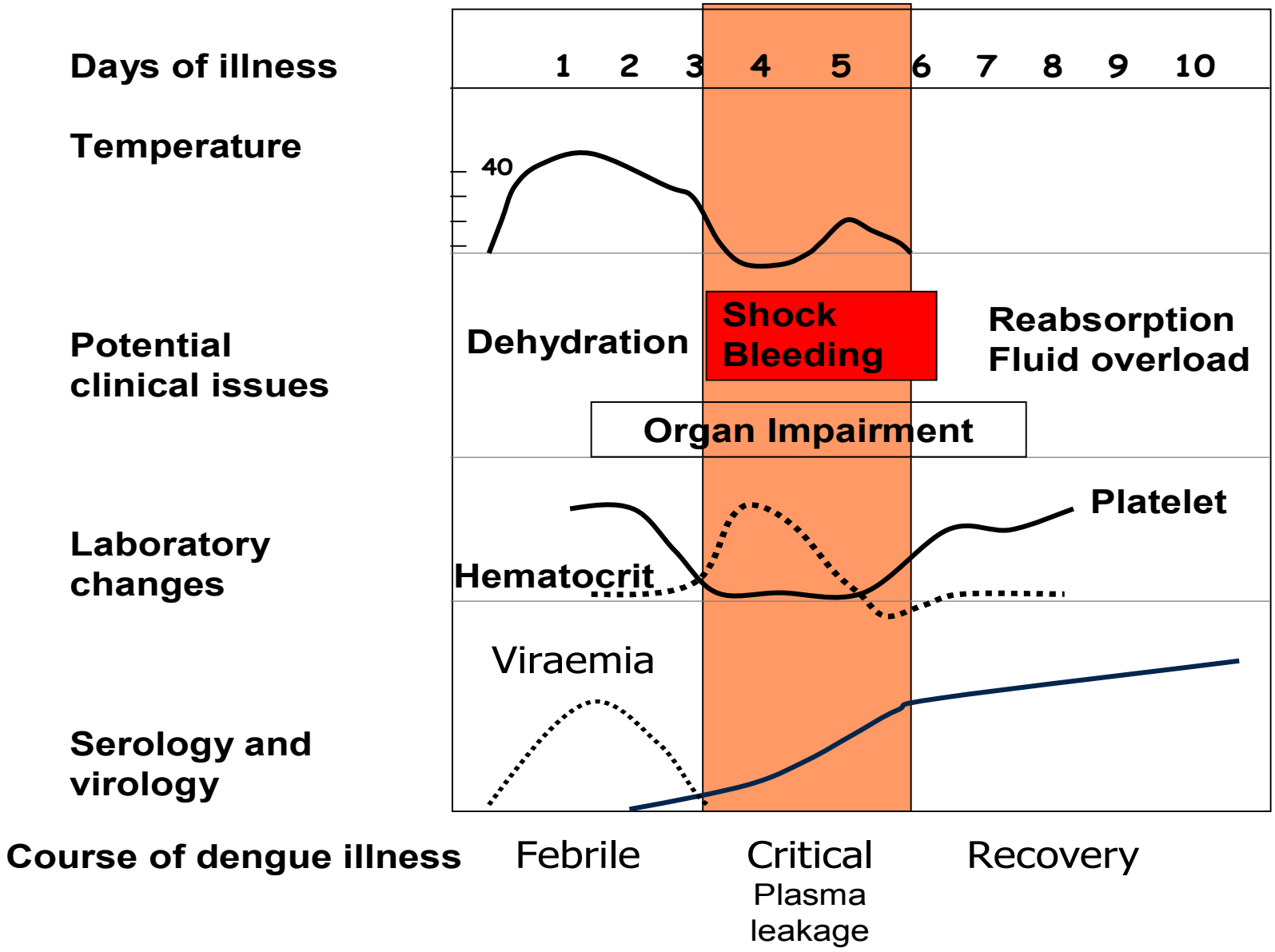
DENGUE FEVER (DF)

DENGUE HEMORRHAGIC FEVER (DHF)

With or without } bleeding

With or without } Shock

DENGUE SHOCK SYNDROME (DSS)



CLINICAL DENGUE COURSE (WHO, 2009)

Clinical diagnosis of Dengue Fever based on WHO's criteria, 1997

Fever (2- 7 days) with ≥ 2 of the followings:

- **Headache**
- **Retro-orbital pain**
- **Myalgia/ arthralgia**
- **Rash**
- **Nausea and vomiting**
- **Haemorrhagic manifestations (positive tourniquet test(*), petechiae, gum bleeding, epistaxis, menorrhagia, or GI bleeding)**
- **Leukopenia**

Clinical diagnosis of DHF based on WHO's criteria, 1997

Clinical: * Fever

* Bleeding manifestations

* Shock

Laboratory:

* Evidence of plasma leakage: Rising Hct ≥ 20%; pleural effusion; ascites.

* Thrombocytopenia

≤ 100000/mm^3.

Diagnosis

Grading severity

*Grade I	Non-shock
*Grade II	DHF
*Grade III	DSS
*Grade IV	

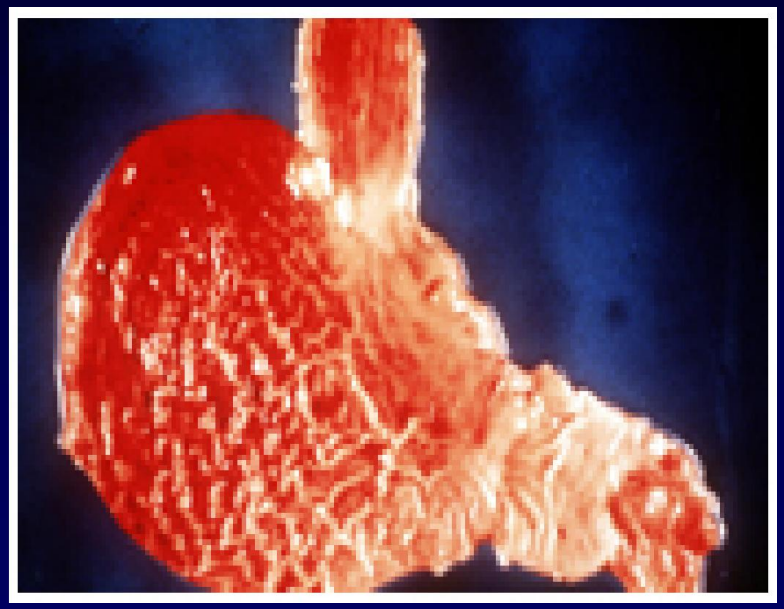
Clinical findings of DHF patients

Fever	**4.4 ±0.9 days (2-7 days)**
Petechiae	**57%**
GI bleeding	**12%**
Gum bleeding	**7%**
Epistaxis	**14%**
Hepatomegaly	**86-98%**
Shock	**27%**

(Lan, Hung et al. (1998). *Dengue Bulletin*, 22:150-161)

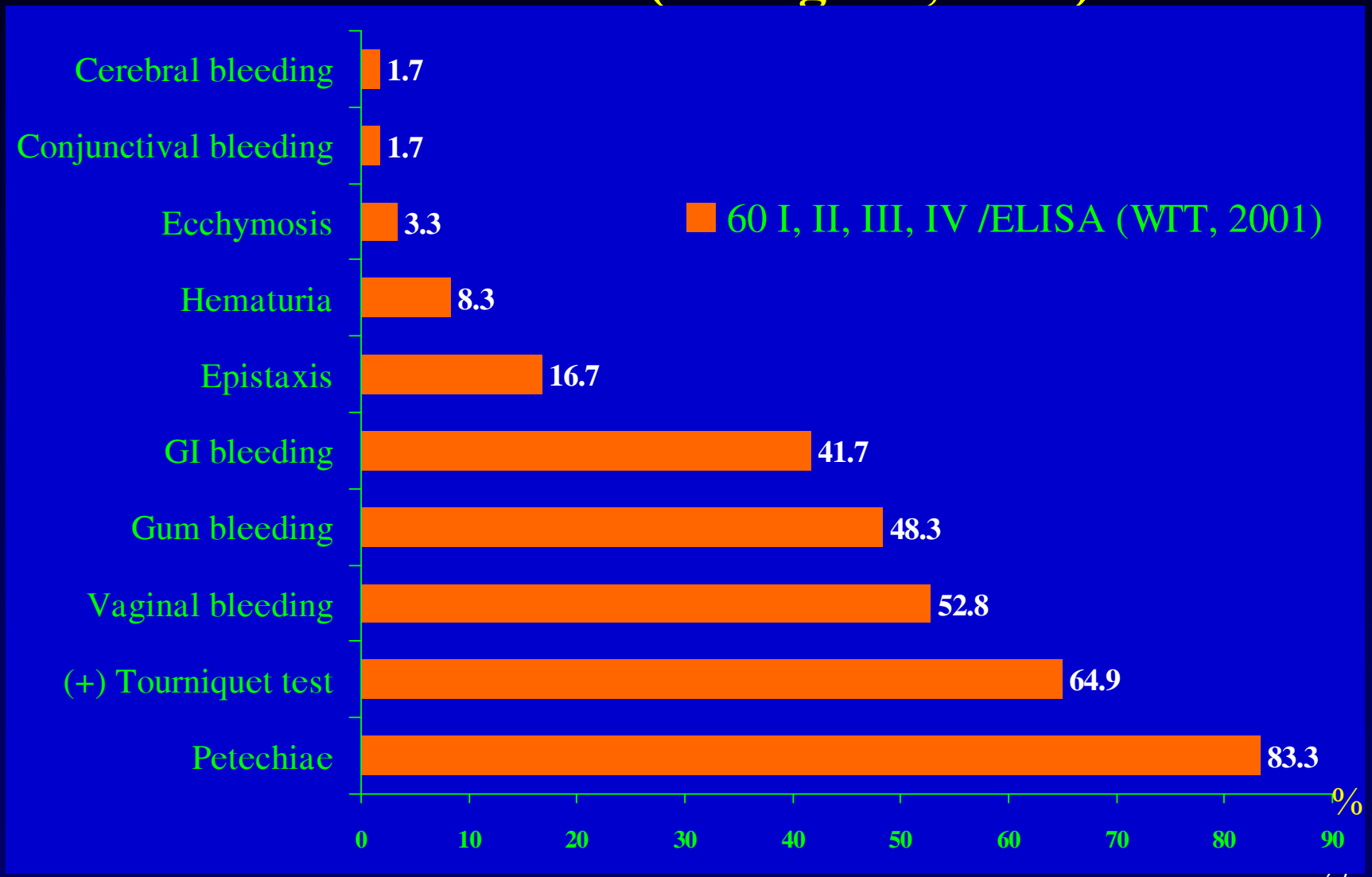
Bleeding manifestations

The tourniquet test (+); petechiae; gum bleeding; epistaxis, GI bleeding.

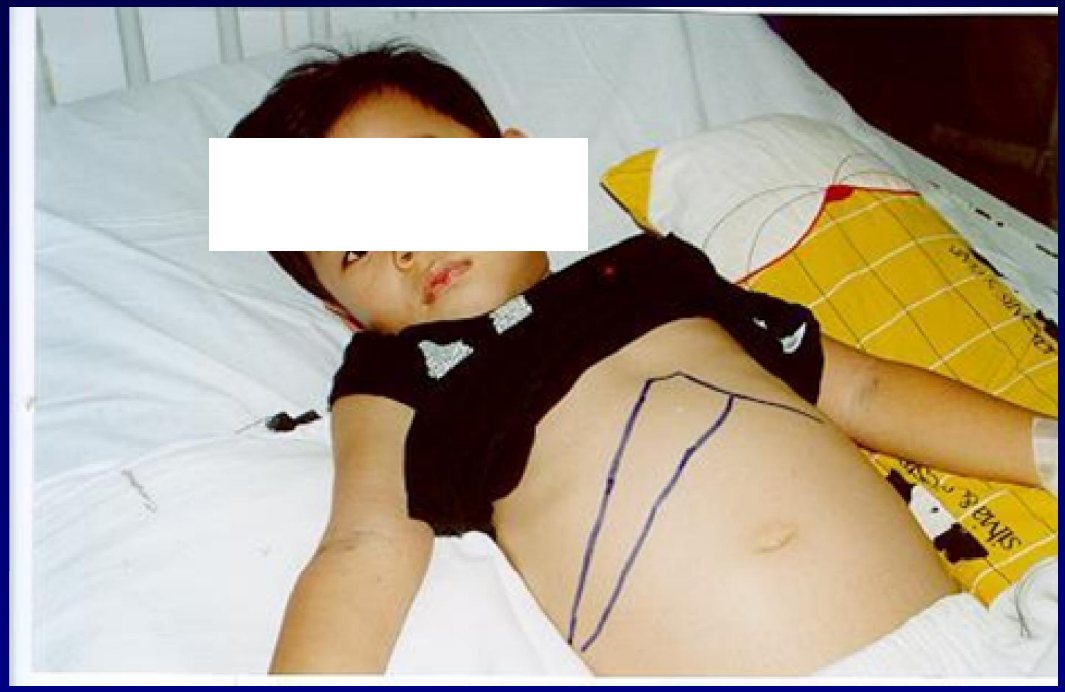


Severe GI bleeding in fatal DHF (Nath B, 1997)

Bleeding manifestations in 60 adults with DHF/DSS (Trung DT, 2001)



Hepatomegaly- Liver dysfuctions



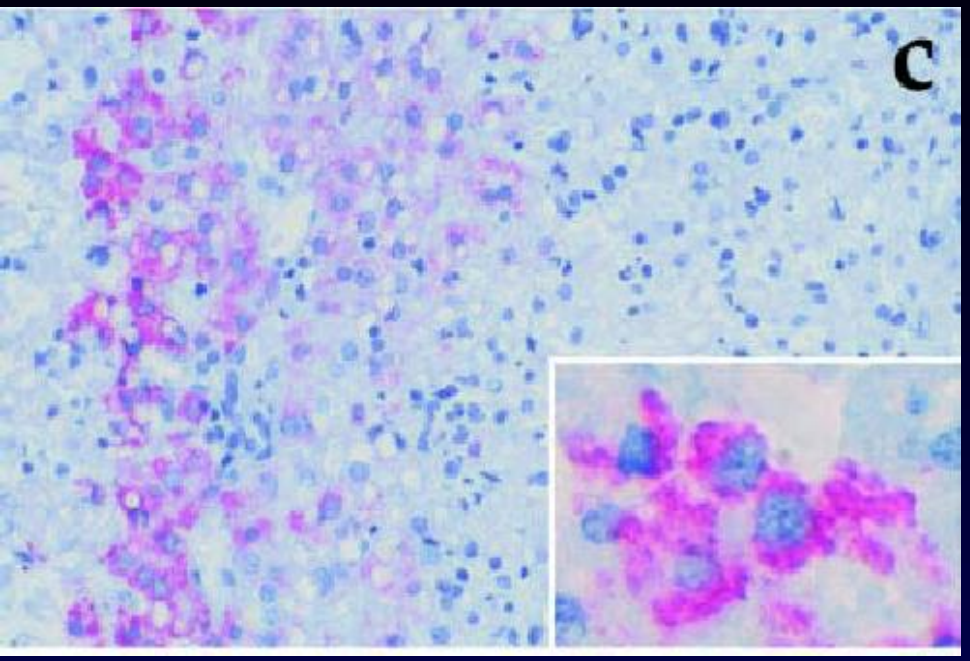
- Hepatomegaly 87-94%.
- Thailand: 85-93% (Kalayanarooj,2000); Philippines, India 4-20% (Hayes *et al*.,1988, Agarwal *et al*.,1999)

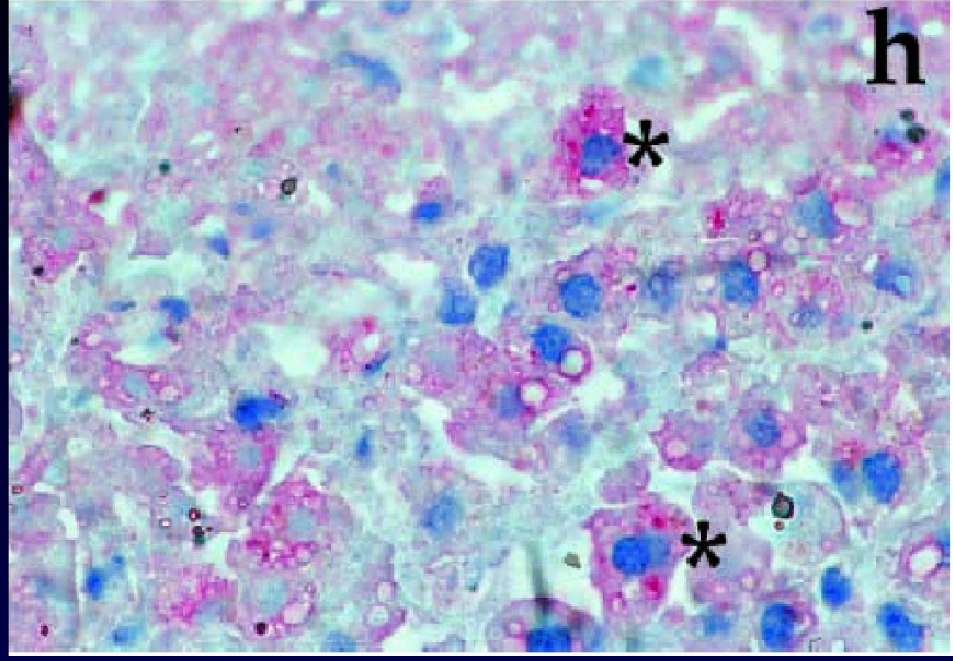
Liver damage in Dengue patients

*AST, ALT↑- mild to moderate liver dysfunction; some patients may suffer acute liver failure

⟶ Dengue encephalopathy [Lan, Hung,1997, Res. Virol. 148: 273-277; Cam et al.,1999,AJTMH, 65:848-851]

* Liver biopsy in fatal DHF- severe diffuse hepatitis, dengue antigen in hepatocytes, apoptosis [Huerre, Lan *et al*., 2001,Virchows Arch,438:107-115].



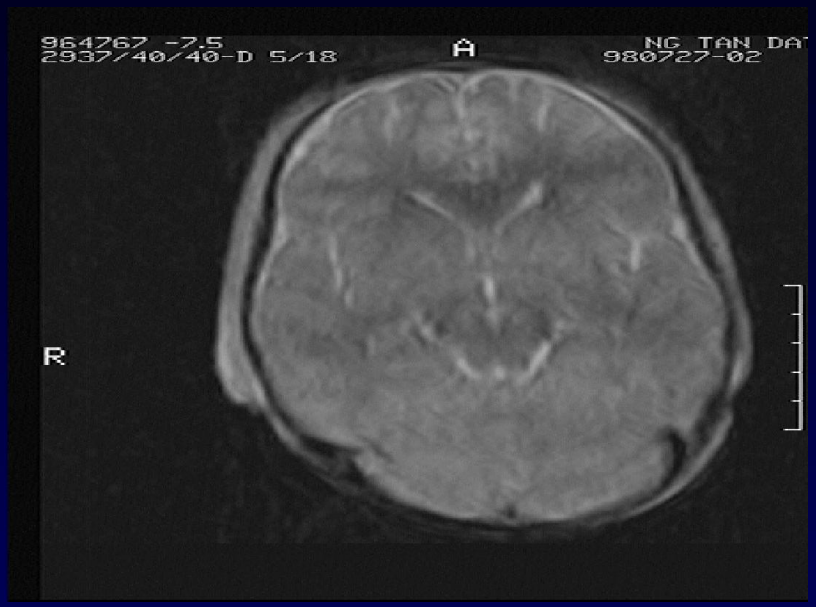


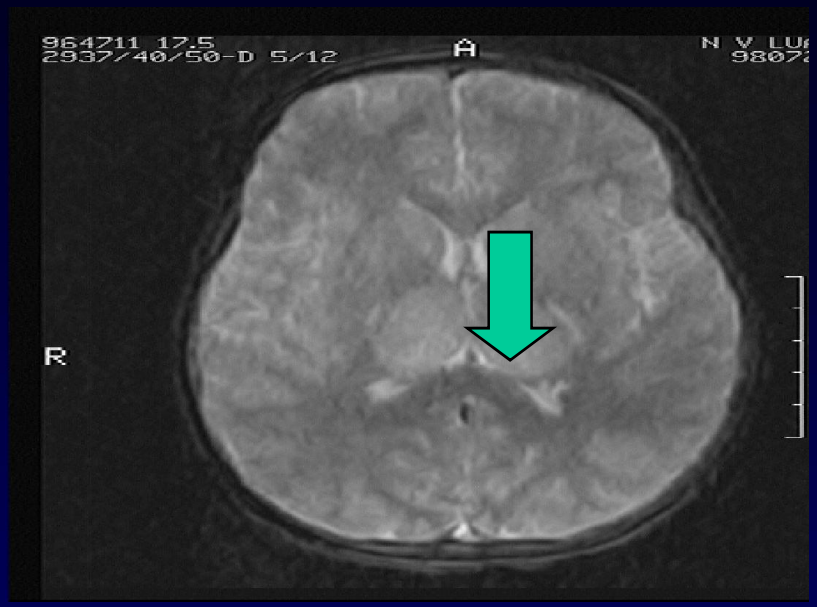
Liver: Immunohistochemistry with DEN-3 antibody, APAAP and fast red- Detection of DEN virus antigen in and around areas of necrosis (x250). Inset: x1000

Immunohistochemistry: Councilman bodies containing dengue virus antigens APAAP and fast red (x400)

[Heurre, Lan et al (2001) Virchows Arch 438:107-115]

Dengue encephalopathy





Cerebral edema (MRI, T1WI)

(Cam BV et al.(2001). AJTMH 65, 848 - 851

Cerebral encephalitis (MRI, T2WI)

DSS, leading cause of death in Dengue patients

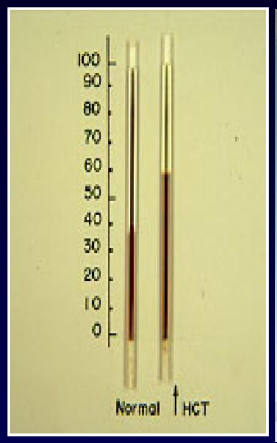
* 8,802 (27.1%) DSS cases during 1991-2003.

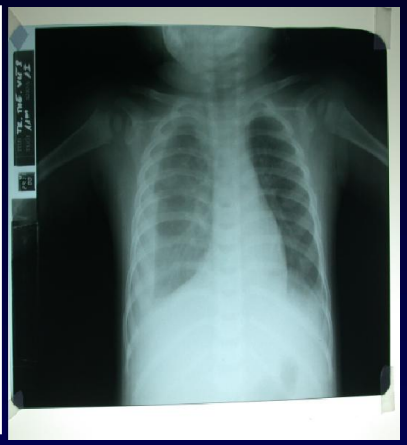
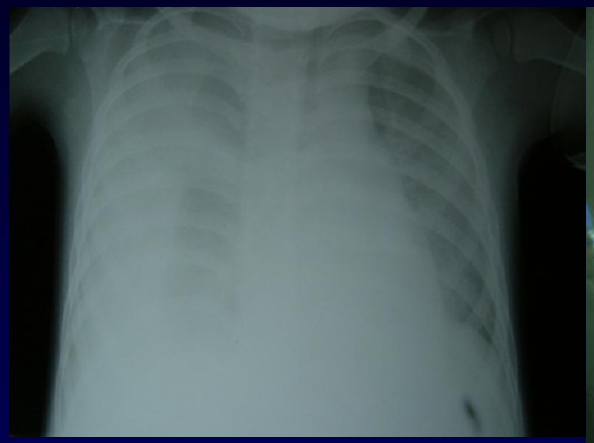
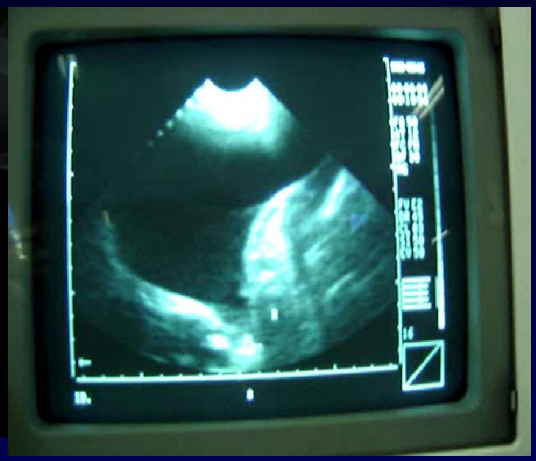
* 85 % of cases going into shock on 4, 5 th day.

Dengue shock syndrome (DSS)

- **Grade III DSS:** Circulatory failure with tachycardia, weak pulse, pulse pressure ≤ 20 mm Hg or hypotension for age; cold, clammy skin; restlessness.
- **Grade IV DSS:** Profound shock with undetectable pulse and blood pressure.

Evidence of plasma leakage



[Suchitra N., 2003; Hung NT, 2004]

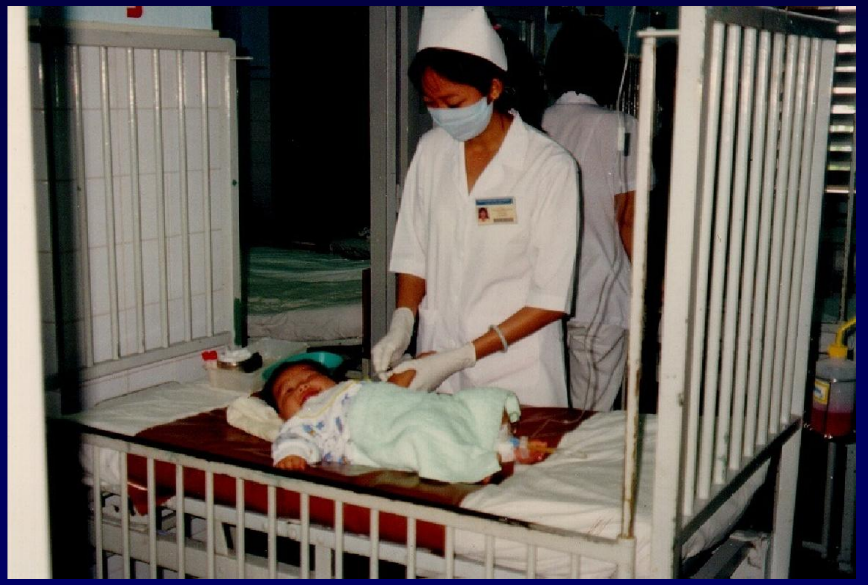
Evidence of Plasma leakage: Rising Hct ≥ 20%; pleural effusion; ascites

DHF IN INFANTS (107 infants)

95.3% had primary dengue infections

Age: 6.7 ± 2.5 months (1-11 months)

Fever	5.2 ±1.8 days (2-13 days)
Petechiae	99.6%
GI bleeding	7.4%
Hepatomegaly	97.1%
Shock	25.7%



[Hung et al. (2004). *J of Infectious Diseases*, 189:221-232]

Laboratory findings

	Total DHF (n=245)	Non-shock DHF (n=182)		DSS (n=63)
• Peak Hct (%)	40.2±4.3	39.1±3.5	*P<0.001*	43.6±4.8
• Increase in Hct (%)	34.4±14.1	31.1±12.6	*P <0.001*	44.1±13.6
• Lowest platelet count, $\times 10^3/mm^3$	66.8±37.5	71.4± 39.1	*P<0.001*	53.5±28.5

Increase in Hct ≥ 20%: 224 (91.4%)

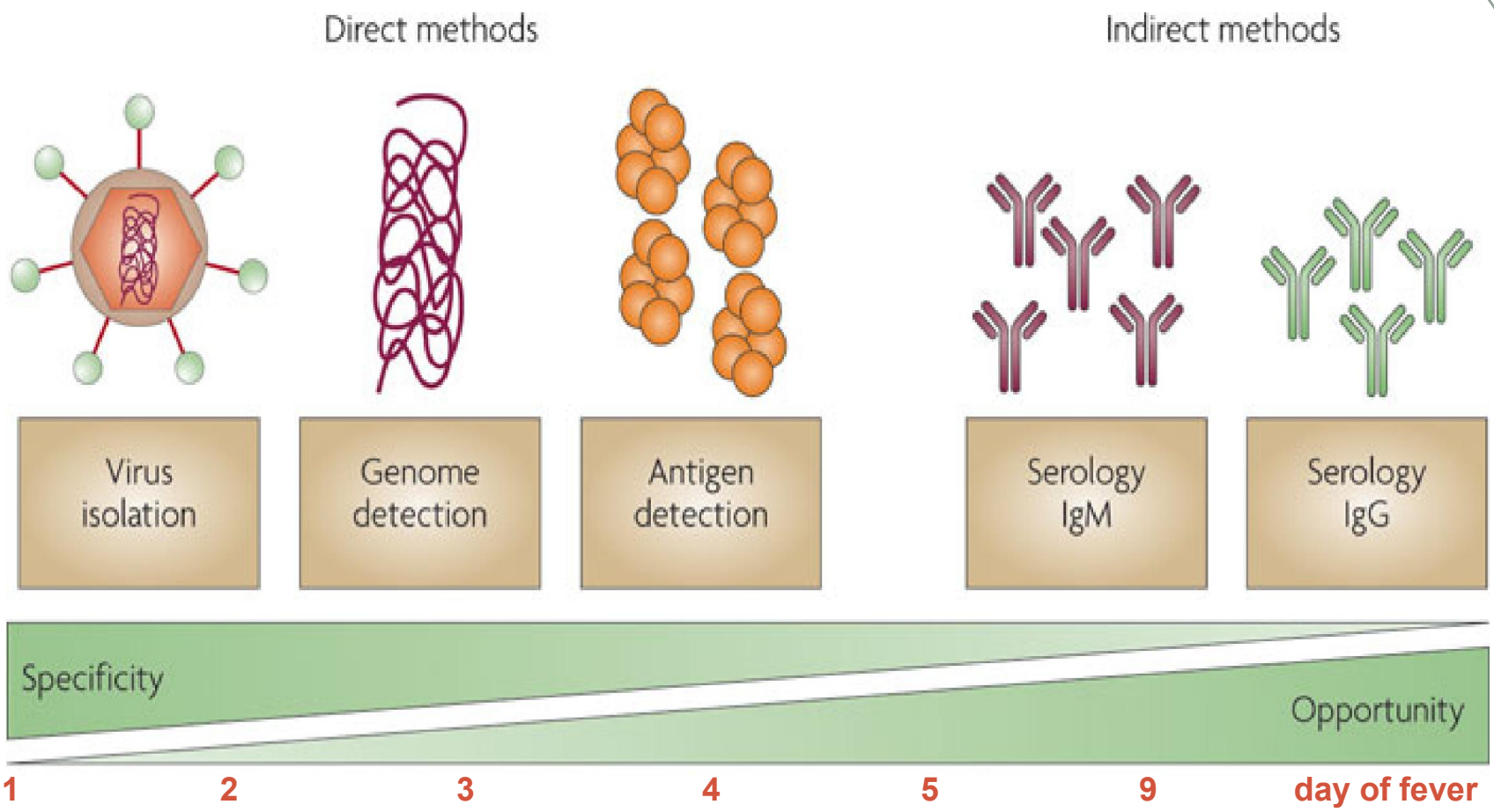
Thrombocytopenia (≤100×10^3/mm^3): 230 (93.8%)

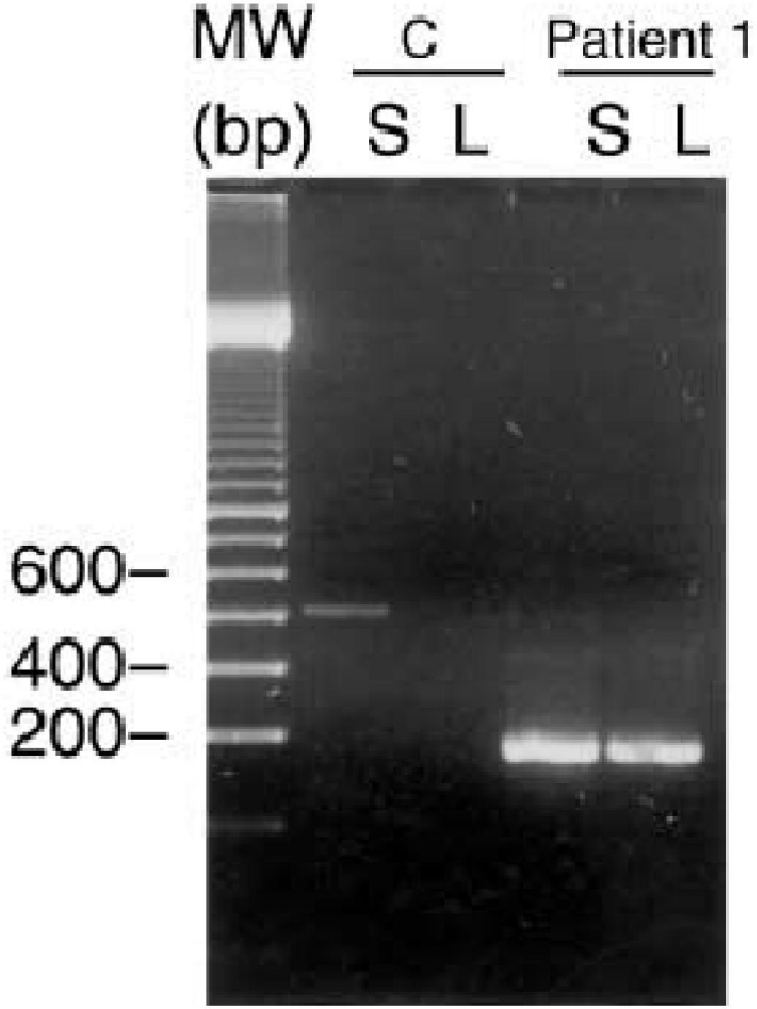
[Hung et al. (2004). *J of Infectious Diseases*, 189:221-232]

Diagnostic tests of Dengue

- Virus isolation, RT-PCR
- ELISA, Rapid test: IgM, IgG
- NS-1 antigen detection

Diagnostic tests

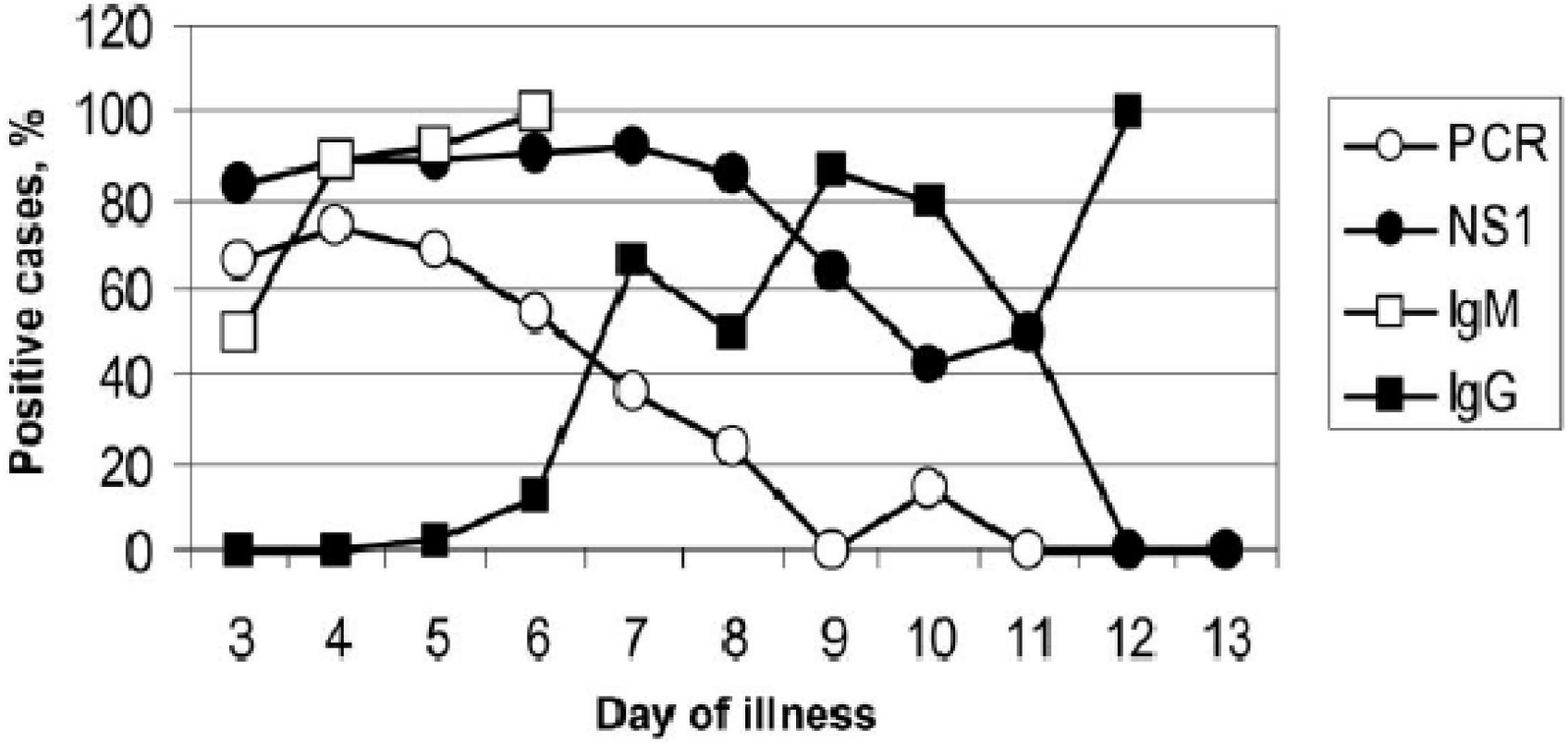




Semi-nested PCR

*** C : control**

*** DEN-3: in serum(S) and liver (L)**
(Huerre, Lan et al. (2001) Virchows Arch 438:107-115)



Kinetics of IgM, IgG, PCR and NS1 in acute plasma of confirmed dengue cases. NS1 antigen as a early viral maker [Simmons et al. JID 2007; 196:416–24]

Differential Diagnosis

- **Other arboviral infections**
- **Measles, rubella, enterovirus infections, adenovirus infections and influenza.**
- **Typhoid, malaria, leptospirosis, viral hepatitis, rickettsial diseases, and bacterial sepsis.**

Systematic reviews [Bandyopadhyay et al Trop Med and Int Health, 2006, 11:1–16]

1. Systematic literature review: 37 studies (post 1975)

2. Results: Severe dengue without fulfilling the WHO criteria for DHF

- Dengue with haemorrhagic manifestations but without vascular leakage
- Dengue with shock syndrome, but without fulfilling the 4 WHO criteria, up to 18 % of patients with shock syndrome
- Frequently organ failure is reported causing severe disease

3. Conclusion: the WHO dengue case classification needs revision

Tropical Medicine and International Health doi:10.1111/j.1365-3156.2006.01678.x

VOLUME 11 NO 8 PP 1238–1255 AUGUST 2006

Classifying dengue: a review of the difficulties in using the WHO case classification for dengue haemorrhagic fever

Shibani Bandyopadhyay[1], L

1 *Public Health Consultant, Ge*
2 *Department of Paediatrics, F*
3 *Special Programme for Resea*

Time for reassessment?

Am. J. Trop. Med. Hyg., 73(6), 2005, pp. 1059–1062

SHORT REPORT: ASSESSMENT OF THE WORLD HEALTH ORGANIZATION SCHEME FOR CLASSIFICATION OF DENGUE SEVERITY IN NICARAGUA

Lancet Inf Dis 2006; 6: 297-302

Personal View

Severe dengue: the need for new case definitions

José G Rigau-Pérez

Viewpoint

Lancet 2006; 368: 170-173

The WHO dengue classification and case definitions: time for a reassessment

Jacqueline L Deen, Eva Harris, Bridget Wills, Angel Balmaseda, Samantha Nadia Hammond, Crisanta Rocha, Nguyen Minh Dung, Nguyen Thanh Hung, Tran Tinh Hien, Jeremy J Farrar

Classification Schemes for Dengue
the DENCO Study

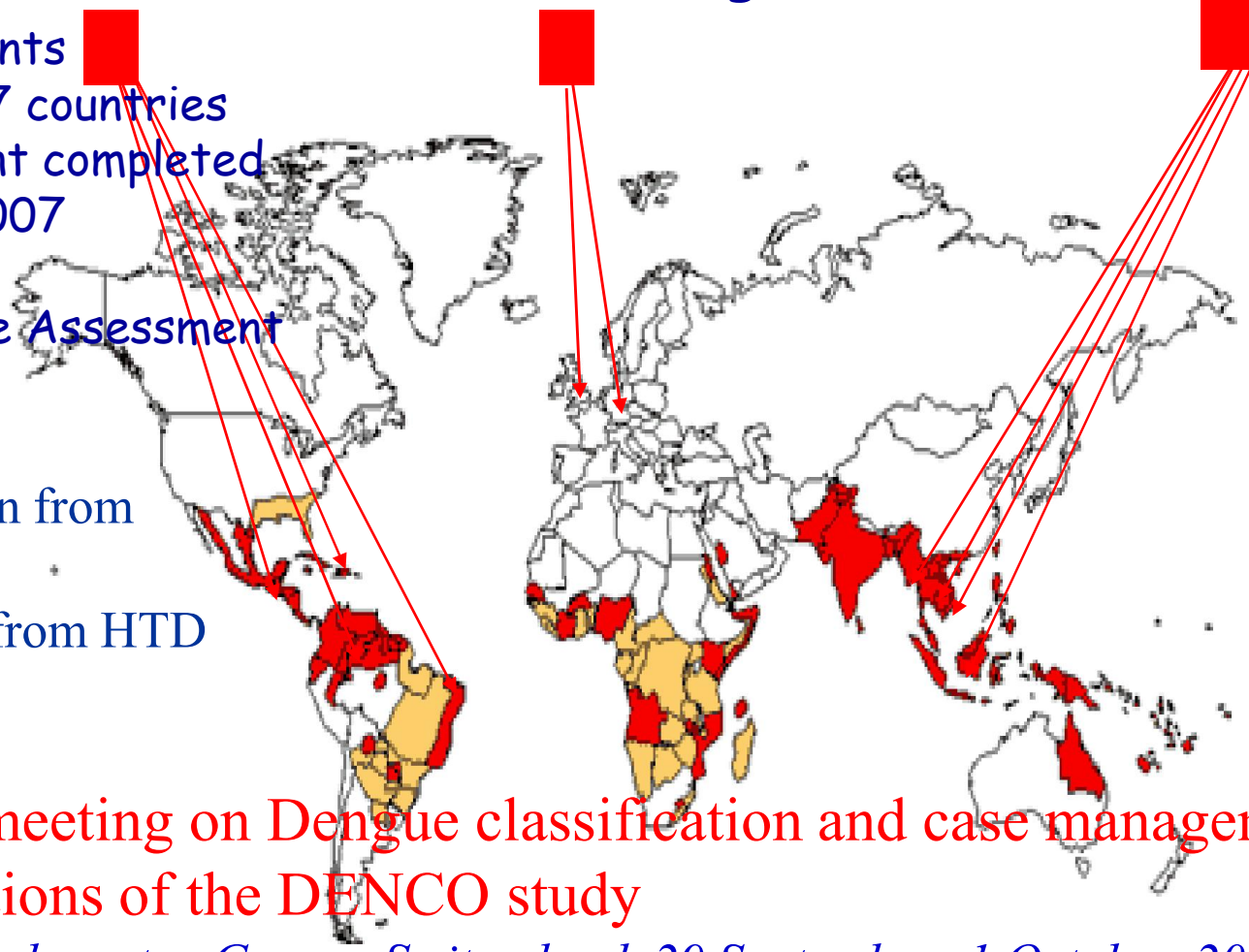
The Americas

Heidelberg & Geneva

Asia

2232 patients
9 Sites in 7 countries
Recruitment completed
Analysis 2007
Phase II
Prospective Assessment
2008

Vietnam:
591 children from
CH 1 & 2.
300 adults from HTD

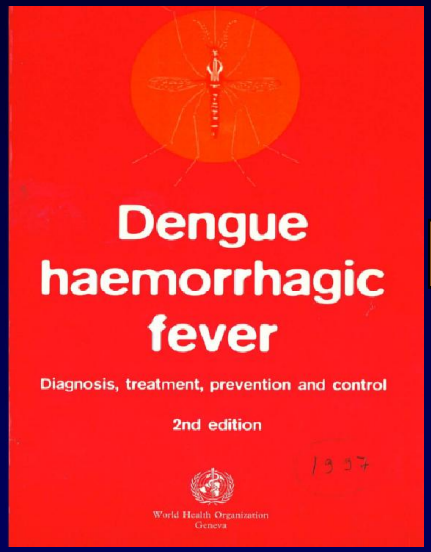


Expert meeting on Dengue classification and case management:
Implications of the DENCO study

WHO Headquarter, Geneva Switzerland, 29 September -1 October, 2008

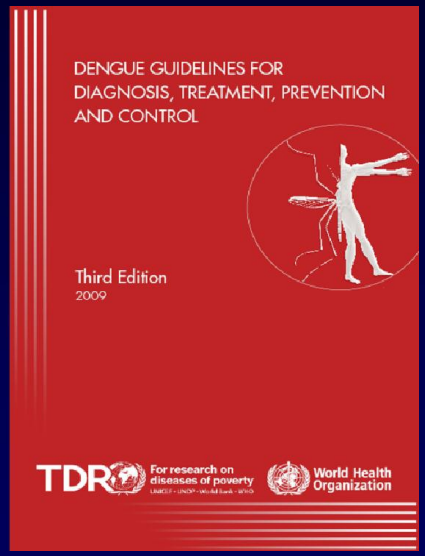
WHO & TDR: New Dengue Guidelines: translating research into practice

The 2nd edition (1997)

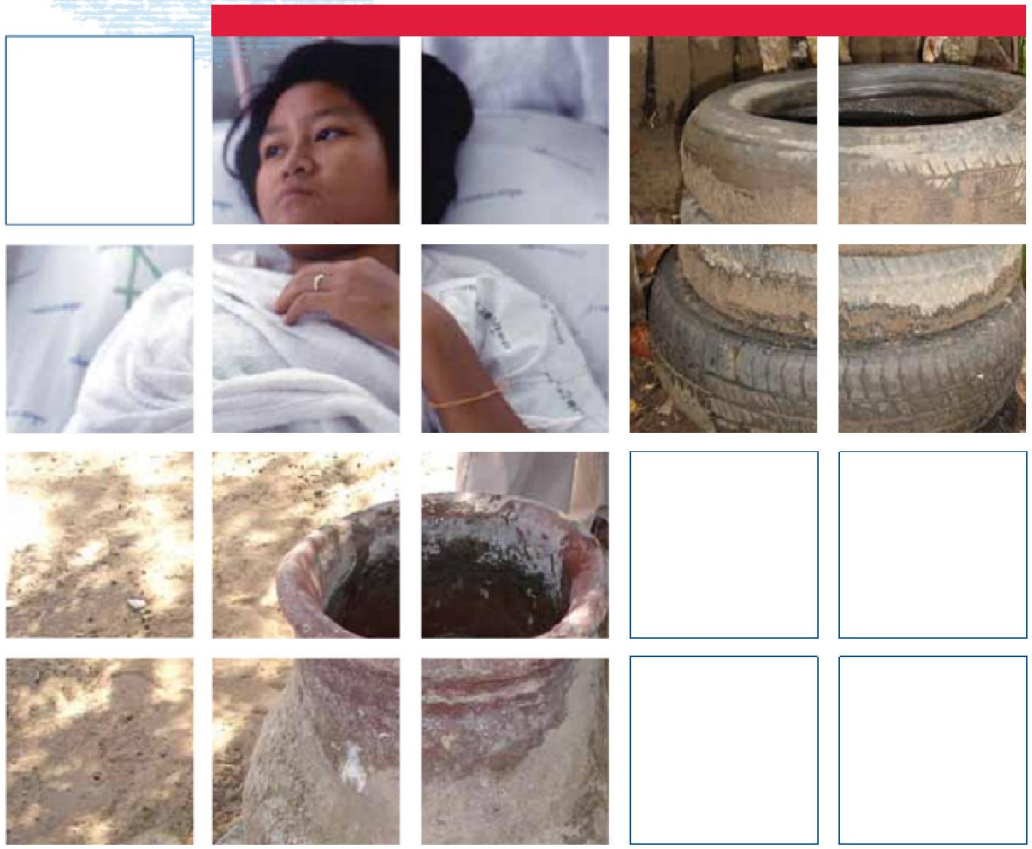


A collaboration of the wider dengue group at WHO & WHO Regional Offices & more than 70 international dengue experts

The new edition (2009)



(Olaf Horstick, TDR, Geneva, Switzerland)

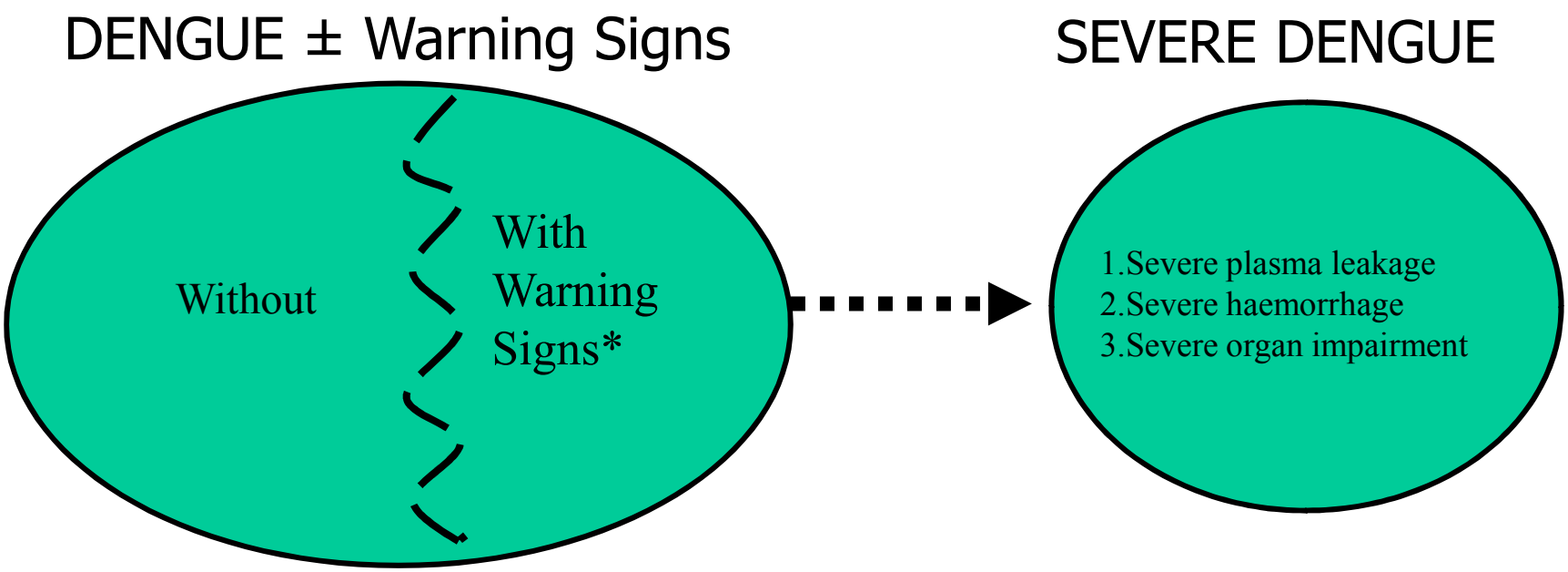

HANDBOOK FOR CLINICAL
MANAGEMENT OF DENGUE
World Health Organization
TDR
For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

WHO, 2012

Preceding Dengue Classification

- **Presumptive Diagnosis**
- **Fever**
- **Anorexia and nausea**
- **Rash**
- **Aches and pains**
- **± Warning signs**
- **Leucopenia**
- **Positive tourniquet test**
- **Neighbourhood dengue/history of travel to dengue endemic area**

Dengue Classification

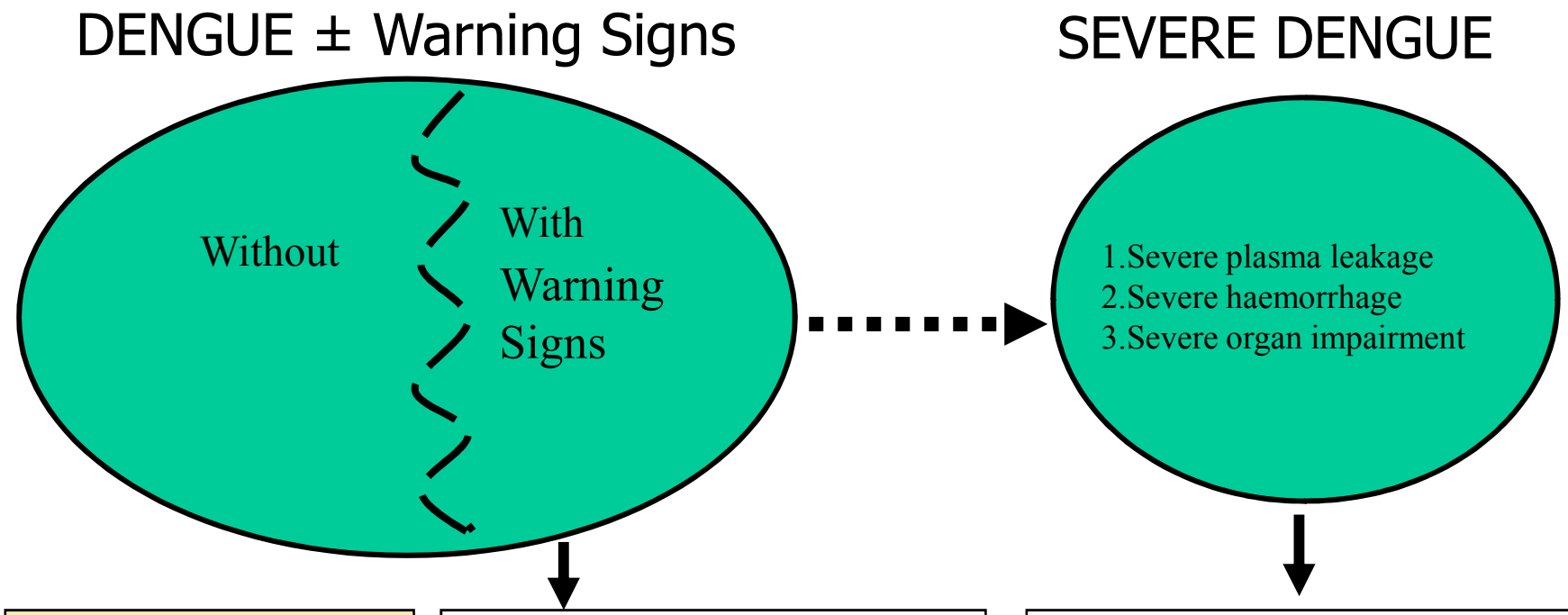


Presumptive Diagnosis
- Fever
- Anorexia and nausea
- Rash
- Aches and pains
- ± Warning signs
- Leucopenia
- Tourniquet test +

Neighbourhood dengue/history of travel to dengue endemic area

- *Requiring strict observation and eventually IV fluids plus other medical interventions*

Dengue Classification



Presumptive Diagnosis
- Fever
- Anorexia and nausea
- Rash
- Aches and pains
- ± Warning signs
- Leucopenia
- Tourniquet test +

Neighbourhood dengue/history of travel to dengue endemic area

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

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*

* *Requiring strict observation and medical intervention*

The Revised WHO dengue case classification, 2009

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

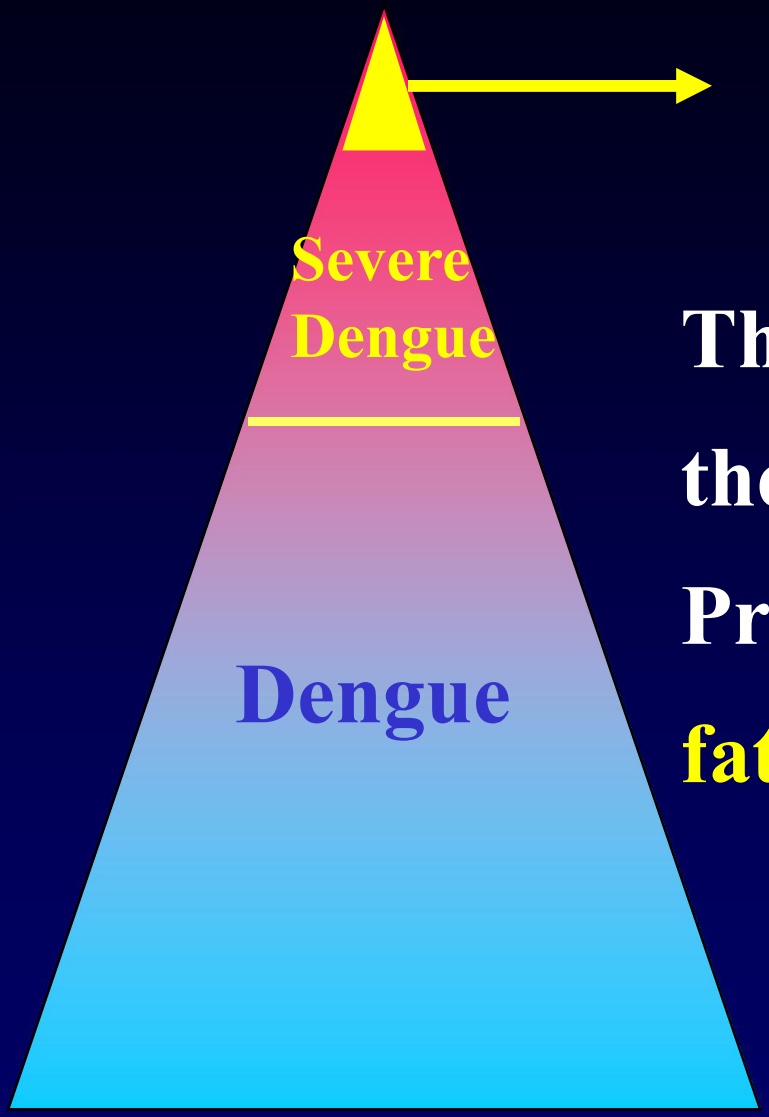
3. Severe organ involvement
- Liver: AST or ALT>=1000
- CNS: Impaired consciousness
- Heart and other organs

WHO/TDR 2009

Warning signs

Clinical	**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**

3. Management



CFR <1- 5%

The primary objectives of the Dengue Control Program: **Reducing case-fatality rate & morbidity rate**

*** In less severe cases (non-shock DHF) patients will recover spontaneously or shortly after intravenous fluid administration.**

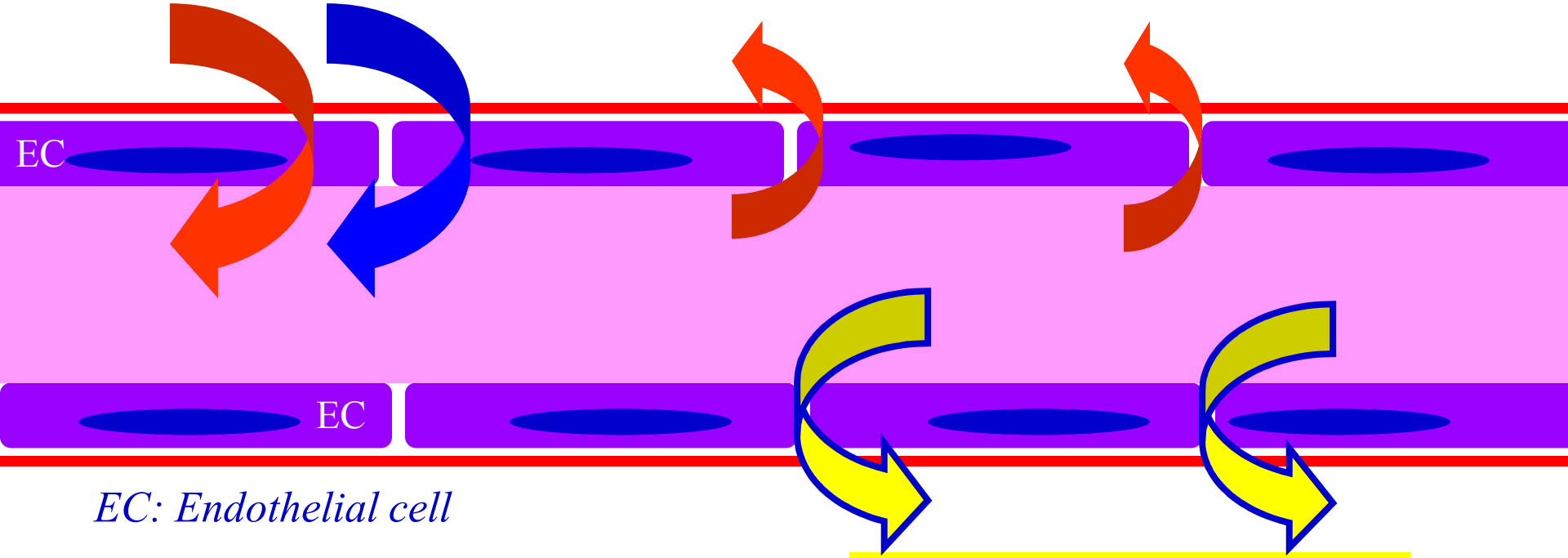
*** In more severe cases (DSS), patients may die within 12- 24 hours if appropriate treatment is not promptly administered. Volume replacement is the mainstay of treatment of DSS.**

Replacement of plasma loss as the principle of management of DSS

IV fluid replacement

Blood transfusion

Hemorrhage



EC: Endothelial cell

Plasma leakage

[Hung& Lan (2003), *Dengue Bulletin*, 27:144-148]

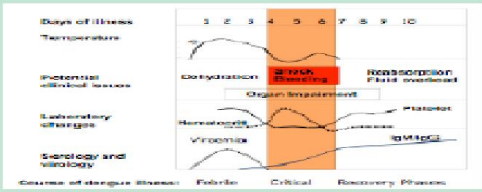
Dengue Case Management

Assessment

Presumptive Diagnosis:
Live in / travel to endemic area plus
Fever and two of the following:
- Anorexia and nausea
- Rash
- Aches and pains
- Warning signs
- Leucopenia
- Tourniquet test positive

Lab.-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 of platelet count



Classification

negative

Co-existing conditions
Social circumstances

negative

positive

positive

Dengue without warning signs

Dengue with warning signs

Severe Dengue

Management

Group A
May be sent home

Group criteria
Patients who do not have warning signs
AND
who are able:
- To tolerate adequate volumes of oral fluids
- To pass urine at least once every 6 hours

Laboratory tests
- Full blood Count (FBC)
- Haematocrit (Hct)

Treatment
Advice for:
- Adequate bed rest
- Adequate fluid intake
- Paracetamol, 4 gram max. per day in adults and accordingly in children

Patients with stable Hct can be sent home

Monitoring
- Daily review for disease progression:
  - Decreasing WBC
  - Defervescence
  - Warning signs (until out of critical period)
- Advice for immediate return to hospital if development of any warning signs
- Written advice of management (e.g. home care card for dengue)

Discharge criteria:
-> all of the following criteria must be present
- No fever for 48 hours
- Improvement in clinical picture
- Increasing trend of platelet count
- No respiratory distress
- Stable haematocrit without intravenous fluids

Group B
Referred for in-hospital care

Group criteria
Patients with any of the following features:
- Co-existing conditions such as pregnancy, infancy, old age, diabetes mellitus
- Social circumstances such as living alone, living far from hospital

OR
Existing warning signs:
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleeding
- Lethargy/ restlessness
- Liver enlargement >2cm
- Laboratory: increase in Hct

Laboratory tests
- Full blood Count (FBC)
- Haematocrit (Hct)

Treatment
- Encouragement for oral fluids
- If not tolerated, start intravenous fluid therapy 0,9% saline or Ringer Lactate at maintenance rate

Monitoring
- Temperature pattern
- Volume of fluid intake and losses
- Urine output – volume and frequency
- Warning signs
- Hct, white blood cell and platelet counts

Group C
Require emergency treatment

Group criteria
Patients with any of the following features:
- Severe plasma leakage with shock and/or fluid accumulation with respiratory distress
- Severe bleeding
- Severe organ impairment

Laboratory tests
- Full blood Count (FBC)
- Haematocrit (Hct)
- Other organ function tests as indicated

Treatment of compensated shock:
- Start I.V. fluid resuscitation with isotonic crystalloid solutions at 5-10 ml/kg/hr over 1 hr
- Reassess patient's condition.

If patient improves:
- I.V. fluids should be reduced gradually to 5-7 ml/kg/hr for 1-2 hr, then to 3-5 ml/kg/hr for 2-4 hr, then to 2-3 ml/kg/hr for 2-4 hr and then reduced further depending on haemodynamic status
- I.V. fluids can be maintained for up to 24 - 48 hours

If patient still unstable:
- Check Hct after first bolus
- **If Hct increases/ still high (>50%),** repeat a second bolus of crystalloid solution at 10-20 ml/kg/hr for 1 hr.
- If improvement after second bolus, reduce rate to 7-10 ml/kg/hr for 1-2 hr, continue to reduce as above
- **If Hct decreases,** this indicates bleeding and need to cross-match and transfuse blood as soon as possible

Treatment of hypotensive shock
- Initiate I.V. fluid resuscitation with crystalloid or colloid solution at 20 ml/kg as a bolus for 15 min

If patient improves
- Give a crystalloid / colloid solution of 10 ml/kg/hr for 1 hr, then reduce gradually as above

If patient still unstable
- Review the Hct taken before the first bolus
- **If Hct was low** (<40% in children and adult females, < 45% in adult males) this indicates bleeding, the need to crossmatch and transfuse (see above)
- **If HCT was high** compared to the baseline value, change to I.V. colloids at 10-20 ml/kg as a second bolus over 30 to 1 hour, reassess after second bolus
- **If improving** reduce the rate to 7-10 ml/kg/hr for 1-2 hours, then back to I.V. crystalloids and reduce rates as above
- If condition still unstable, repeat Hct after second bolus
- **If Hct decreases,** this indicates bleeding, see above
- **If Hct increases/** remains high (> 50%), continue colloid infusion at 10-20 ml/kg as a bolus over 1 hr, then reduce to 7-10 ml/kg /hr for 1-2 hours, then change back to crystalloid solution and reduce rate as above

Treatment of haemorrhagic complications:
- Give 5-10 ml/kg of fresh packed red cells or 10-20 ml/kg fresh whole blood

Monitoring
- Vital signs and peripheral perfusion (1-4 hourly until patient is out of critical phase
- Urine output (4-6 hourly)
- Hct (before and after fluid replacement, then 6-12 hourly)
- Blood glucose
- Other organ functions (renal profile, liver profile, coagulation profile, as indicated)

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO
World Health Organization

Treatment of non-shock DHF (grade I, II)

(Group A – patients who may be sent home)

Most patients can be managed as outpatients

Reduce high fever:

* Paracetamol 10 mg/kg x 4-6 times
* Tepid sponging

Nutritional support:

* Eat favorite food
* Drink fruit juices, ORS, plain water

Counsel mother/ caretakers

* How to take care the child at home.

* Bring the child to the hospital immediately when warning signs of shock appeared.

Admission criteria

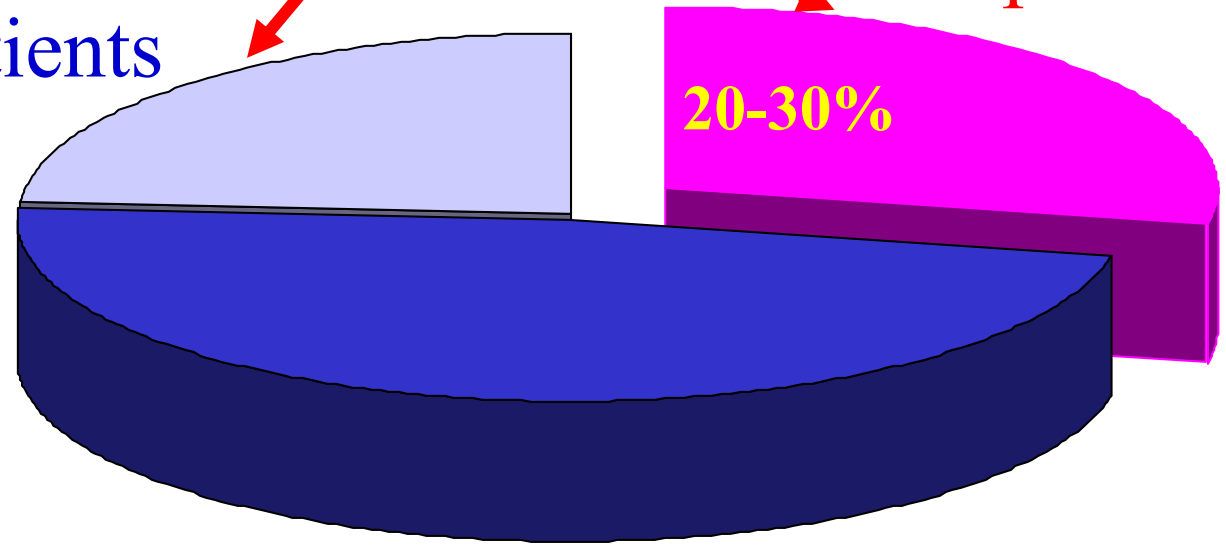
1. Patients with severe Dengue → Require emergency treatment
2. Patients with:
   * warning signs;
   * co-existing conditions;
   * certain social circumstances

→ Referred for in-hospital management

IV fluid therapy

30% of non-shock Dengue patients

DSS patients



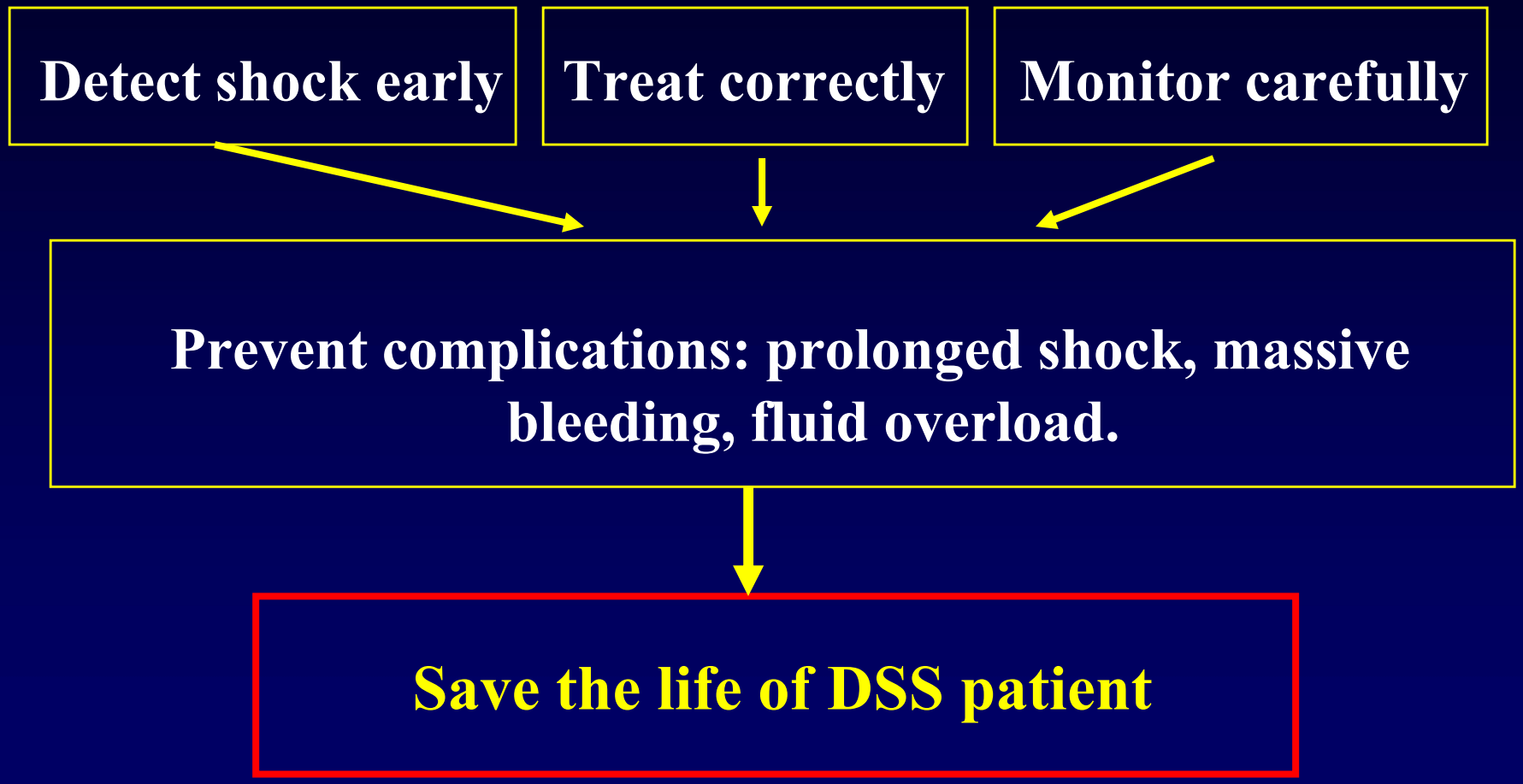
Oral rehydration → 70% of non-shock Dengue patients

IV fluid in non-shock Dengue (30% of cases)

- **Type of IV fluid:** **Ringer Lactate (RL), Ringer Acetate (RA), 0.9% saline**
- **Rate of fluid:** **Start with 5 - 7 ml/ kg/hr, then slow down gradually**

	Children (n=77)	Infants (n= 145)
* Average amount of fluid	105 ±36.7 mL/kg	102.1 ±28.4 mL/kg
* Duration of intravenous transfusion	20 ± 8.6 hrs	25.9 ± 8.1 hrs *[Hung et al. (2006). Am. J. Trop. Med. Hyg.,74(4):684-691]*

Principles of treatment of DSS (grade III, IV)



IV fluid for DSS patients

- **Type of intravenous fluid:** RL; 0.9% saline; colloid solution: dextran-40,70, hydroxyethyl starch .
- **Rate of intravenous fluid:**

  * **Grade III:** start with 15-20 ml/ kg/ hr.

  * **Grade IV:** start with 20 ml/ kg/dose IV push for 15 minutes until blood pressure, pulse can be measured, then reduce to 10 - 20 ml/ kg/ hr.

Average amount of intravenous fluid in DSS patients

	Children* (n=218)	Infants* (n= 63)
- Average amount of fluid	121.7 ±38.6 mL/ kg	129.8 ±36.9 mL/kg
- Duration of IV fluid transfusion	21 ± 8.1 hrs	25.7 ± 10.2 hrs

** [Hung et al. (2006). Am. J. Trop. Med. Hyg.,74(4):684-691]*

Average amount of fluid in adults with DSS <= 80 ml/ kg/ 24 hrs *[Hien TT, 2005]*

Randomized Control Trials for the treatment of Dengue

1. Dung NM et al. Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous-fluid regimens. Clin Infect Dis. 1999, 29(4):787-94
2. Ngo NT et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. Clin Infect Dis. 2001, 32(2):204-13
3. BA Wills et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med. 2005, 353(9):877-89

Conclusions from 3 randomized control trials

1. The majority of children with DSS can be treated successfully with isotonic crystalloid solutions.
2. If a colloid is judged to be necessary a medium molecular weight preparation which combines good initial plasma volume support with good intravascular persistence and an acceptable side effect profile is probably the preparation of choice.
3. Further research is needed to determine whether early treatment with a colloid confers a true advantage in those with severe shock.

Patients at risk of severe bleeding:

- Profound/prolonged/refractory shock;
- Multi-organ failure; severe metabolic acidosis;
- Given non-steroidal anti-inflammatory agents; on anticoagulant therapy;
- Pre-existing peptic ulcer disease;
- Have any form of trauma

- **Blood transfusion is life-saving and should be given as soon as severe bleeding is recognized. Do not wait for the HCT to drop too low before deciding on blood transfusion.**
- **Give 5–10ml/kg of fresh-packed red cells or 10–20 ml/kg of FWB.**

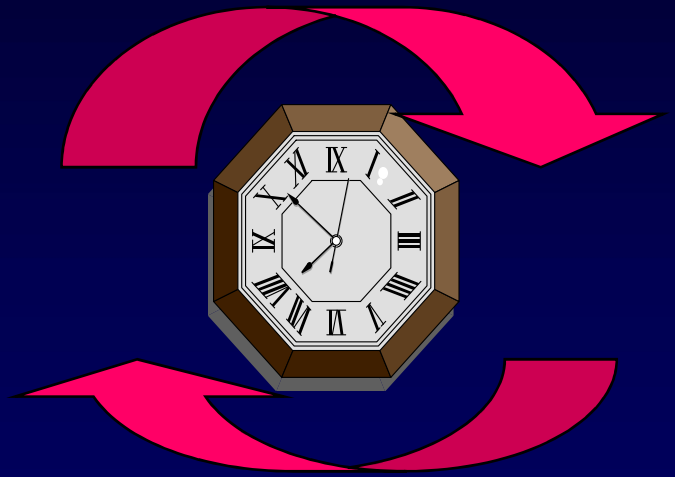
(WHO, 2009)

No evidence to support the practice of transfusing platelet concentrates and/or fresh-frozen plasma for severe bleeding. It is being practised when massive bleeding persists but it will exacerbate the fluid overload

(WHO, 2009)

Monitoring DHF/DSS patients

DHF/DSS patients should be under constant and careful observation.



* Clinical: general condition, appetite, capillary refill time.
* Vital signs.
* Hematocrit.
* Intake, output.

4. Prevention

- Vector control
- Vaccine

New vector-control approaches

The release of genetically modified male mosquitoes that sterilize the wild-type female population, thereby reducing egg output and the population size of the next generation that would be available for potential transmission of the DV.

(Simons CP et al. 2012)

Embryonic introduction of strains of the obligate intracellular bacterium wolbachia into A. aegypti. Strikingly, wolbchia-infected A. aegypti are partially resistant to DV infection and can invade natural Aegypti populations, suggesting the possibility of induction of widespread biologic resistance to DV in A. aegypti populations.

(Simons CP et al. 2012)

World Health Organization

Questions and Answers on Dengue Vaccines: Phase III study of CYD-TDV in Latin America

November 2014

- **WHO goal of reducing dengue morbidity by at least 25% and mortality by at least 50% by 2020.**

- **The vaccine candidate currently at the most advanced clinical development stage is a live attenuated tetravalent dengue vaccine developed by Sanofi Pasteur (CYD-TDV).**

THE LANCET
Articles

Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial

*Maria Rosario Capeding, Ngoc Huu Tran, Sri Rezeki S Hadinegoro, Hussain Imam HJ Muhammad Ismail, Tawee Chotpitayasunondh, Mary Noreen Chua, Chan Quang Luong, Kusnandi Rusmil, Dewa Nyoman Wirawan, Revathy Nallusamy, Punnee Pitisuttithum, Usa Thisyakorn, In-Kyu Yoon, Diane van der Vliet, Edith Langevin, Thelma Laot, Yanee Hutagalung, Carina Frago, Mark Boaz, T Anh Wartel, Nadia G Tornieporth, Melanie Saville, Alain Bouckenooghe, and the CYD14 Study Group**

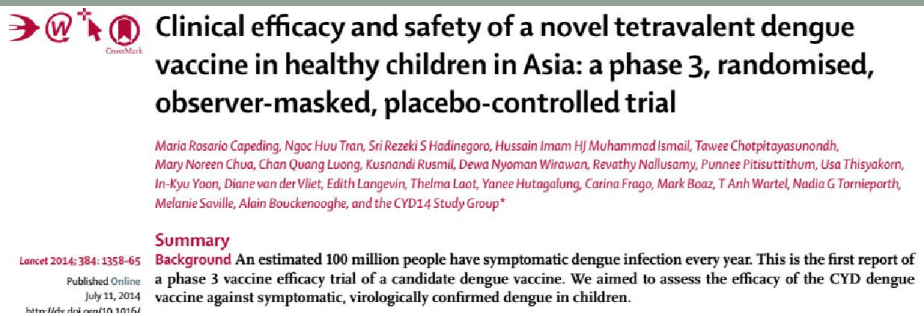
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

Luis Villar, M.D., Gustavo Horacio Dayan, M.D., José Luis Arredondo-García, M.D., Doris Maribel Rivera, M.D., Rivaldo Cunha, M.D., Carmen Deseda, M.D., Humberto Reynales, M.D., Maria Selma Costa, M.D., Javier Osvaldo Morales-Ramírez, M.D., Gabriel Carrasquilla, M.D., Luis Carlos Rey, M.D., Reynaldo Dietze, M.D., Kleber Luz, M.D., Enrique Rivas, M.D., Maria Consuelo Miranda Montoya, M.D., Margarita Cortés Supelano, M.D., Betzana Zambrano, M.D., Edith Langevin, M.Sc., Mark Boaz, Ph.D., Nadia Tornieporth, M.D., Melanie Saville, M.B., B.S., and Fernando Noriega, M.D., for the CYD15 Study Group*

Results of efficacy in Asia



Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial

Maria Rosario Capeding, Ngoc Huu Tran, Sri Rezeki S Hadinegoro, Hussain Imam HJ Muhammad Ismail, Tawee Chotpitayasunondh, Mary Noreen Chua, Chan Quang Luong, Kusnandi Rusmil, Dewa Nyoman Wirawan, Revathy Nallusamy, Punnee Pitisuttithum, Usa Thisyakorn, In-Kyu Yoon, Diane van der Vliet, Edith Langevin, Thelma Laot, Yanee Hutagalung, Carina Frago, Mark Boaz, T Anh Wartel, Nadia G Tornieporth, Melanie Saville, Alain Bouckenooghe, and the CYD14 Study Group*

Lancet 2014; 384: 1358–65
Published Online
July 11, 2014

Summary

Background An estimated 100 million people have symptomatic dengue infection every year. This is the first report of a phase 3 vaccine efficacy trial of a candidate dengue vaccine. We aimed to assess the efficacy of the CYD dengue vaccine against symptomatic, virologically confirmed dengue in children.

Randomly assigned 10 275 children to receive either vaccine (n=6851) or placebo (n=3424). 250 cases of virologically confirmed dengue took place more than 28 days after the third injection.

* The primary endpoint was achieved **with 56·5% (95% CI 43·8–66·4) efficacy.**

* Recorded 647 serious adverse events (402 [62%] in the vaccine group and 245 [38%] in the control group. Serious adverse events were consistent with medical disorders in this age group and were mainly infections and injuries.

Main objectives of the phase III study of CYD-TDV in Latin America

* Assess the safety and efficacy of CYD-TDV in preventing dengue disease for one year after completion of the vaccination schedule of three doses given 6 months apart.
* Evaluate immunogenicity.

Results

The study population consisted of 20,869 children aged 9 to 16 years in five countries in the Latin America region: Brazil, Colombia, Honduras, Mexico, and Puerto Rico.

The primary efficacy analysis was based on the number of dengue cases of any serotype in vaccinated and control subjects, during a one year observation period from 28 days after the 3rd dose.

Results

In this period, 397 cases of virologically-confirmed dengue were diagnosed.

- **Vaccine efficacy against all dengue serotypes combined in this period (the per-protocol (PP) analysis) was estimated as 60.8% (95% CI 52.0, 68.0).**
- **There was statistically significant protection demonstrated for each of the four serotypes, but the level of protection varied between serotypes. Serotype specific efficacies were secondary trial endpoints: vaccine efficacy against DENV1 was 50.3% (95% CI 29.1, 65.2), against DENV2 was 42.3% (95% CI 14.0, 61.1), against DENV3 was 74.0% (95% CI 61.9, 82.4), and against DENV4 was 77.7% (95% CI 60.2, 88.0).**

There was no evidence of an increase in serious adverse events in the trial, which included follow up for 13 months after the three-dose series, consistent with the safety results from the trial in Asia.

4. How can the Case-fatality rate of Dengue be reduced?

Measures contributing to reduction of case fatality rate in Dengue in Southern Vietnam

Proper organization
& good triage

Supply of enough
equipment and intravenous fluids

Reducing case fatality rate of Dengue

Well trained medical staff
(doctors, nurses)

Education for
mothers/ cartakers

The Challenge of Dengue Management

- **Patients with severe complications** (prolonged shock; massive bleeding; respiratory failure; fulminant hepatitis; dengue encephalopathy).
- **High risk patients:**

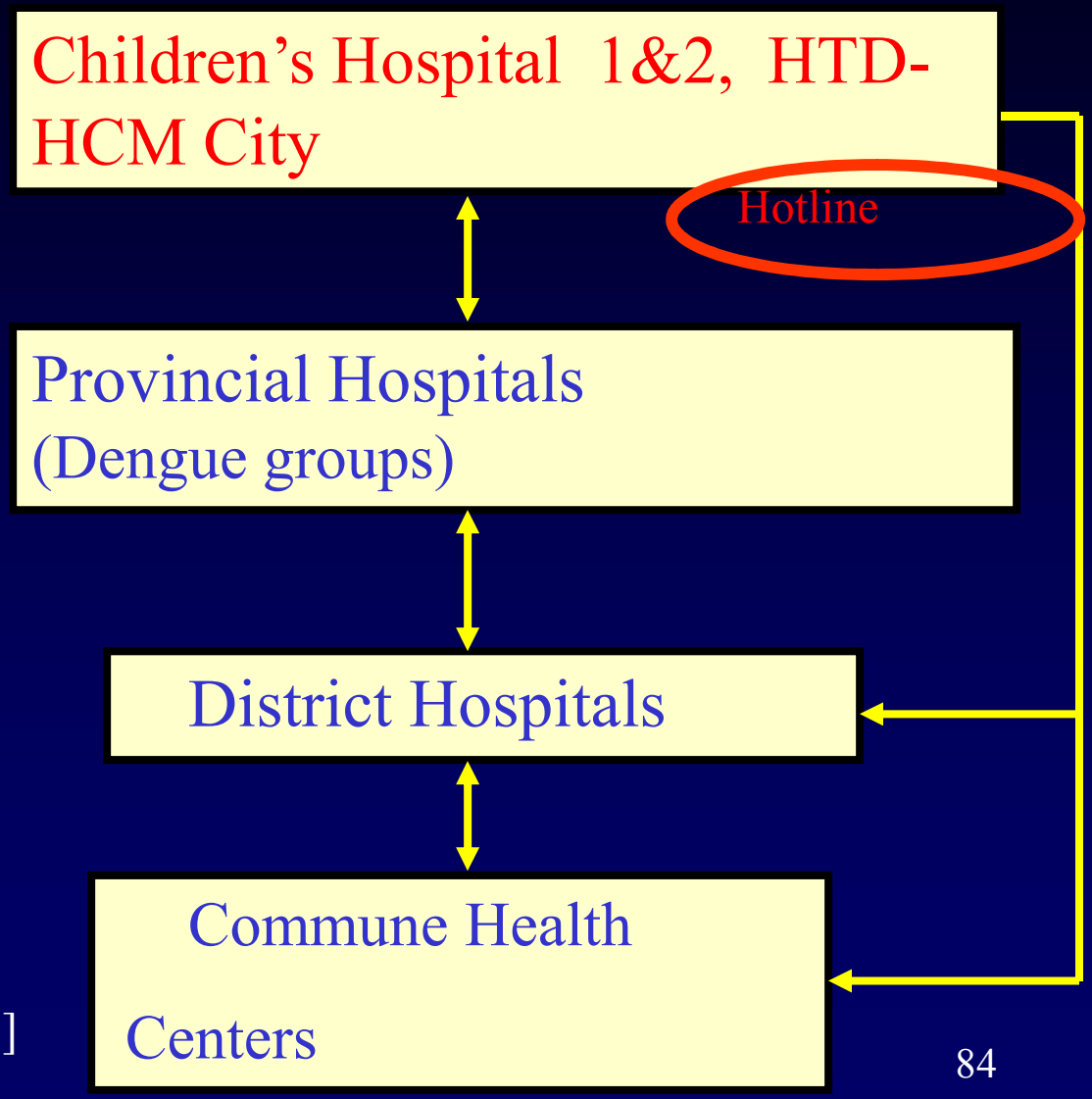
  * Infants < 1 yr old.

  * Obesity

  * Children and adults with underlying diseases (heart, kidney diseases; G6-PD deficiency; thalassemia; asthma; pneumonia,obesity).

Training & network for case management of Dengue

* Conferences/ Video conferences on Dengue
* Training courses for doctors, nurses
* Training of trainers
* Health education for mothers

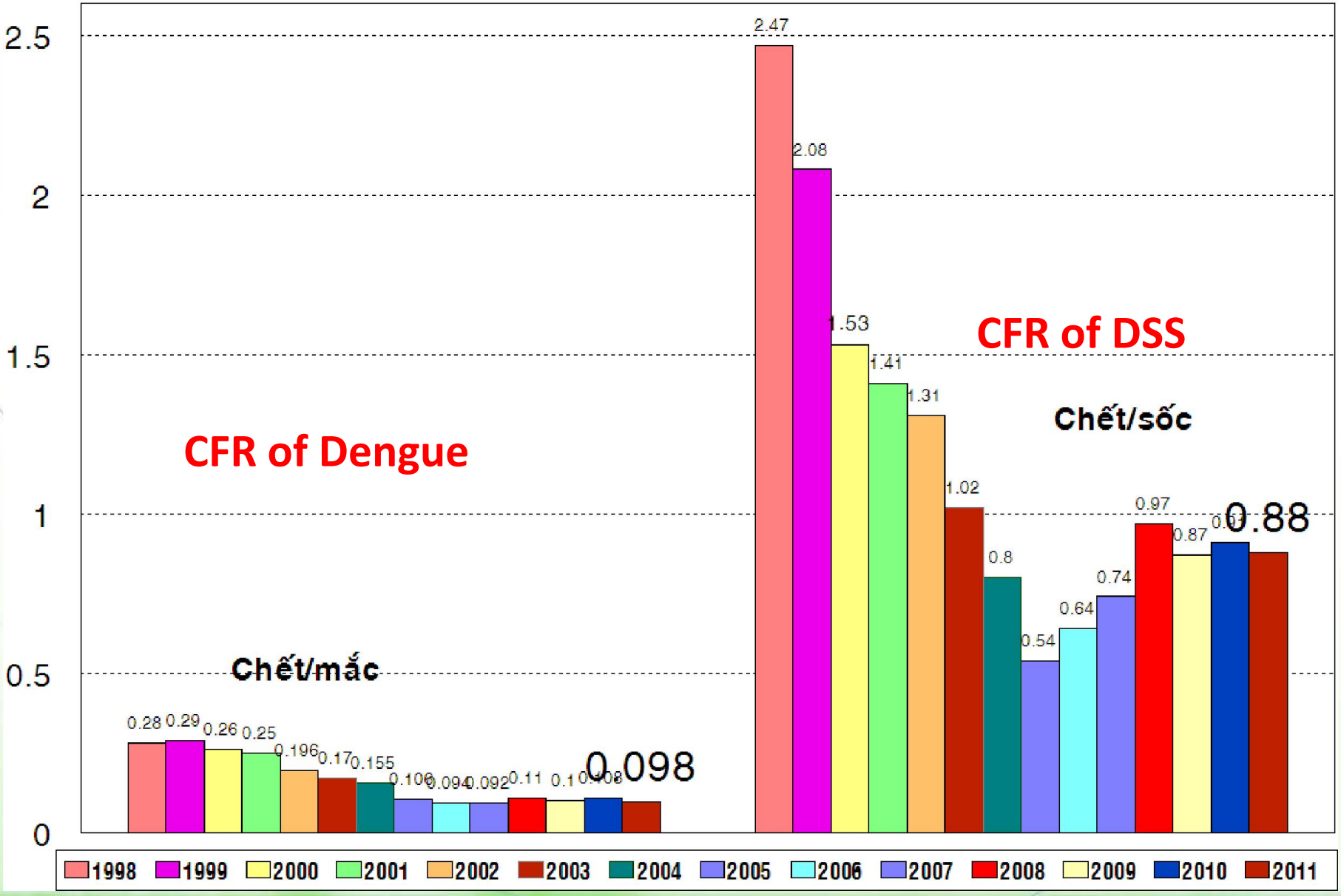


[Hung and Lan (2003), WHO *Dengue Bulletin*, Vol. 27, 144-148]

Training and video-conference on management of Dengue for provincial hospital staffs

On-site intervention: peer review, training, sharing experience, transferring technology on management of Dengue for provincial staff

Case fatality rate of Dengue/DSS in south Vietnam, 1998-2011



Thank you for your attention!