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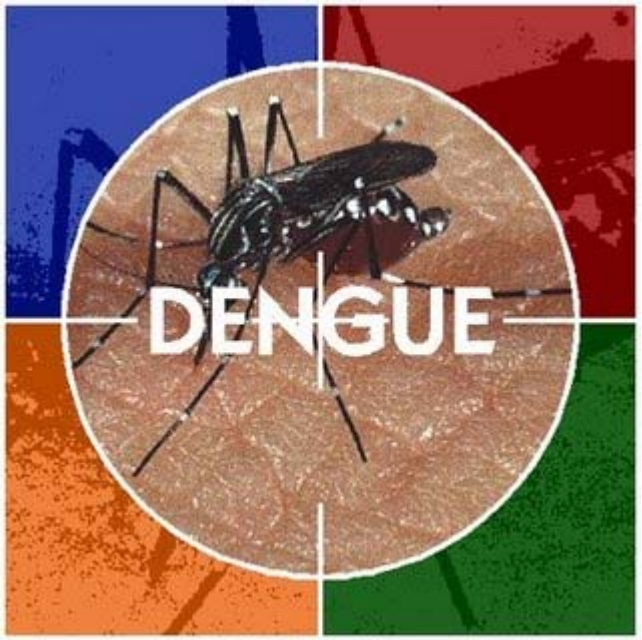
Dengue Infection: A New Paradigm



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PIDST , 27 November 2009

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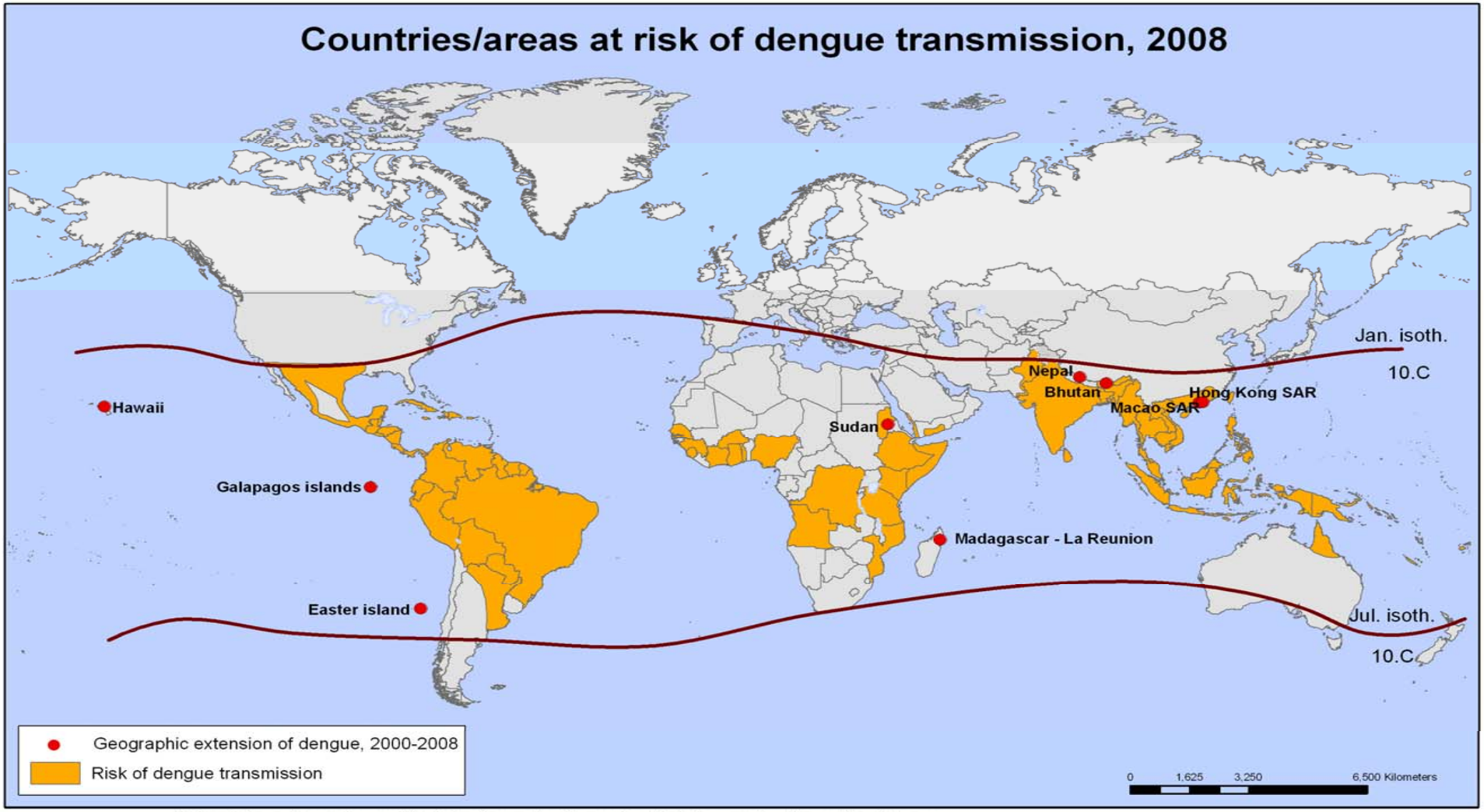
New developments in epidemiology



World Health Organization

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: DengueNet, World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)

http://www.pdvi.org/about_dengue/GBD.asp

New Estimates of the Burden of Dengue

	New Estimates	Earlier Estimates
Population at risk	3.6 billion (55% of world population)	2.5-3 billion (40% of world population)
Endemic countries	124	>100
Dengue Infections*/year	70-500 million	50-100 million
Cases of Dengue Fever/year	36 million	
Case of DHF/DSS/year	2.1 million	250,000-500,000
Deaths/year	21,000	20,000

*** Includes asymptomatic infection which increases risk of more severe disease with subsequent infection**

New Estimates of the Burden of Dengue

Disease	Symptomatic Cases	Deaths	Estimated Countries Affected
Dengue	36 million	21,000	124
Yellow Fever	200,000	30,000	>42
Japanese Encephalitis	50,000	>10,000	>10
Malaria	500 million	>1 million	>105

*** Adapted from: E. Callaway. Dengue fever climbs the social ladder. *Nature* 2007;448:734-5.**

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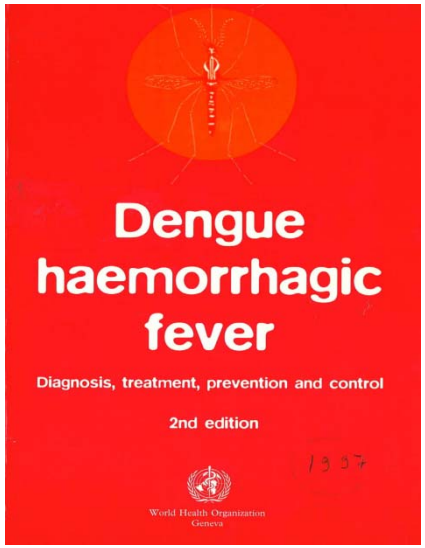
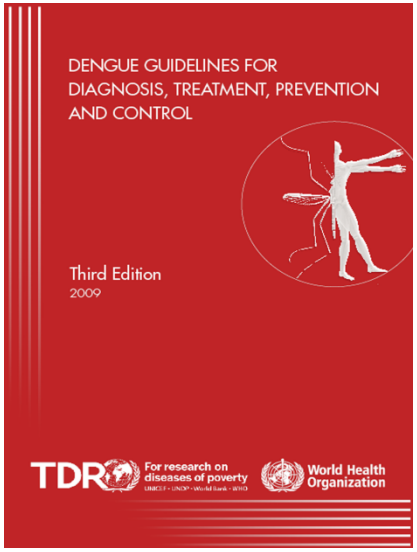
Third edition of the WHO dengue guidelines: translating research into policy and practice

The 2nd edition (1997)



The 3rd edition (2009)



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

Olaf Horstick, UNICEF/UNDP/World Bank/WHO,

Special Programme for Research and Training in Tropical Diseases (TDR), Geneva, Switzerland

Why a new edition?

New developments in

- epidemiology and case classification

- clinical care and organisation of services

- diagnostics

- vector control

- surveillance and response

How was it done?

WHO/Department of Neglected Tropical Diseases leading the initiative, with support from TDR and other departments

1. Writing team

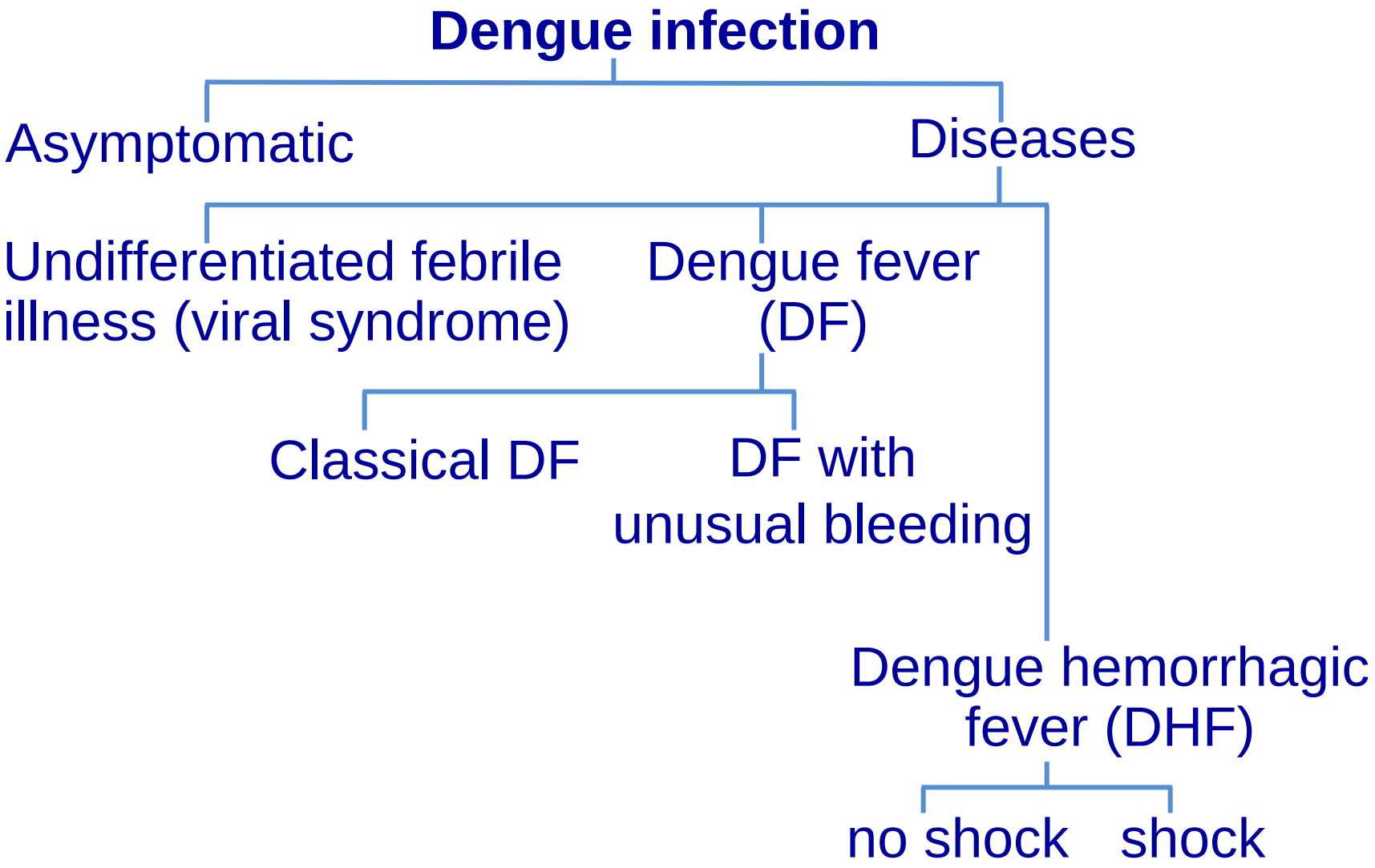
Each chapter had a WHO coordinator and at least one non-WHO lead writer with technical expertise covering epidemiology, pathogenesis and transmission, clinical aspects, vector control, laboratory aspects, surveillance and response and drugs and vaccine development

2. Peer-reviewing

3. Use of evidence specified

4. Guidelines review committee approval (transitional arrangements)

Clinical Manifestation:



Case Definition for DHF-WHO 1997

- ★ Fever, or history of acute fever, lasting 2-7 days, occasionally biphasic
- ★ Hemorrhagic tendency evidenced by :
  - a positive tourniquet test
  - petechiae, ecchymoses or purpura
  - bleeding from mucosa, GI tract, injection site, etc.
- ★ Thrombocytopenia ($\leq$100,000 cell per mm^3)
- ★ Evidence of plasma leakage :
  - a rise in Hct $\geq$20%
  - a drop in Hct following volume – replacement $\geq$20%
  - sign of plasma leakage eg. Pleural effusion, ascites, hypoproteinemia

Danger Signs in Dengue Hemorrhagic Fever

- ★ Abdominal pain – intense and sustained
- ★ Persistent vomiting
- ★ Abrupt change from fever to hypothermia, with sweating and prostration
- ★ Restlessness or somnolence

Martinez Torres E. *Salud Publica Mex* 1995;37(supl):29-44.

1. Recent literature on case classification

The existing evidence		
Systematic reviews:	**Reviews:**	**Single studies:**
Classifying dengue: a review of the difficulties in using the WHO case classification for dengue haemorrhagic fever **Bandyopadhyay S, *et al*.**	**Dengue fever:** new paradigms for a changing epidemiology **Guha-Sapir D, *et al*.** **The WHO dengue classification and case definitions:** time for a reassessment **Deen J, *et al*.** **Severe Dengue:** the need for new case definitions **Rigau-Perez J**	Clinical diagnosis and assessment of severity of confirmed dengue infections in Vietnamese children: is the World Health Organization classification system helpful? Cao Xuan Thanh. **Phuong, *et al*.** **Short report:** Assessment of the World Health Organization scheme for classification of dengue severity in Nicaragua **Balmaseda A, *et al*.**

Plasma Leakage in DHF: Problems of Hemoconcentration !

1. IV. therapy for dehydration, would mask the expected rise in Hct.
2. It may be impossible to measure the Hct in poorly perfused patients.
3. Hemoconcentration may be difficult to document are concerence of bleeding over shock
4. High prevalence of anemia.
5. Difficult to ascertain hemoconcentration with a single Hct.
6. Excessive laboratory workload during epidemic outbreaks.
7. Requirement for blood transfusion.
8. Sudden death of patients where repeat tests could not be performed.

Bandyopadhyay S, *et al*. *Trop Med Inter Health*

Evidence of Pleural Effusion/Ascites

1. Supine position may not demonstrate small pleural effusion, right lateral decubitus or ultrasound may be required
2. Free fluid may become detectable only after IV therapy in mild DHF

small effusion could be detected in DF and non-dengue illnesses (Kalayanarooj S, *et al.*,1997)

Severe dengue not fulfilling all WHO criteria for DHF

1. Dengue with hemorrhage without plasma leakage
   : being reported from various part of the world; Indonesia, India, Philippines, Thailand, South Pacific, Latin America.
   PAHO Guidelines (1994) called “DF with unusual hemorrhage”
2. Dengue with shock without fulfilling the four DHF criteria
   - 57/310 (18%) not fulfill all 4 criteria, would be classified as DF (Phuong *et al.*, 2004)
   - similar experiences in other 6 studies
   - prospective study in Nicaragua, WHO criteria failed to detect patients with shock & severe manifestations of dengue esp. in adults (Balmaseda *et al.*, 2005)
3. Organ dysfunctions as prominent manifestations of severe dengue (out of proportion to the degree of plasma leakage)
   : disorder of the brain and RS are not accounted for in WHO classification. (Bandyopadhyay S, *et al.*, 2006)

Limitation of the WHO classifications scheme & Case definitions

1. The classification scheme distinguishes rigorously between DF, DHF, DSS but there is much overlap between the three.
2. All 4 criteria for DHF might not always be fulfilled/detected.
3. DHF/DSS classification excludes severe dengue disease
4. DHF places under emphasis on hemorrhage when danger sign that should be watched for and managed is plasma leakage leading to shock.

Dean JL, *et al*. *Lancet* 2006;368:170-3.

30% (9/30) virologically confirmed dengue deaths
- G-I bleed before onset of shock
- no evidence of hemoconcentration

Sumarmo *et al.*, *Bull World Health Organ* 1983:61:693-701.

18% (57/310) with shock & laboratory confirmed dengue
- did not meet all 4 WHO criteria for DHF

Phuong CXT, *et al.*, Am J Trop Med Hyg 2004;*70*:172-9.

61% (20/33) infants
69% (194/283) children
77% (20/26) adults
- did not fulfill WHO criteria for DHF

Balmaseda A, *et al.*, Am J Trop Med Hyg 2005;*73*:1059-62.

Studies of the tourniquet test in the diagnosis of laboratory-confirmed dengue

	Age range	Number with positive tourniquet test/total			Ability of the tourniquet test to diagnose dengue infection			
		Dengue fever*	Dengue haemorrhagic fever*	Other febrile illness	Sensitivity	Specificity	PPV	NPV
Bangkok and Kamphaeng Phet, Thailand[1]	6 mo–14 yrs	10/28 (36%)	12/23 (52%)	23/108 (21%)	-	-	49%	75%
		18/28 (64%)†	15/23 (65%)†	42/108 (39%)†	-	-	44%	79%†
Bangkok and Kamphaeng Phet, Thailand[2]	6 mo-15 yrs	154/176 (88%)†	132/142 (93%)†	172/331 (52%)†	90%	48%	62%	83%†
Dong Nai Province, Vietnam[3]	1 mo-15 yrs	119/312 (38%)	129/286 (45%)	4/71 (6%)	42%	94%	98%	17%

* Classified according to WHO criteria.
† Criteria for positivity modified to ten petechiae within the square.

1 Kalayanarooj S, *et al*. *J Infect Dis* 1997;176:313-21.

2 Kalayanarooj S, *et al*. *Dengue Bull* 1999;23:1-7.

3 Phuong CXT, et al. *Trop Med Int Health* 2002;7:125-32.

Deen JL, *et al*. *Lancet* 2006;368:170-3.

Early Diagnosis of DF/DHF*

Acute febrile illness with	% Sensitivity	% Specificity	% PPV
⊕ TT or WBC <5,000/mm^3	90	50-60	60-70
⊕ TT and WBC <5,000/mm^3	74	85	83
⊕ TT and** WBC <5,000/mm^3	53.3	76.3	72.7

* Kalayanarooj S,*et al*. *Dengue Bulletin* 1999;23:1-9.
** DF, Sawadivorn S, *et al*. *Dengue Bulletin* 2001;25:56-64.

2. The DenCo study

Clear distinction between dengue and severe dengue under the following criteria:

Severe dengue

Severe dengue is defined by either one of the following:

1. Severe plasma leakage
- Clinical shock
- Any evidence of fluid accumulation with respiratory distress

2. Severe bleeding as evaluated by clinician

3. Severe organ involvement
- Severe liver involvement with AST >= 1000 or ALT >= 1000
- Impaired consciousness with GCS < 15 or BCS < 5

3. An expert consensus: a series of global meetings

The current classification (DF, DHF, DSS) is not clearly correlated with disease severity

The classification according to severity is not intended to guide medical therapy and case management, treatment guidelines taking into account the warning signs need to be developed

Statement:

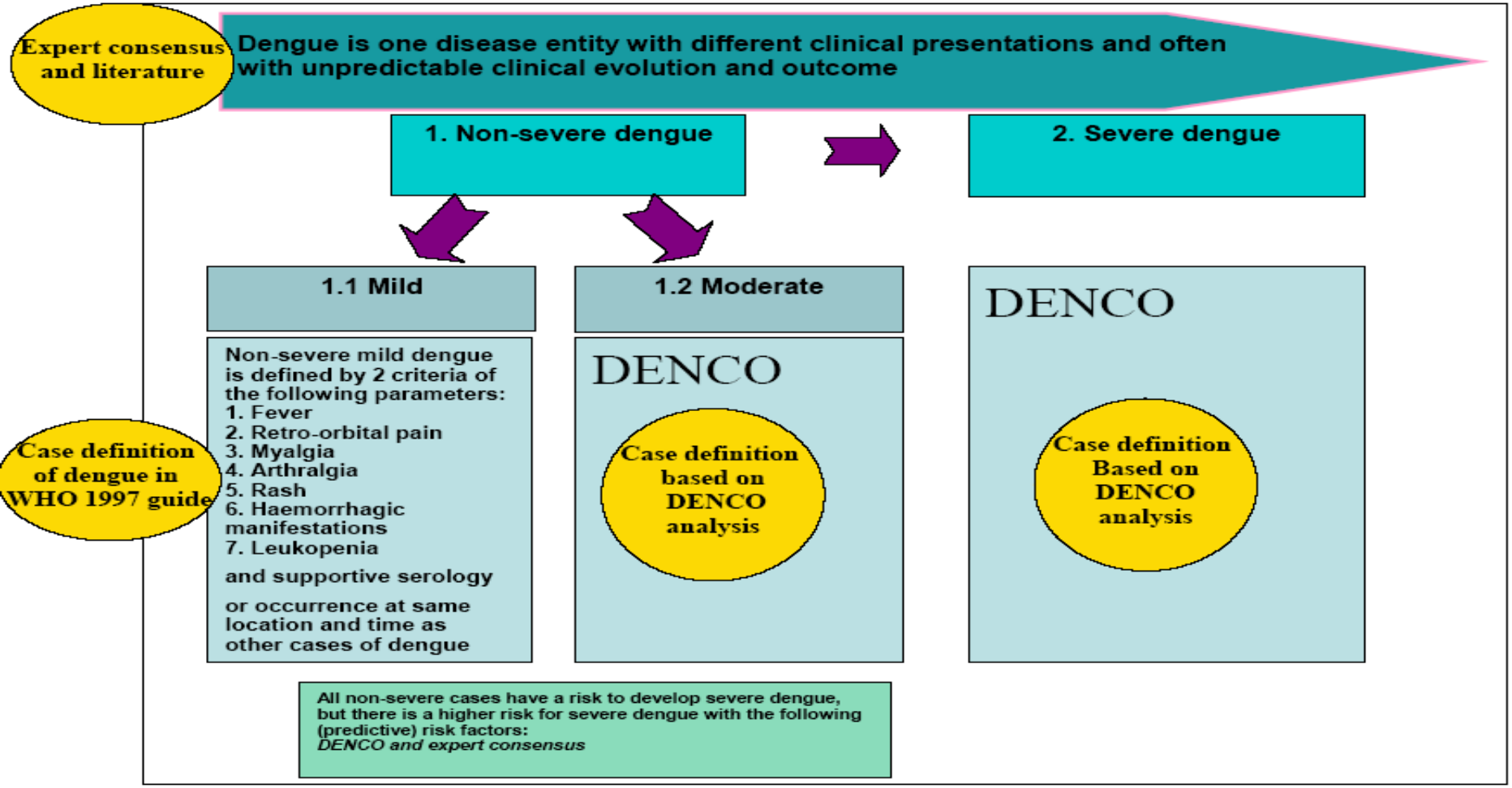
Dengue is just one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome

Observation:

surprising to see consistency across continents

3. Merging the elements

Dengue case classification: sources of evidence



New developments in case 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

WHO/TDR 2009

New developments in case management

Step I: Overall assessment

I.1History, including information on symptoms, past medical and family history.

I.2 Physical examination, including full physical and mental assessment.

I.3 Investigation, including routine laboratory and dengue specific laboratory

Step II: Diagnosis, assessment of disease phase and severity

Step III: Management

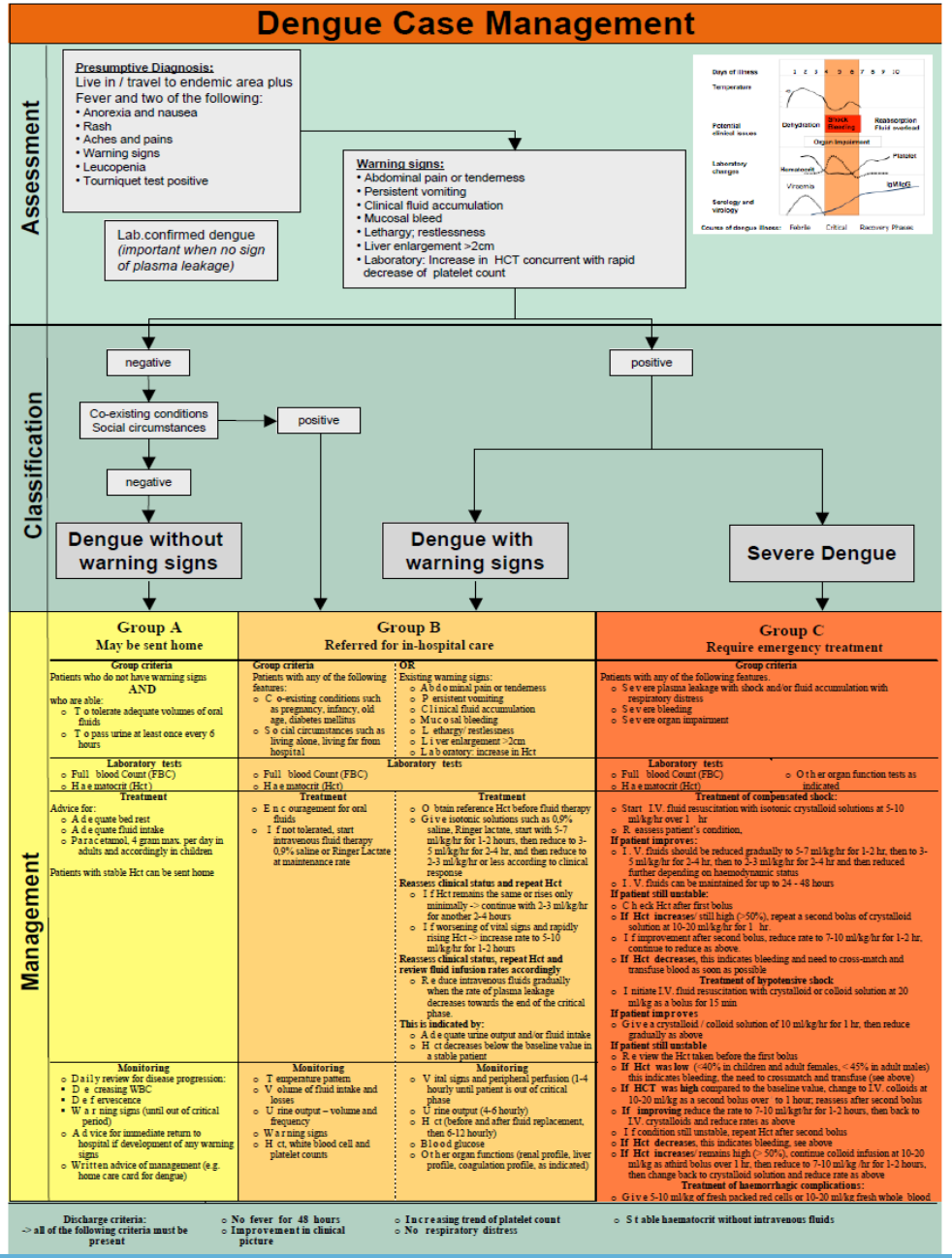
III.1Disease notification

III.2Management decisions: depending on the clinical manifestations and other circumstances, patients may:

- be sent home (Group A),
- be referred for in-hospital management (Group B)
- require emergency treatment and urgent referral (Group C)

New developments in case management

And adding the experiences of other studies and products of research: an algorithm for triage and case management



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

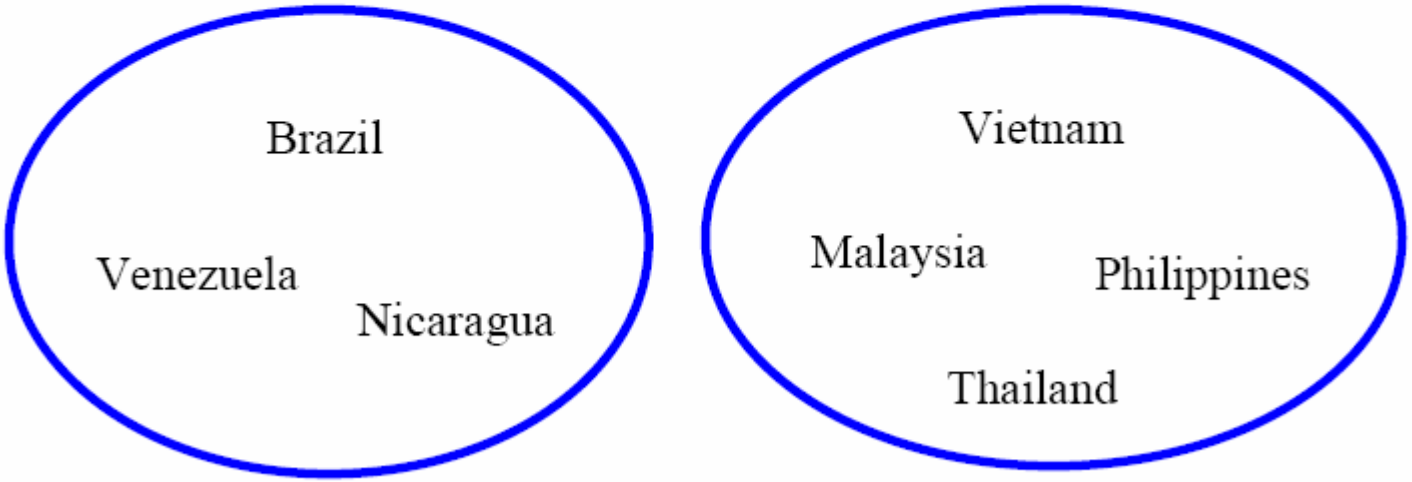
World Health Organization

DENCO clinical study: partners involved

IPK, Cuba

Heidelberg, Germany

TDR, WHO



L America

SE Asia

DENCO Hypotheses

- Hypothesis 1: Clinical epidemiology and symptomatology of dengue infection differ by country and/or region.

- Hypothesis 2: The modified case classification will be able to correctly identify clinically severe cases that would not qualify for severe illness (DHF or DSS) with the case classification currently in use.

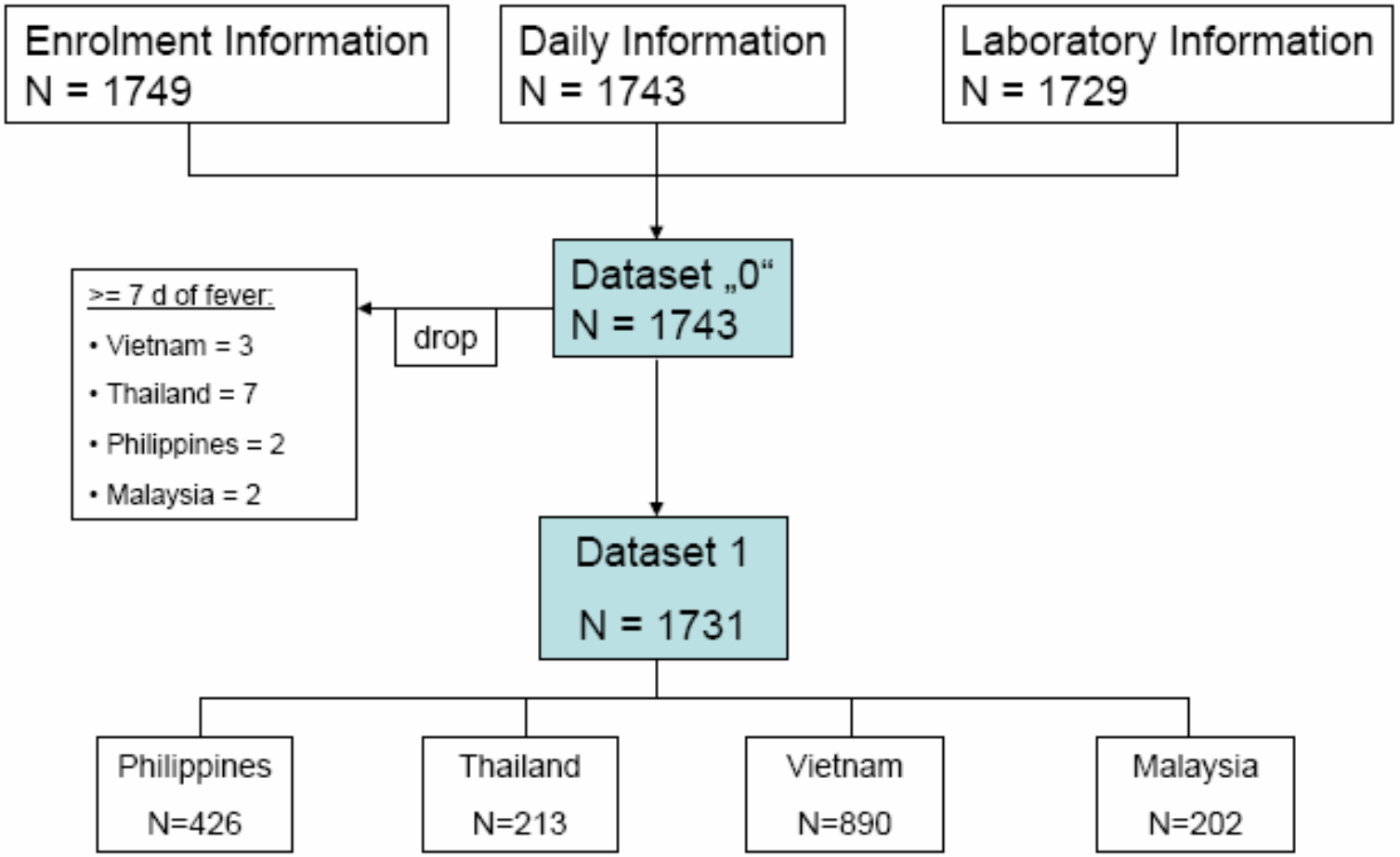
Current state

- ★ Recruitment between August 2006 and May 2007
- ★ 1743 patients in SE Asia
- ★ 525 patients in Latin America
- ★ Data analysis ongoing

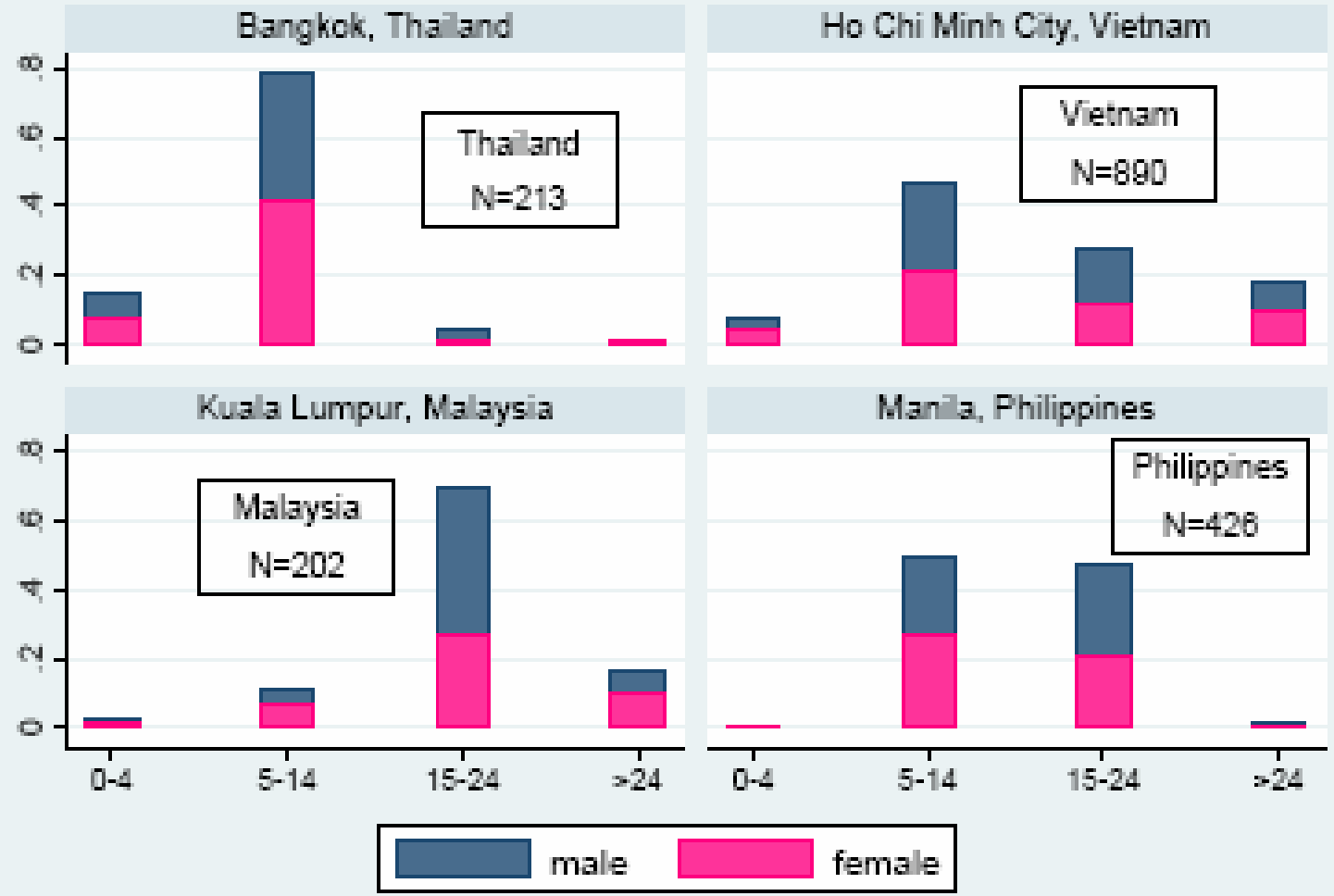
DENCO-Methods

- ★ Prospective hospital based multicentre study-local centres of excellence
- ★ Broad spectrum of patients, recruited early and followed daily with a detailed case report form
- ★ Hct and platelets to be done at least daily
- ★ Other tests (e.g. liver & renal function) done at least twice during acute illness
- ★ X-ray and/or ultrasound on hospitalized patients within 24 g of defervescence
- ★ WHO trained monitoring according to GCP

DENCO: SE-Asia Data



Age groups by country (N=1731)



Plan of Analysis

1. Classification of our patients according to the current WHO classification
2. Developing a revised classification of severity with the help of the clinicians' evaluation of the patients-represented in the medical interventions.
3. Compare 1 and 2 according to sensitivity and specificity

Why are we doing this?

Better representation of disease severity as perceived by clinicians-useful for improved triage of patients

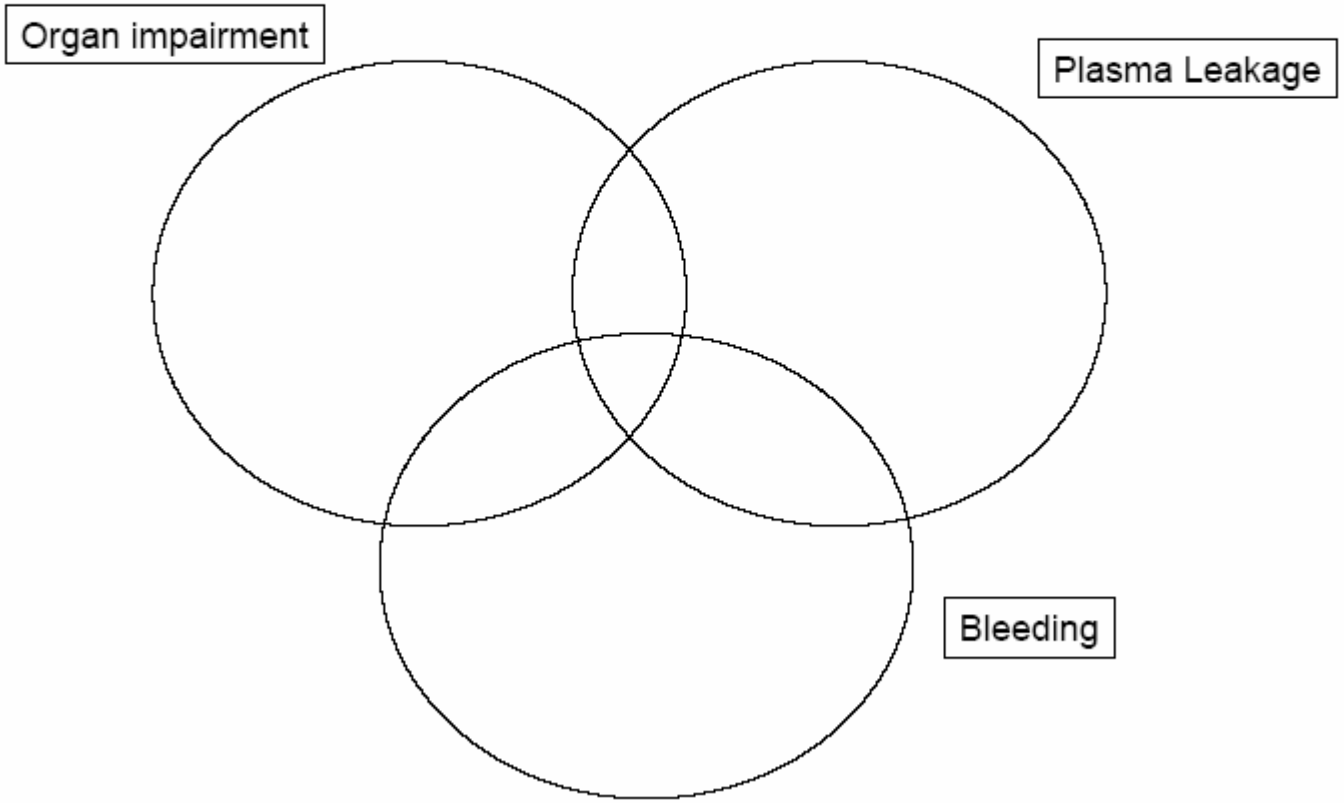
★ Identification & validation of warning signs
★ Pathogenesis studies

Vaccine/intervention studies: outcomes to be prevented

Empirically based outcome:
-Mild
-Moderate
-Severe Dengue

Standardized surveillance

Is it possible to describe Denge according to clinical syndromes?



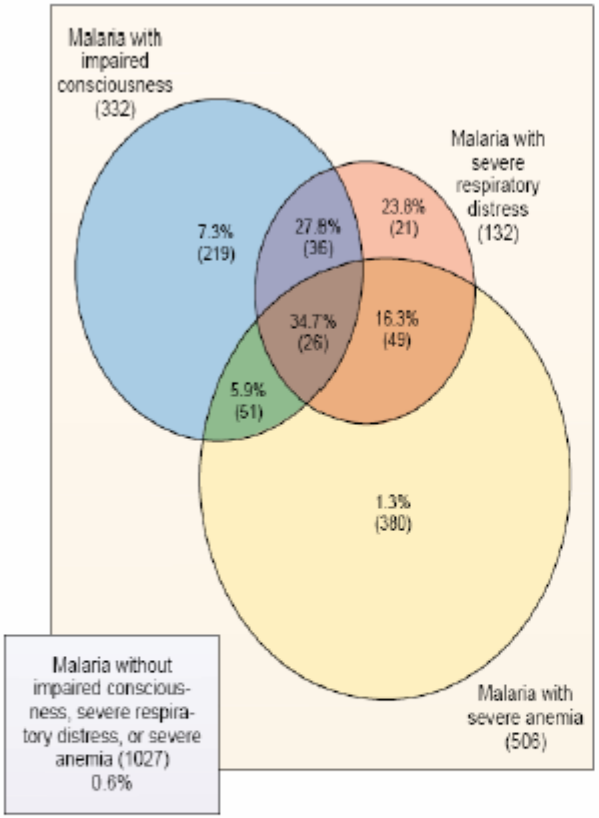


Figure 1. Prevalence, Overlap, and Mortality for Major Clinical Subgroups of Severe Malaria.

Total numbers are given in parentheses, and mortality is given as a percentage. Slight discrepancies between totals in the figure and in the text are due to missing values, as indicated in Table 1. Thus, 26 children did not have their hemoglobin concentrations recorded on admission; of these, 1 had severe respiratory distress and 4 had disturbed consciousness. Two children for whom hemoglobin concentrations were recorded did not have the severity of their respiratory distress recorded.

Example Malaria

Source: Marsh et al., NEJM, 1995, 332, vol. 21, 1399-401

Dengue case classification by severity

Dengue ± warning signs

Severe dengue

Criteria for dengue ± warning signs

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(important when no sign of plasma leakage)

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** 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

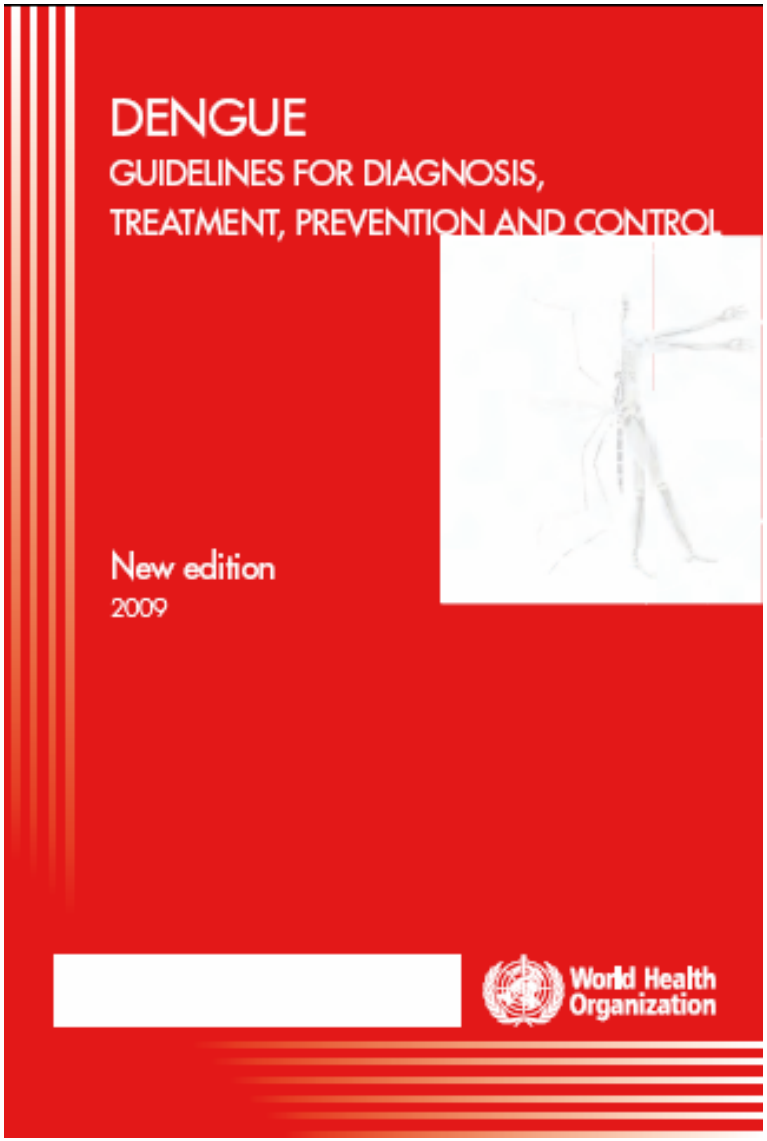
3. Severe organ involvement
- Liver: AST or ALT>=1000
- CNS: Impaired consciousness
- Heart and other organs

WHO/TDR 2009

The third edition of the WHO dengue guidelines are not an attempt to divide the world, but practical guidelines with evidence based recommendations and best practice advice

The third edition of the WHO dengue guideline

- ★ *Publication August 2009*
- ★ *3000 English and 2000 Spanish hardcopies*
- ★ *Webversion*
- ★ *Dissemination at appropriate conferences to target dengue experts and programme managers*



http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf

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
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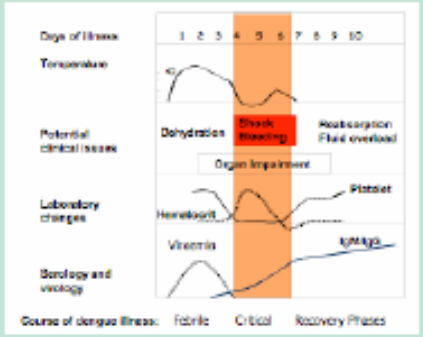

Classification

negative

Co-existing conditions
Social circumstances

positive

negative

Dengue without warning signs

positive

Dengue with warning signs

Severe Dengue

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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)

Group B
Referred for in-hospital care

Group criteria	OR
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	**Existing warning signs:** • Abdominal pain or tenderness • Persistent vomiting • Clinical fluid accumulation • Mucosal bleeding • Lethargy/restlessness • Liver enlargement >2 cm • 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	• Obtain reference Hct before fluid therapy • Give isotonic solutions such as 0,9% saline, Ringer lactate, start with 5-7 ml/kg/hr for 1-2 hr, then reduce to 3-5 ml/kg/hr for 2-4 hr, and then reduce to 2-3 ml/kg/hr or less according to clinical response

Group B (2)
Referred for in-hospital care

Treatment

Reassess clinical status and repeat Hct

- If Hct remains the same or rises only minimally -> continue with 2-3 ml/kg/hr for another 2-4 hr
- If worsening of vital signs and rapidly rising Hct -> increase rate to 5-10 ml/kg/hr for 1-2 hr

Reassess clinical status, repeat Hct and review fluid infusion rates accordingly

- Reduce intravenous fluids gradually when the rate of plasma leakage decreases towards the end for the critical phase

This is indicated by:

- Adequate urine output and/or fluid intake
- Hct decreases below the baseline value in a stable patient

Monitoring

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

- 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)

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 hr

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 m/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

Group C (2)
Require emergency treatment

Treatment of compensated 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 ½ 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 third 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

Welcome to Thailand in October 2011 for the 9th International Congress of Tropical Pediatrics

Theme

“Global Partnerships & Networking for Child Health”