



Dengue

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UNCLASSIFIED



Case Presentation

- 18 year old native from Thailand (moved to US at 10 years of age) presents in August with 2 days of illness including fever, headache, bone pain, and nausea 3 days after returning from a vacation in Puerto Rico. He vacationed in San Juan, stayed in a hotel, ate and drank local foods and beverages from the hotel and restaurants, and swam in the hotel pool and ocean. He does not recall mosquito exposure and did not reliably use DEET. He had no animal exposures. He has no past medical history except for a single STI. He takes no medications to include those acquired OTC. He does not abuse ETOH nor use illicit drugs.
- The LEAST likely diagnosis would be:
 - 1. chikungunya
 - 2. dengue
 - 3. leptospirosis
 - 4. acute HIV



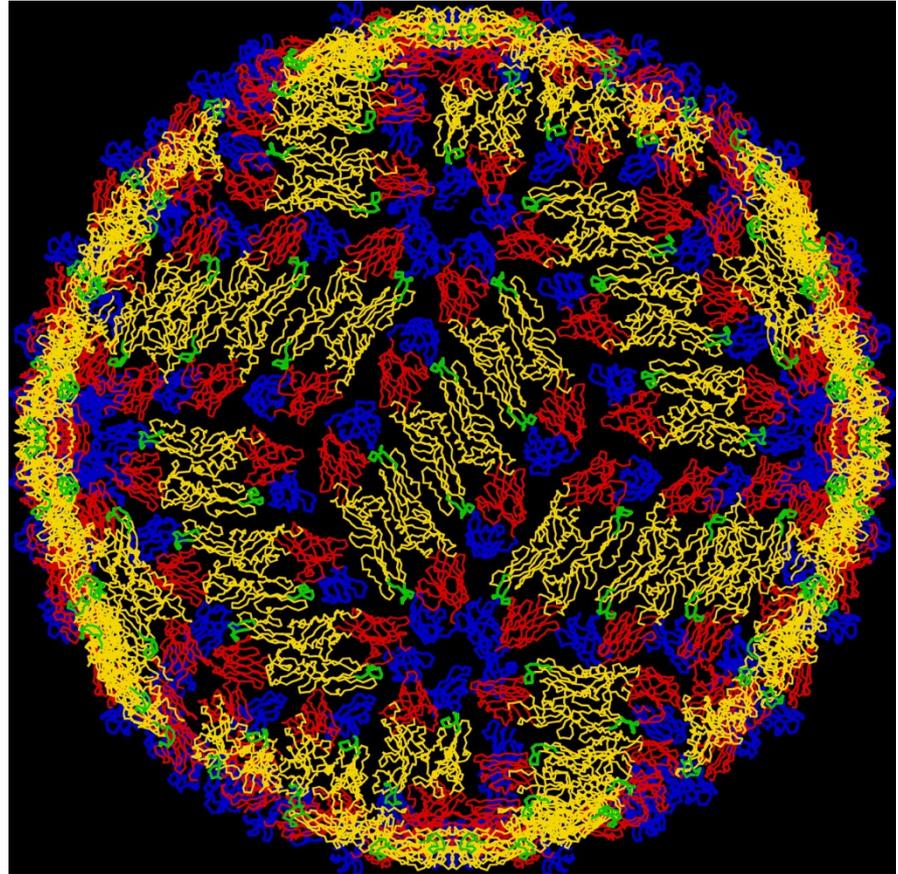
Lecture Objectives

1. Attendees will understand the **global distribution** of dengue virus circulation and disease.
2. Attendees will understand the spectrum of **dengue clinical phenotypes** and the clinical and laboratory findings and parameters which distinguish mild from severe forms of the disease.
3. Attendees will understand the nuances of **treating dengue** and best management practices.
4. Attendees will become familiar with **countermeasure development** efforts.



Lecture Outline

- Basics
- Epidemiology
- Clinical Phenotypes
- Pathophysiology
- Diagnostics
- Treatment
- Vaccine Development



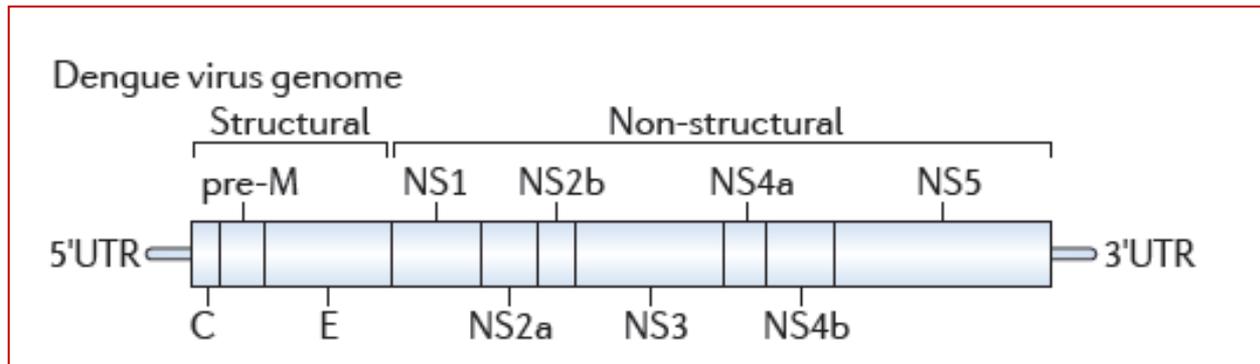
Kuhn, R., Purdue University



Dengue

- Basics

- Family Flaviviridae, Genus Flavivirus, Species Dengue
 - Same family as WNV, YF, JE, Zika
- RNA virus, 3 structural and 7 non-structural genes
 - Different functions during infection process
 - Different targets for drugs/vaccines



- 4 dengue virus types: DENV-1-4
 - Multiple genotypes within each dengue virus type



Is dengue a threat to the blood supply?

Transfusion Medicine, 2009, 19, 66–77

D. Teo,*¹ L. C. Ng†¹ & S. Lam* *Blood Services Group, Health Sciences Authority, and †Environmental Health Institute, National Environment Agency, Singapore

• Transmission

- Feeding vector
- Laboratory acquired
- Blood supply?
- Organ donation?

• Vector

- *Aedes aegypti*
- *Aedes albopictus*



Table 3. Dengue and donor deferral

Country	Donor deferral measures for dengue
Singapore*	6 months deferral for history of dengue infection 3 weeks deferral for history of fever No travel-related deferral for dengue
Hong Kong*	6 months deferral for history of dengue infection 2 weeks deferral for history of fever No travel-related deferral for dengue
Sri Lanka*	No specific deferral for history of dengue infection 2 weeks deferral for history of fever No travel-related deferral for dengue
Australia†	4 weeks deferral for history of dengue infection No travel-related deferral for dengue
New Zealand‡	4 weeks deferral for history of dengue infection No travel-related deferral for dengue
UK‡	2 weeks deferral for history of dengue infection No travel-related deferral for dengue
United States‡	4 weeks deferral for history of dengue infection No travel-related deferral for dengue

*Endemic for dengue.

†Non-endemic except parts of Northern Australia.

‡Non-endemic.

Dengue Epidemiology



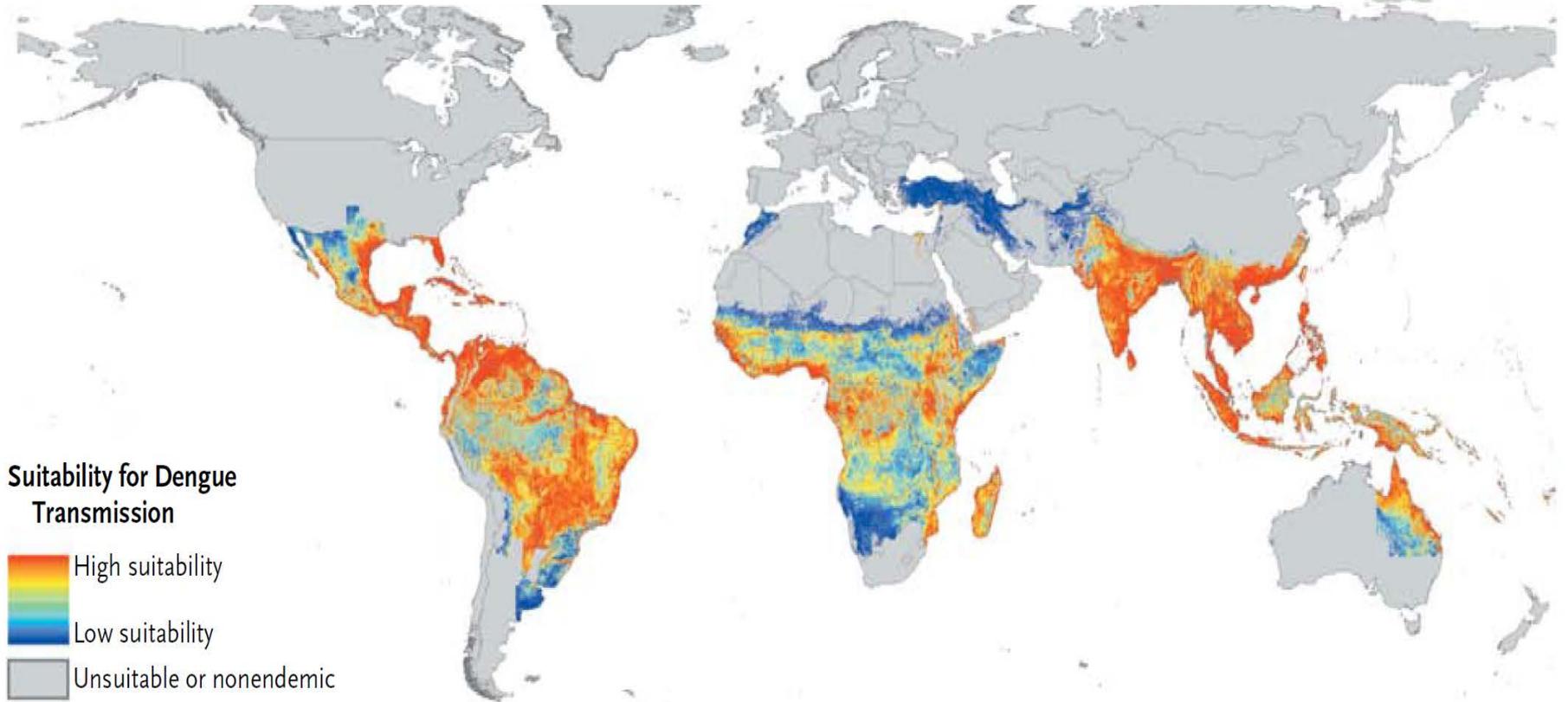
Dengue Ward: QSNICH, Bangkok, Thailand (Photo: Christopher Brown, IHT)



Dengue

N Engl J Med 2012;366:1423-32.

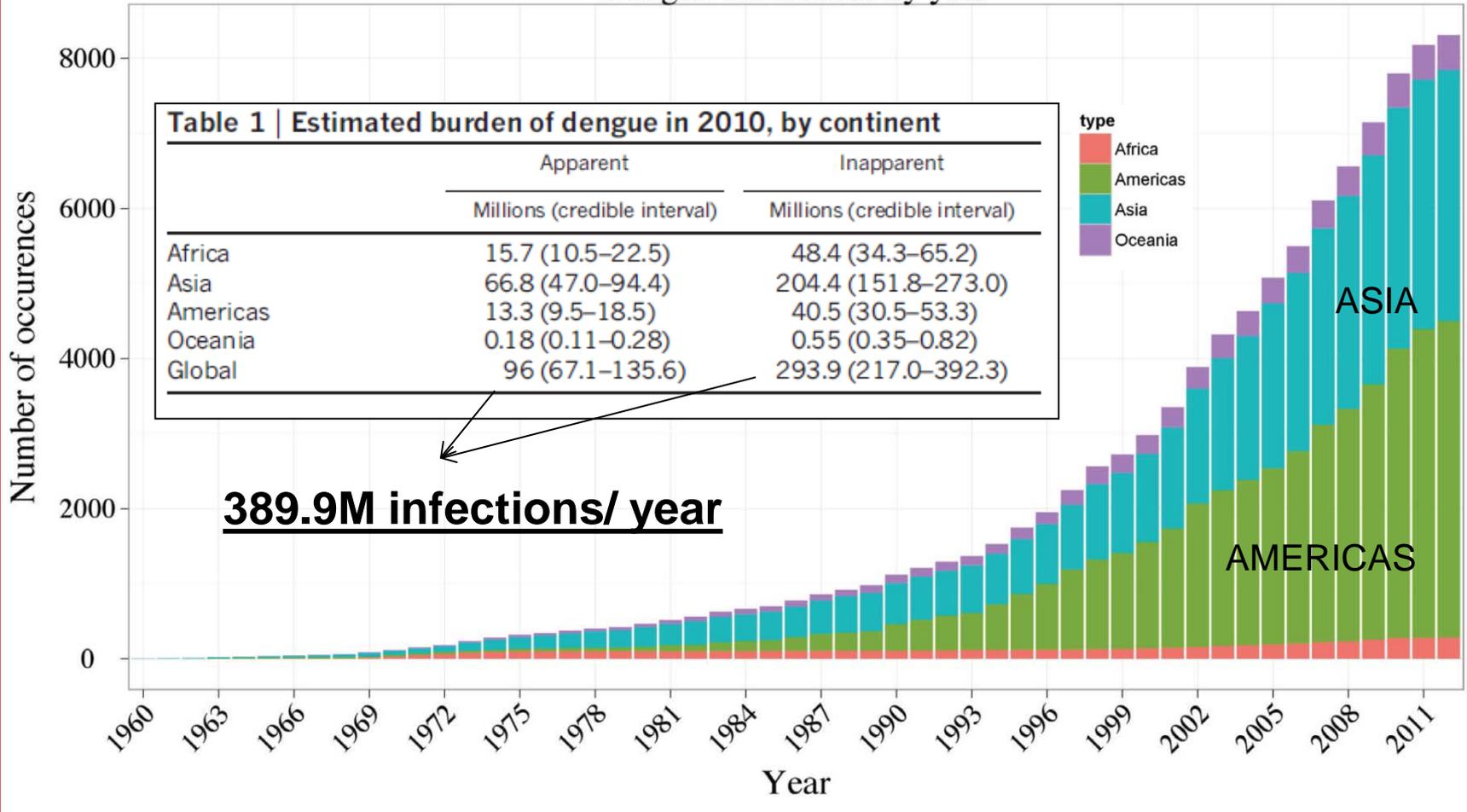
Areas supporting dengue virus transmission.



Dengue Burden

Under-estimated and under-reported

Dengue occurrences by year

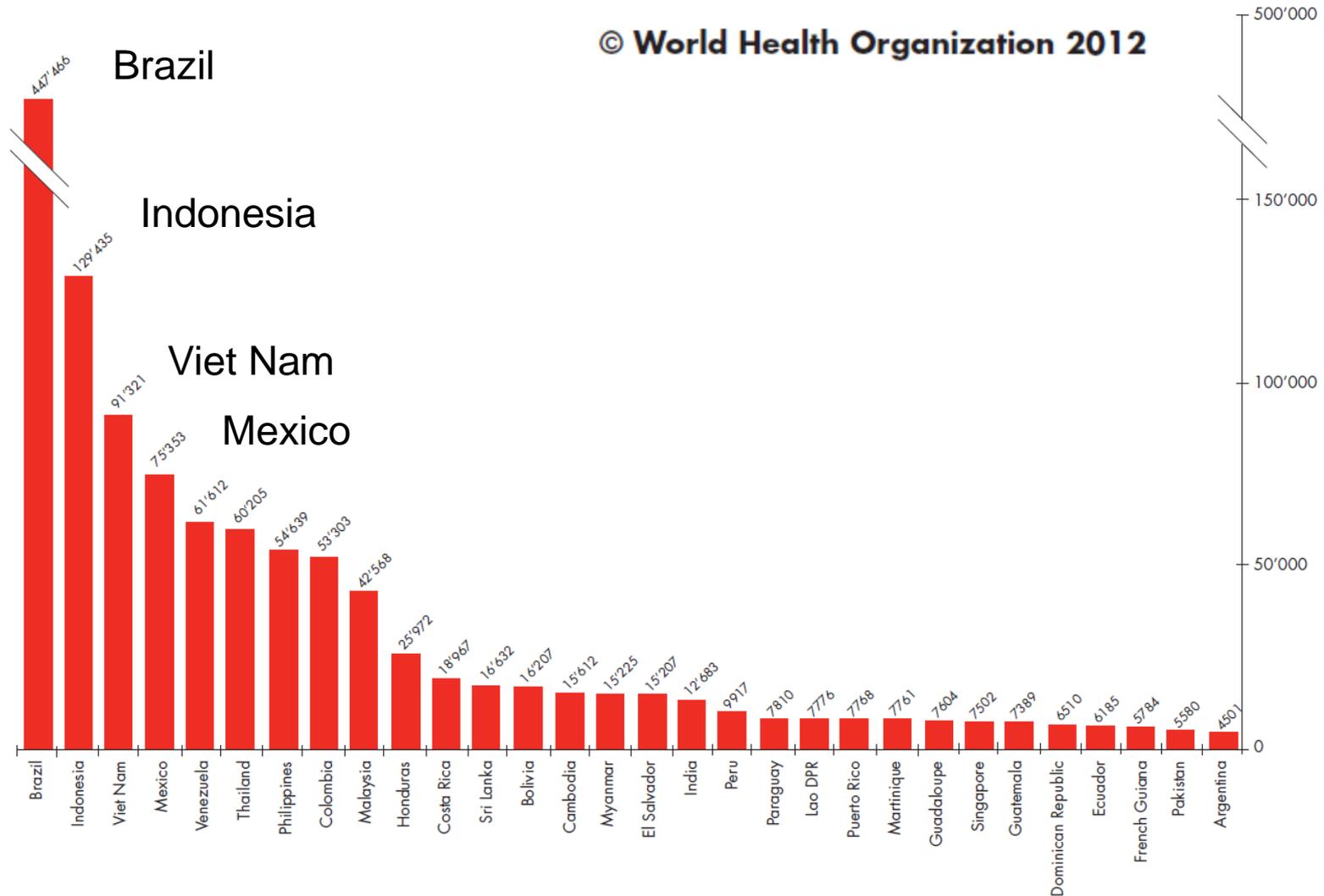


Bhatt et al., Nature. 2013 Apr 7.

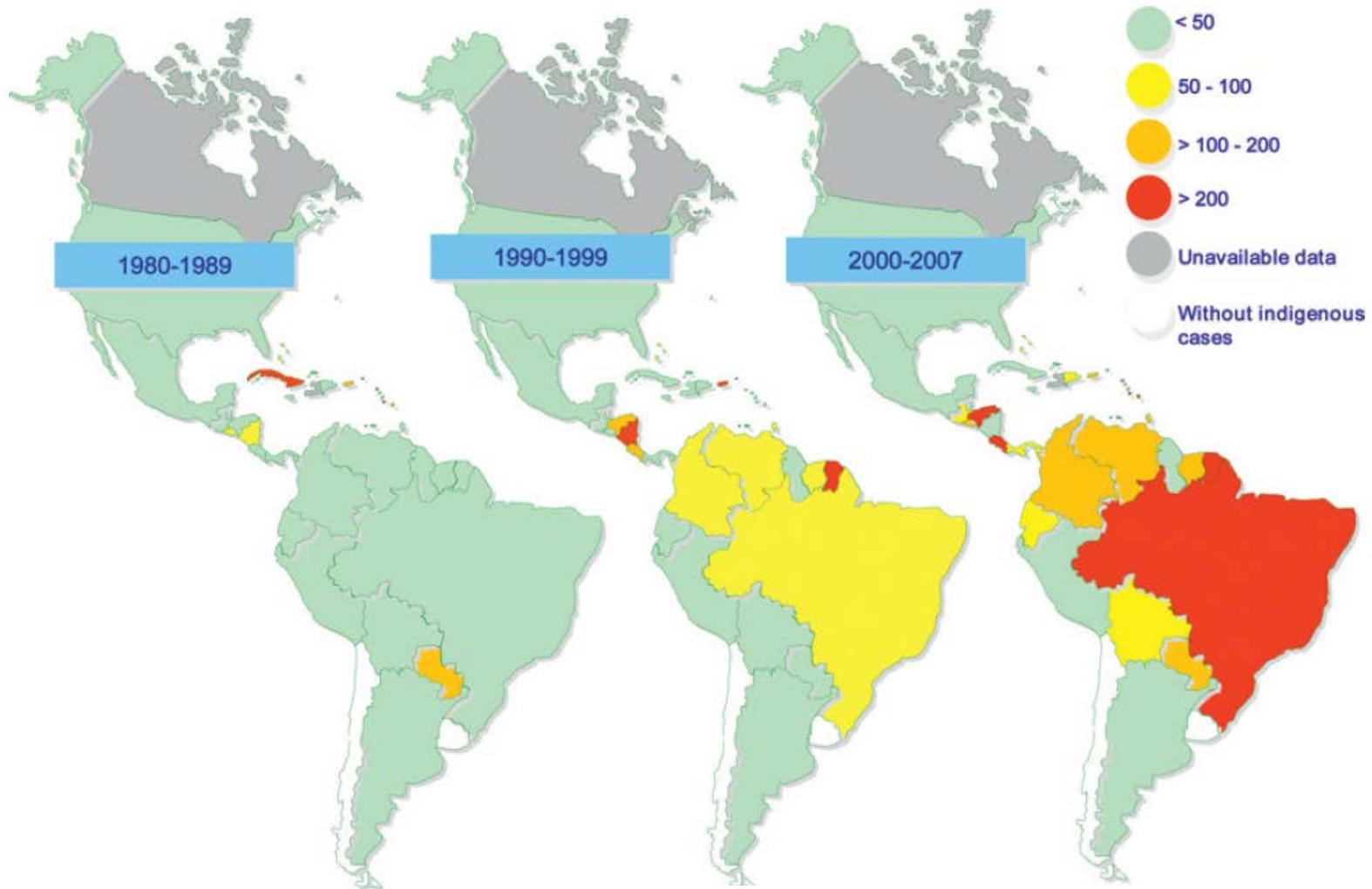


GLOBAL STRATEGY FOR DENGUE PREVENTION AND CONTROL

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



Average dengue incidence per 100,000 by country, Region of the Americas, 1980–2007.



Am. J. Trop. Med. Hyg., 82(1), 2010, pp. 128–135





PUBLIC HEALTH 127 (2013) 11-17

Middle East Pakistan

Table 1 – Confirmed cases and deaths from 2006 to 2011 in the affected areas of Pakistan.

Year	Khyber Pakhtunkhwa		Sindh				Punjab			
	Cases	Deaths	All parts		Karachi		All parts		Lahore	
			Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
2006 ^a	31	1	1500	50	1500	50	800	1	400	0
2007 ^a	0	0	950	22	950	20	258	0	258	0
2008 ^a	30	4	585	6	585	6	1450	20	1358	9
2009 ^a	100	7	550	7	550	7	300	2	300	2
2010 ^b	0	0	5000	35	4500	16	4000	3	4000	3
2011 ^b	296	8	952	18	755	15	21,314	337	17,493	290

a Data collected from National Institute of Health Islamabad.

b Data collected from provincial health departments.



Africa

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 8, August 2011

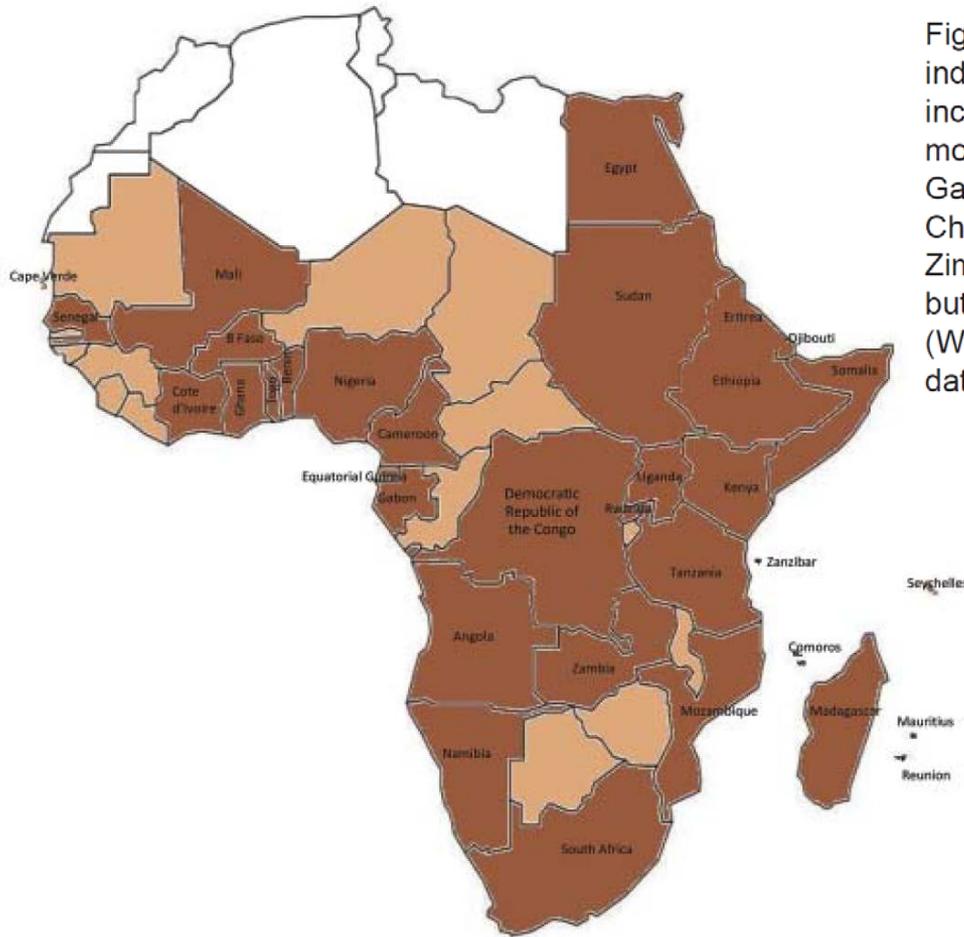


Figure. Dengue and *Aedes aegypti* mosquitoes in Africa. Brown indicates 34 countries in which dengue has been reported, including dengue reported only in travelers, and *Ae. aegypti* mosquitoes. Light brown indicates 13 countries (Mauritania, The Gambia, Guinea-Bissau, Guinea, Sierra Leone, Liberia, Niger, Chad, Central African Republic, Republic of the Congo, Malawi, Zimbabwe, and Botswana) in which dengue has not been reported but that have *Ae. aegypti* mosquitoes. White indicates 5 countries (Western Sahara, Morocco, Algeria, Tunisia, and Libya) for which data for dengue and *Ae. aegypti* mosquitoes are not available.

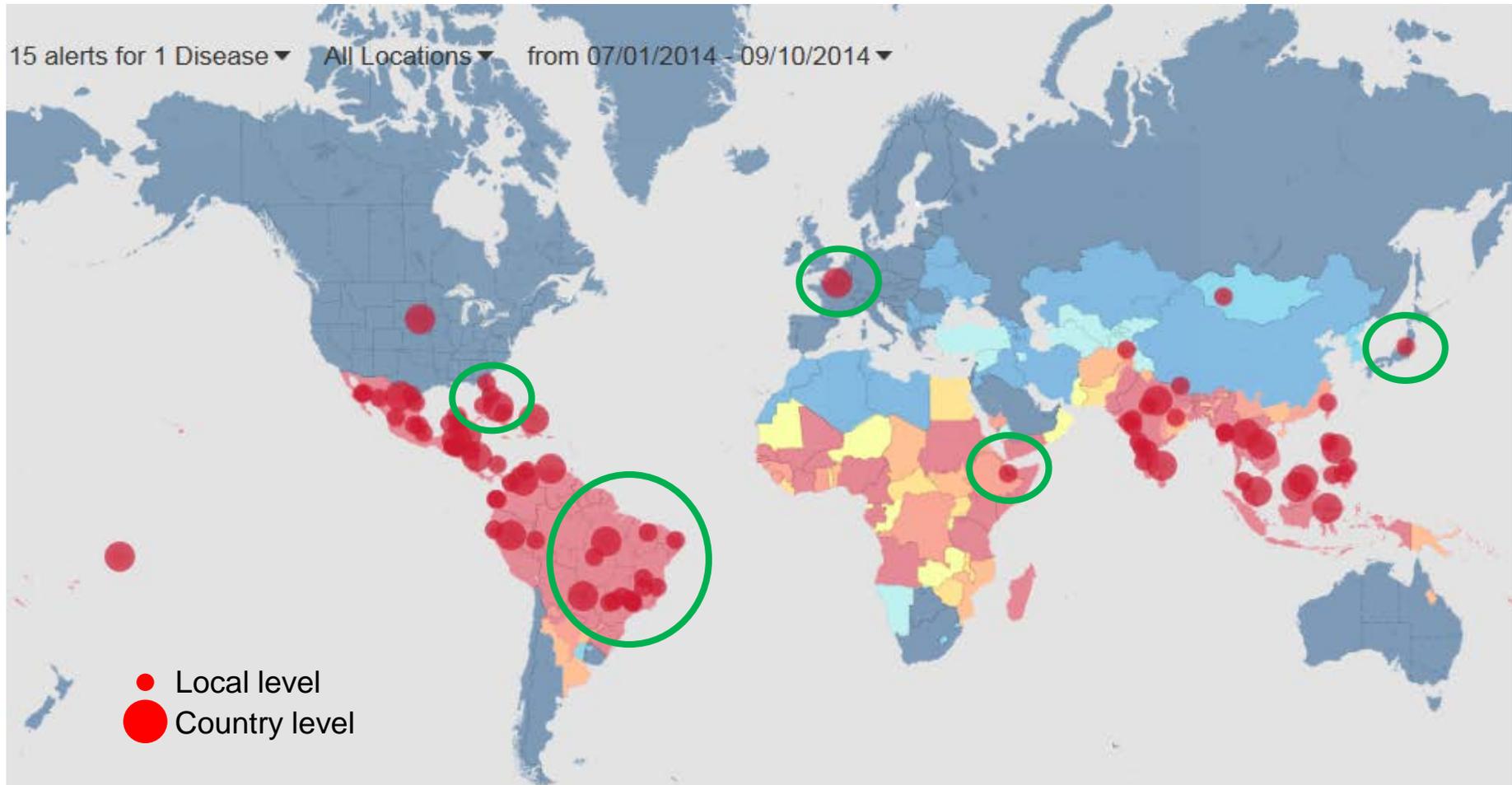
Brown – dengue reported

Light Brown – dengue not reported but vector exists

White – data not available



CDC Dengue Map – 1 JUL – 10 SEP 2014



Reporting sources – WHO, MOHs, ProMed, GeoSentinel, EuroSurveillance, World Org



High financial and human cost

Economic Impact of Dengue Illness in the Americas

Donald S. Shepard,* Laurent Coudeville, Yara A. Halasa, Betzana Zambrano, and Gustavo H. Dayan
Brandeis University, Waltham, Massachusetts; Sanofi Pasteur, Lyon, France; Sanofi Pasteur, Swiftwater, Pennsylvania

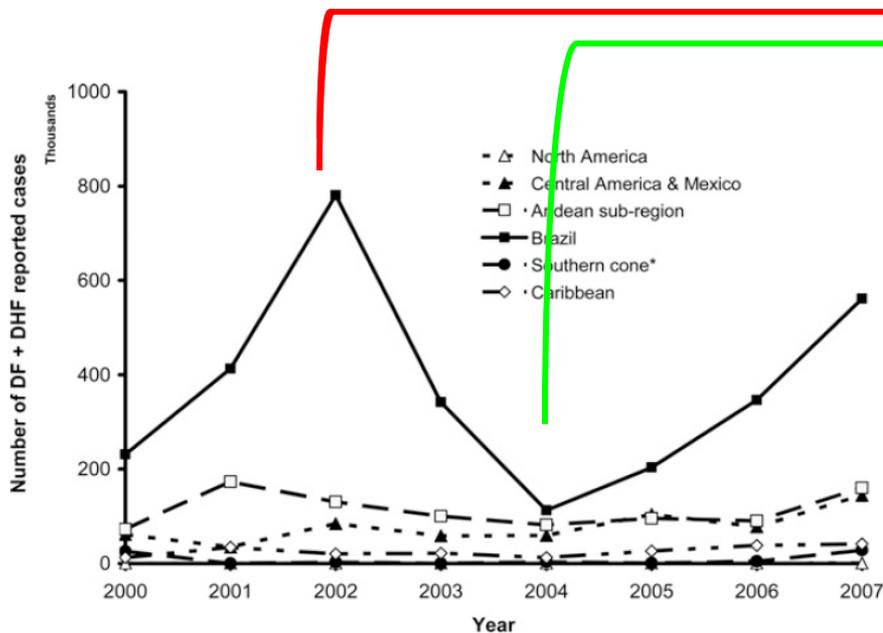


FIGURE 1. Number of dengue reported cases in the Americas from 2000 to 2007.

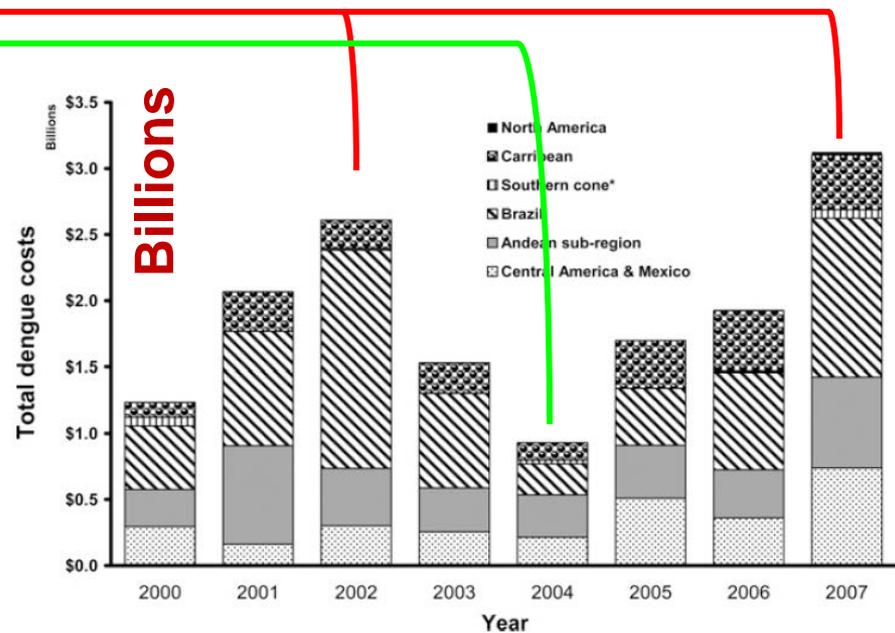
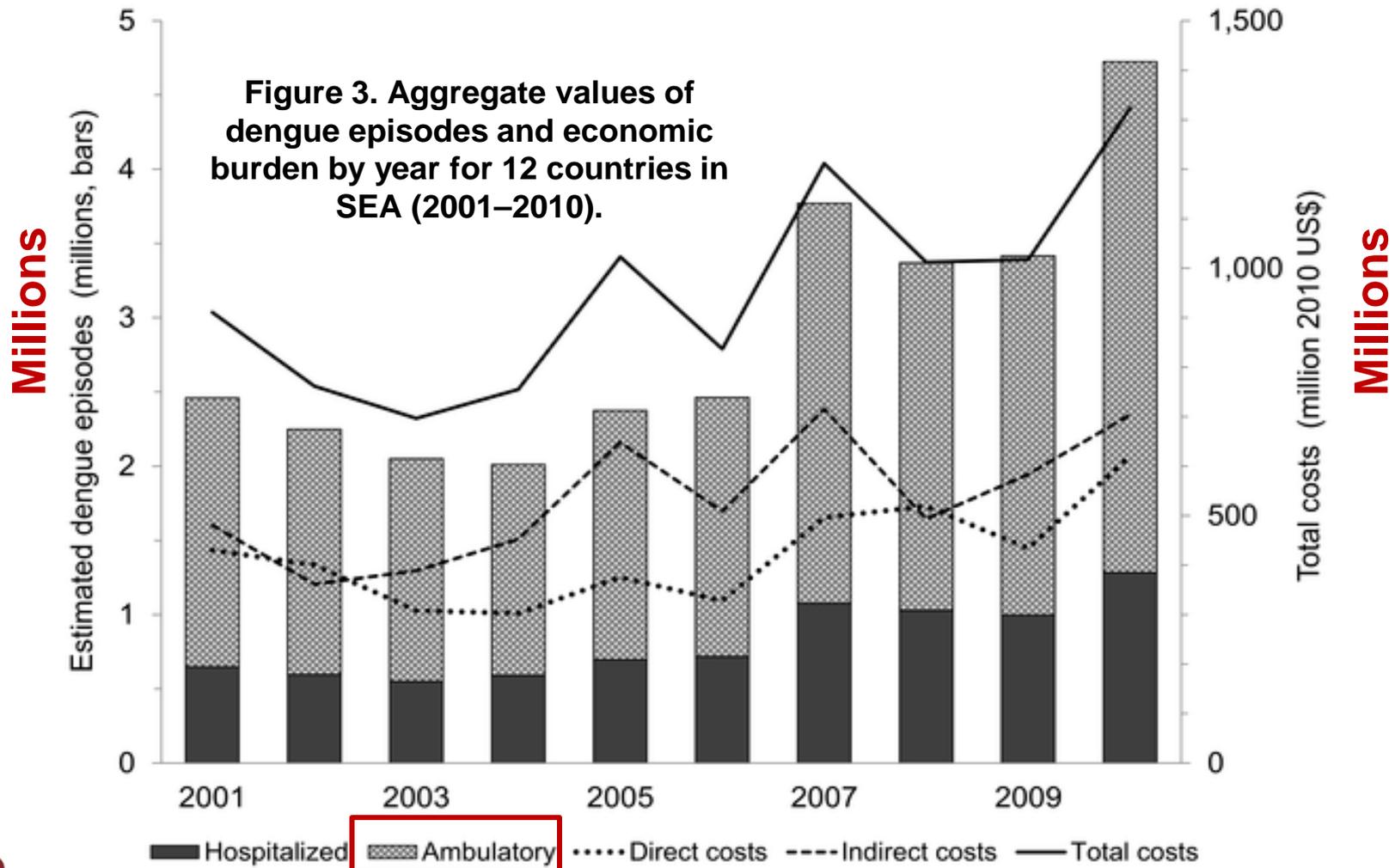


FIGURE 3. Annual economic burden in the Americas from 2000 to 2007 (in 2010 US\$).



Economic and Disease Burden of Dengue in Southeast Asia

Shepard DS, Undurraga EA, Halasa YA (2013) PLoS Negl Trop Dis 7(2): e2055.

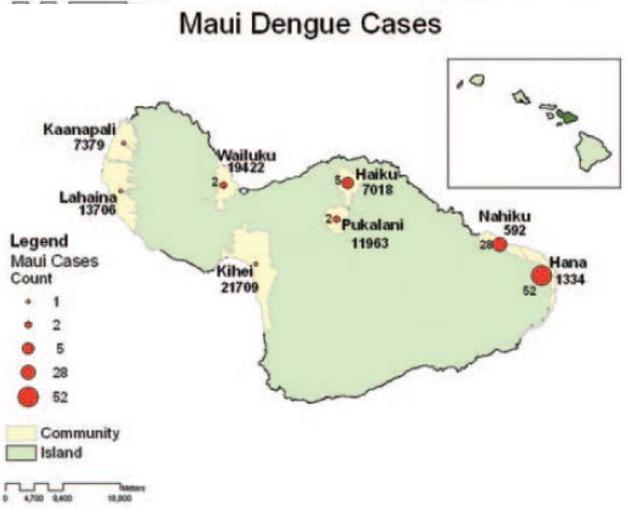
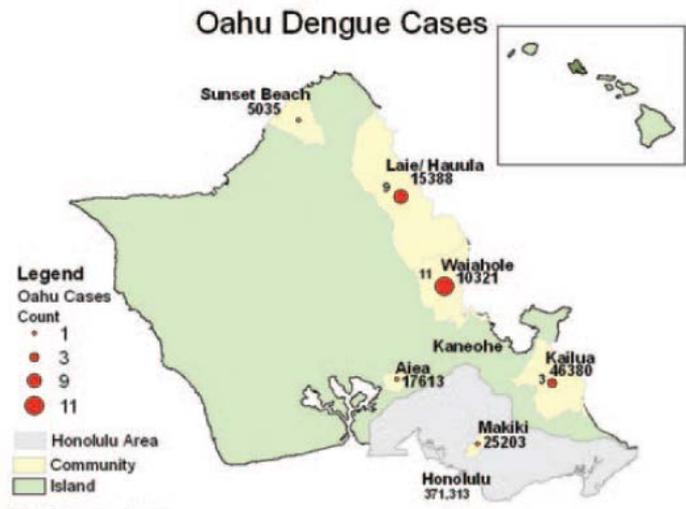
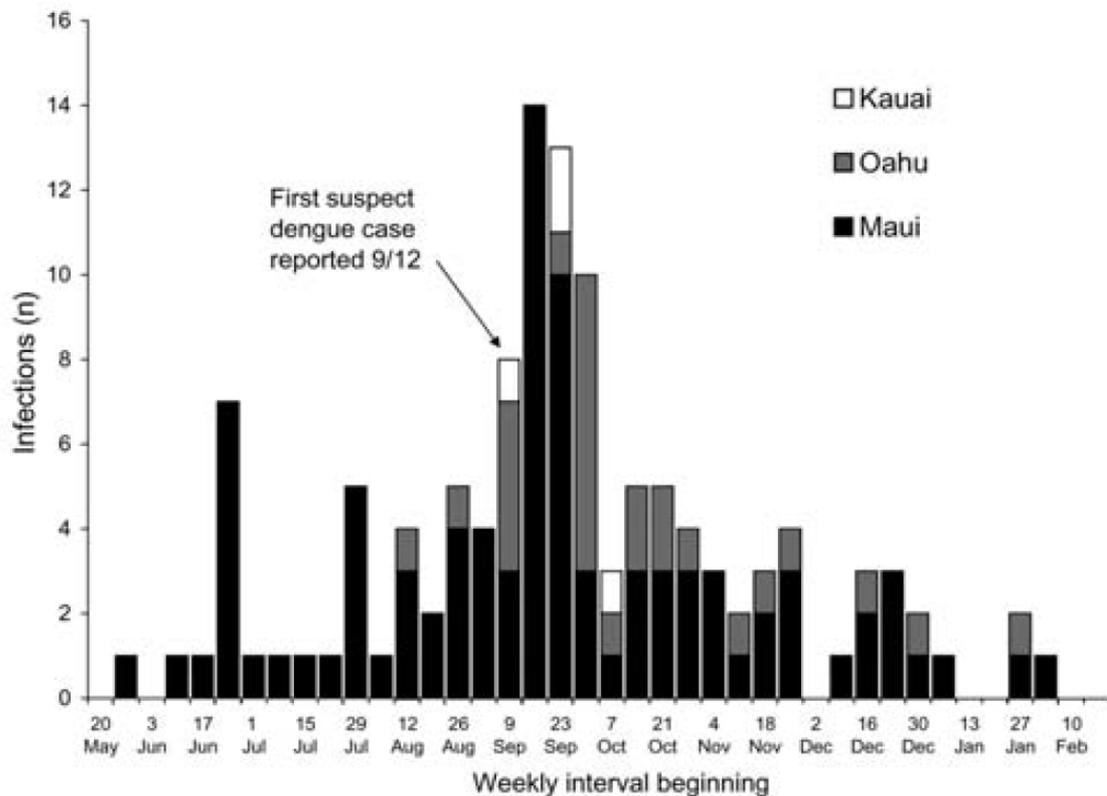


United States

Dengue Fever, Hawaii, 2001–2002

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 11, No. 5, May 2005

Paul V. Effler,* Lorrin Pang,* Paul Kitsutani,† Vance Vorndam,† Michele Nakata,* Tracy Ayers,*
 Joe Elm,* Tammy Tom,* Paul Reiter,† José G. Rigau-Perez,† John M. Hayes,† Kristin Mills,*
 Mike Napier,‡ Gary G. Clark,† and Duane J. Gubler*
 for the Hawaii Dengue Outbreak Investigation Team¹



United States

Identification of Dengue Fever Cases in Houston, Texas, with Evidence of Autochthonous Transmission Between 2003 and 2005

VECTOR-BORNE AND ZOOONOTIC DISEASES
Volume 13, Number 0, 2013
© Mary Ann Liebert, Inc.
DOI: 10.1089/vbz.2013.1413

Am. J. Trop. Med. Hyg., 59(1), 1998, pp. 95–99

DENGUE SURVEILLANCE IN TEXAS, 1995

JULIE A. RAWLINGS, KATHERINE A. HENDRICKS, CHRISTINE R. BURGESS, RICHARD M. CAMPMAN,
GARY G. CLARK, LAURA J. TABONY, AND MARY ANN PATTERSON

*Infectious Disease Epidemiology and Surveillance Division and Bureau of Laboratories, Texas Department of Health, Austin,
Texas; Dengue Branch, Centers for Disease Control and Prevention, San Juan, Puerto, Rico*

Dengue Hemorrhagic Fever --- U.S.-Mexico Border, 2005

MMWR[™]

Weekly

August 10, 2007 / 56(31);785-789

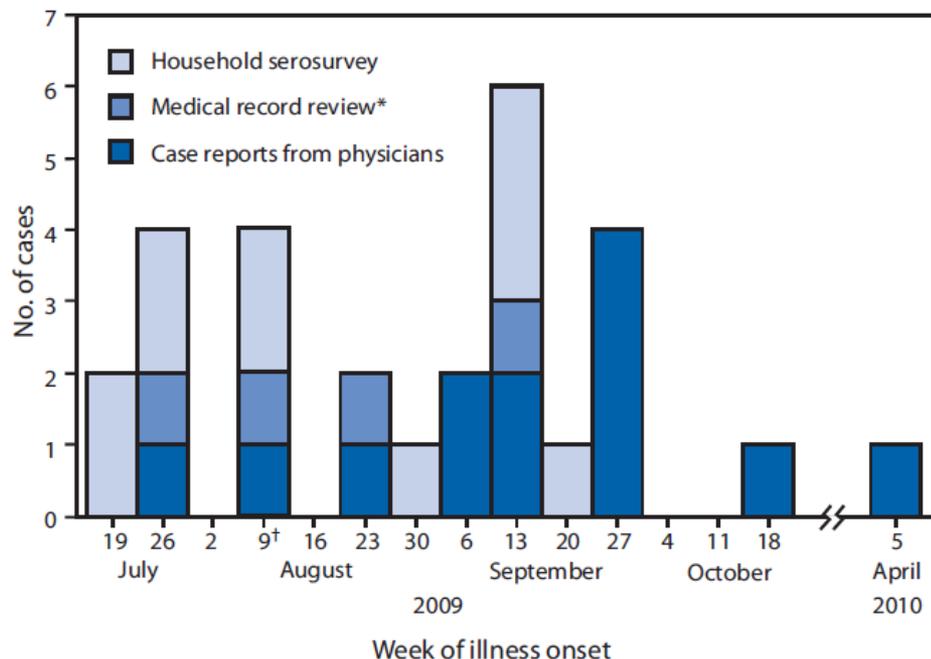
Am. J. Trop. Med. Hyg., 78(3), 2008, pp. 364–369

Epidemic Dengue and Dengue Hemorrhagic Fever at the Texas–Mexico Border:
Results of a Household-based Seroepidemiologic Survey, December 2005



Locally Acquired Dengue — Key West, Florida, 2009–2010

FIGURE. Number of locally acquired dengue cases (N = 28), by week of illness onset and method of identification — Key West, Florida, 2009–2010



* Two cases identified in both household serosurvey and medical record review are shown as record review cases.

† Week of illness onset in index patient.

TABLE. Characteristics of patients (N = 28) with locally acquired dengue — Key West, Florida, 2009–2010

Characteristic	No.	(%)*
Sex		
Male	19	(68)
Female	9	(32)
Age group (yrs)		
<20	1	(4)
21–40	11	(39)
41–60	11	(39)
>60	5	(18)
Race		
White	24	(86)
Black	3	(11)
Asian/Pacific Islander	1	(4)
Ethnicity		
Non-Hispanic	25	(89)
Hispanic	3	(11)
Symptoms		
Fever	28	(100)
Headache	22	(79)
Myalgia	23	(82)
Arthralgia	18	(64)
Eye pain	14	(50)
Rash	15	(54)
Bleeding	6	(21)

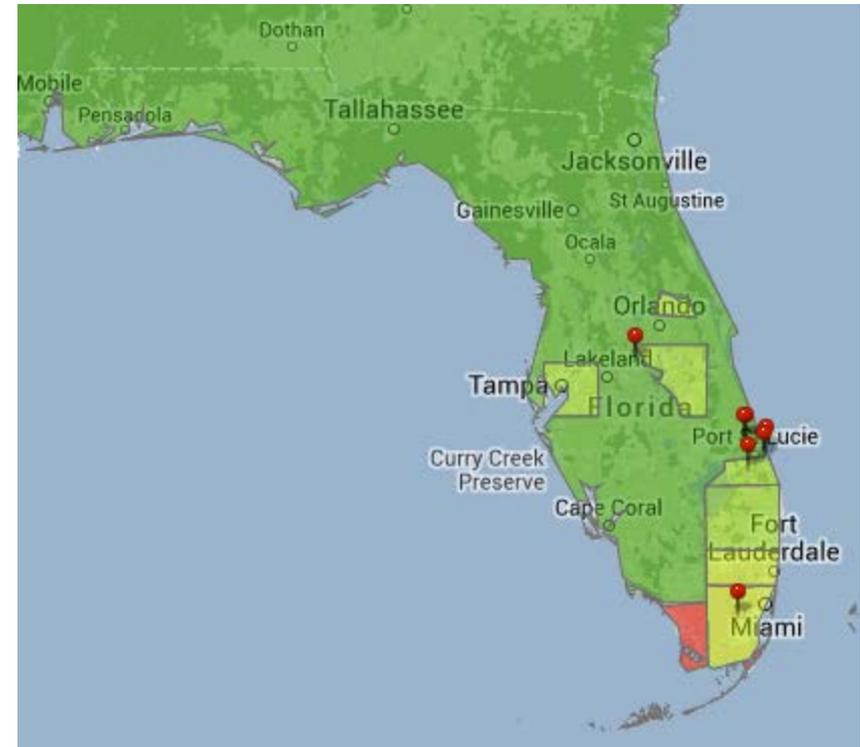
* Percentages might not add to 100% because of rounding.



Florida 2013

- Locally Acquired Dengue as of SEP 2013:
 - 22 cases
 - 20 residents, 2 out of state
 - Martin (21) and Miami-Dade (1)
- Imported (traveler) Dengue 2013:
 - 88 cases imported into Florida
- 69 / 110 cases serotyped by PCR

Serotype	# of cases
DENV-1	50
DENV-2	1
DENV-3	3
DENV-4	16
2013 total	69



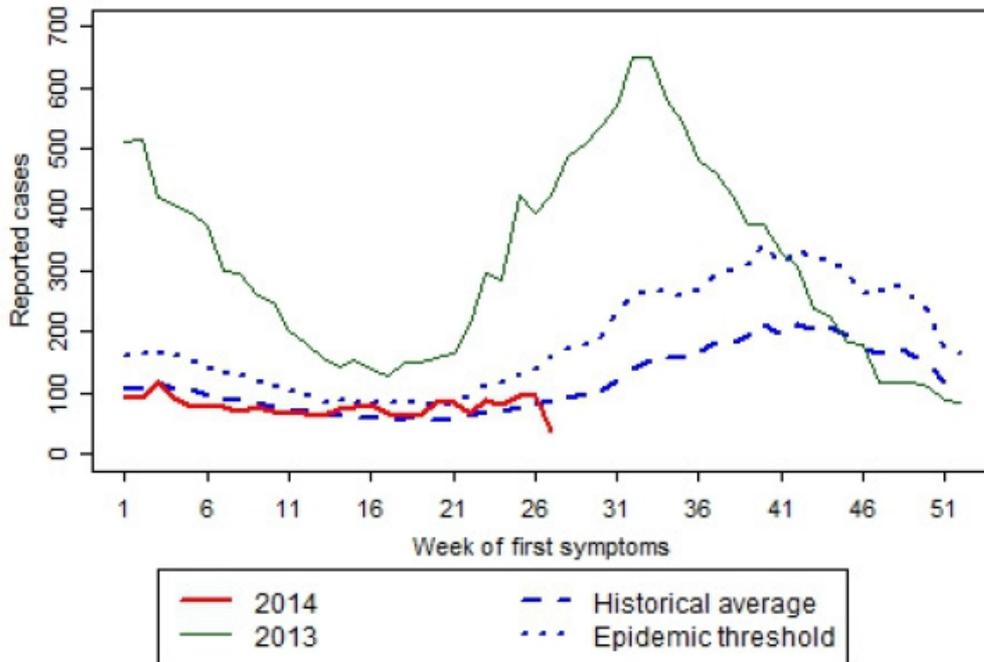
CDC Dengue Map, 15 OCT 2013

References: 5) Florida Dept. of Health Website 6) *Florida Arbovirus Surveillance: Week 36 September 2013*

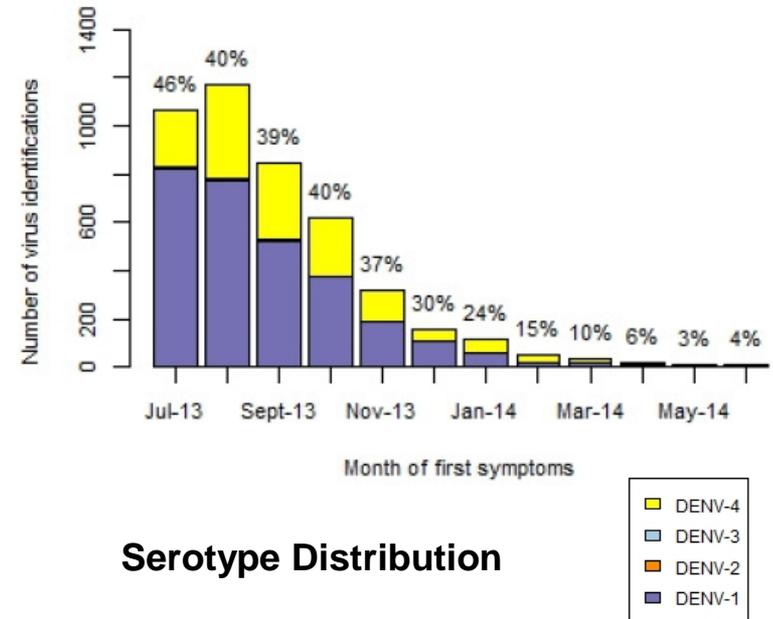


Puerto Rico

Suspected cases reported compared to the historical average



Total viral identifications in the last 12 months



Serotype Distribution

Totals through 29 JUL 2014: 2,468 suspected, 381 confirmed, 2 severe (DHF), 0 deaths
 Totals through 31 DEC 2013: 18,164 suspected, 9,032 confirmed, 50 severe (DHF), 12 deaths

References: 1) CDC Website 4) *Dengue Surveillance Weekly Report*, CDC, December 2013



Spectrum of Disease and Relation to Place of Exposure among Ill Returned Travelers

David O. Freedman, M.D., Leisa H. Weld, Ph.D., Phyllis E. Kozarsky, M.D., Tamara Fisk, M.D.,* Rachel Robins, M.D., Frank von Sonnenburg, M.D., Jay S. Keystone, M.D., Prativa Pandey, M.D., and Martin S. Cetron, M.D., for the GeoSentinel Surveillance Network†

Table 3. Etiologic Diagnoses within Selected Syndrome Groups, According to Travel Region.*

Syndrome and Cause	All Regions	Caribbean	Central America	South America	Sub-Saharan Africa	South Central Asia	Southeast Asia	Other or Multiple Regions†
			number of cases per 1000 patients with syndrome					
Systemic febrile illness (n= 3907)								
Specific pathogen or cause reported‡	594	459	527	446	718	522	547	454
Malaria‡	352	65	133	133	622	139	130	234
Dengue‡	104	238	123	138	7	142	315	35
Mononucleosis (due to Epstein–Barr virus or cytomegalovirus)‡	32	70	69	79	10	17	32	63
Rickettsial infection‡	31	0	0	0	56	10	16	24
<i>Salmonella typhi</i> or <i>S. paratyphi</i> infection‡	29	22	25	17	7	141	26	24
No specific cause reported‡	406	541	473	554	282	478	453	546

‡ P<0.01 for the comparison among regions.

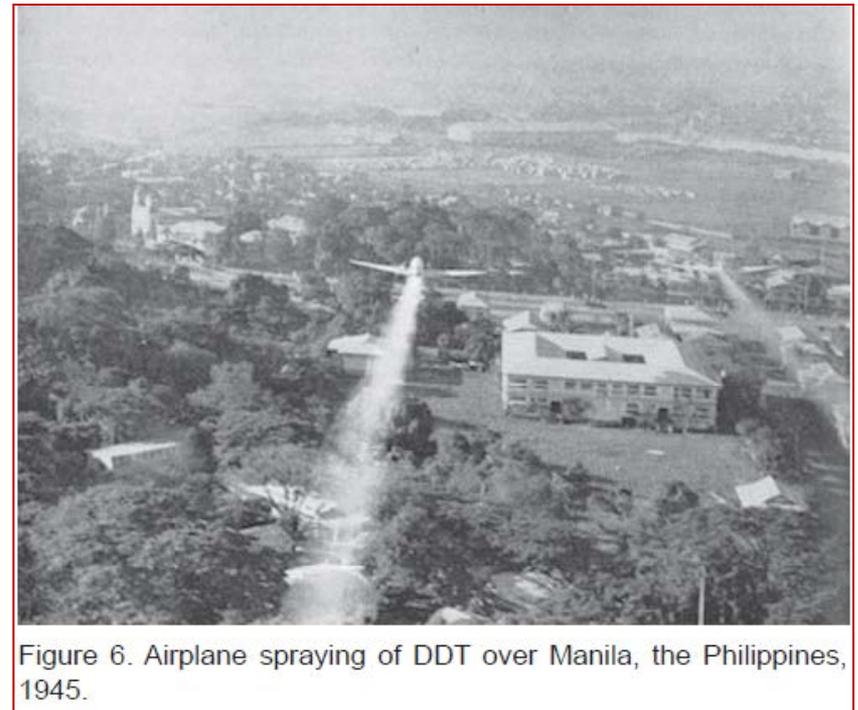
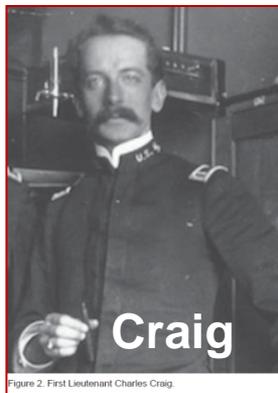
*“With respect to specific diagnoses, malaria was one of the three most frequent causes of systemic febrile illness among travelers from every region, **although travelers from every region except sub-Saharan Africa and Central America had confirmed or probable dengue more frequently than malaria.**”*



Dengue and US Military Operations - from the Spanish-American War through Today

Robert V. Gibbons, Matthew Streitz, Tatyana Babina, and Jessica R. Fried

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 18, No. 4, April 2012



Dengue Risk / Threat to DoD

- **Prevalence and Risk to Soldiers (2003-2012)**

- Total Cases: 631

- Active Duty: 177; Reserve: 35; MHS Beneficiaries: 419
- No record of attributable deaths

- Dengue Mission Impact Projections

- Not severe: hospitalized ~5-7 days, low functioning ~14-28 days
- Severe: evacuation to MTF, ICU care?, death?, LDD >1 month

- Deployment

- DODSR: 500 samples, deployed between 2006-2008
 - 11.2% seroprevalence of dengue antibody
 - 2.4% with monovalent profile (high risk with next infection)

References: *Dengue Tetravalent Vaccine CDD; +DMSS



Seroprevalence of DENV Exposure in Deployed Personnel

- DODSR, 1000 samples, first time deployers, 2008-2011
- 250 samples selected per COCOM
- Tested for presence of neutralizing antibody by microneut assay
- Overall 7.6% seroprevalence rate of past dengue exposure
- 1.5% seroconversion rate during deployment (first infection)
- Increased self report of fever during deployment in those with antibodies

Seroprevalence Based on 1,000 Post-Deployment Samples in First Time Deployers

	Central America	South America	Asia	Africa	Total
Percent	4.8%	12.4%	7.2%	6.0%	7.6%



Seroprevalence of DENV Exposure in USASOC Personnel

- USASOC and WRAIR viral disease threat characterization
- Pre- and post-deployment sample collection in deploying SOC personnel
- Tested for presence of neutralizing antibody by microneut assay
- NOV 2013: 411 pre-deployment and 7 post-deployment samples tested
 - N = 56 pre-deployment positive (13.6%)
 - N = 8 pre-deployment monovalent profiles (2.0%)
 - N = 2/7 post-deployment seroconversions (qualitative [neg to pos])
- **Summary: USASOC personnel are highly primed to dengue, a proportion are in high risk category for severe disease with secondary infection, clinical impact will likely not be documented, is this knowledge changing approach to febrile patient during deployment?**

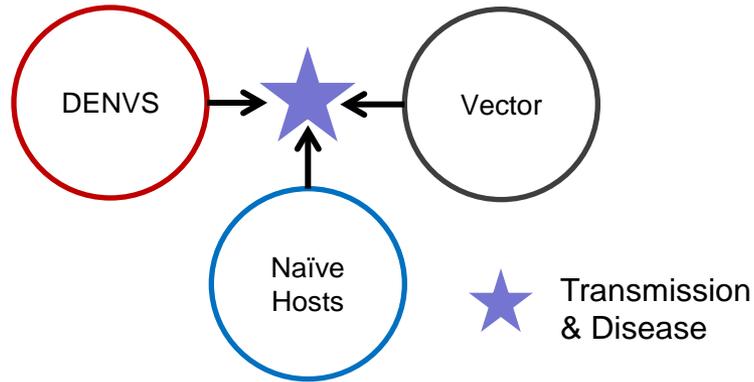


DOD Infectious Disease Threats

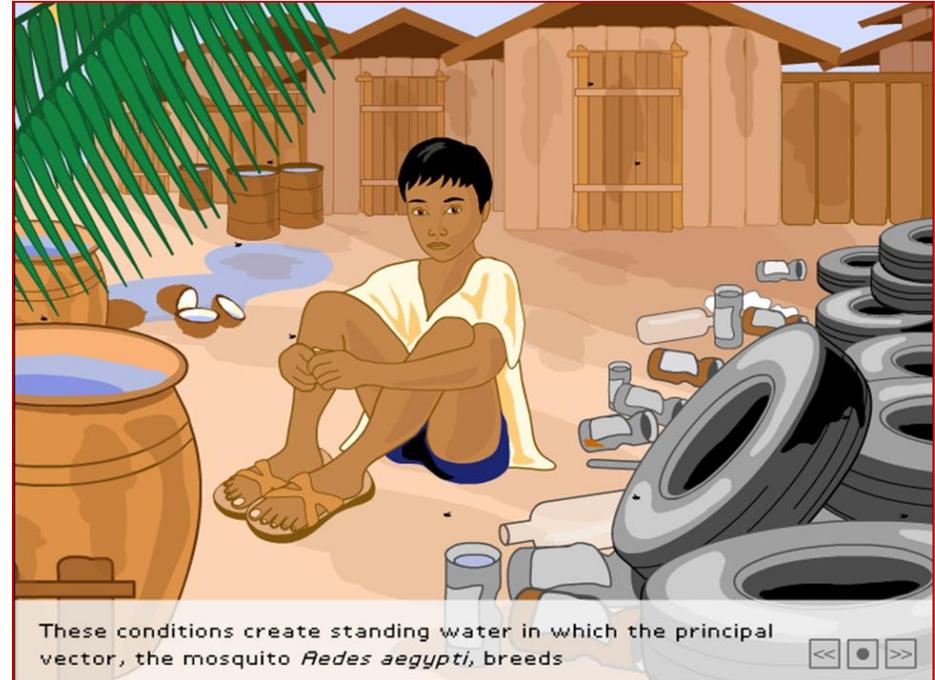
Disease	2010 COCOM panel rank	ID-IDEAL Rank
Malaria	1	2
Dengue	2	3
Diarrhea, bacterial	3	1
MDR wound pathogens	4	NA
Leishmaniasis	5	19
Q fever (Coxiella burnetti)	6	26
Norovirus / viral diarrhea	7	NA
Influenza	8	NA
Leptospirosis	10	7
Diarrhea, protozoal	11	11
TB	12	NA
CCHF	13	10
HIV	14	8
HFRS	15	17
Chikungunya	16	4
Meningococcal meningitis	17	20
Plague	18	27
Rickettsioses	19	18
Viral encephalitides	20	NA



Factors Driving Transmission



- DENVs
 - Travel in hosts
 - Viral evolution
- Naïve hosts
 - Population growth
 - Increased urbanization
- Vector
 - Ecologic changes
 - Evolution

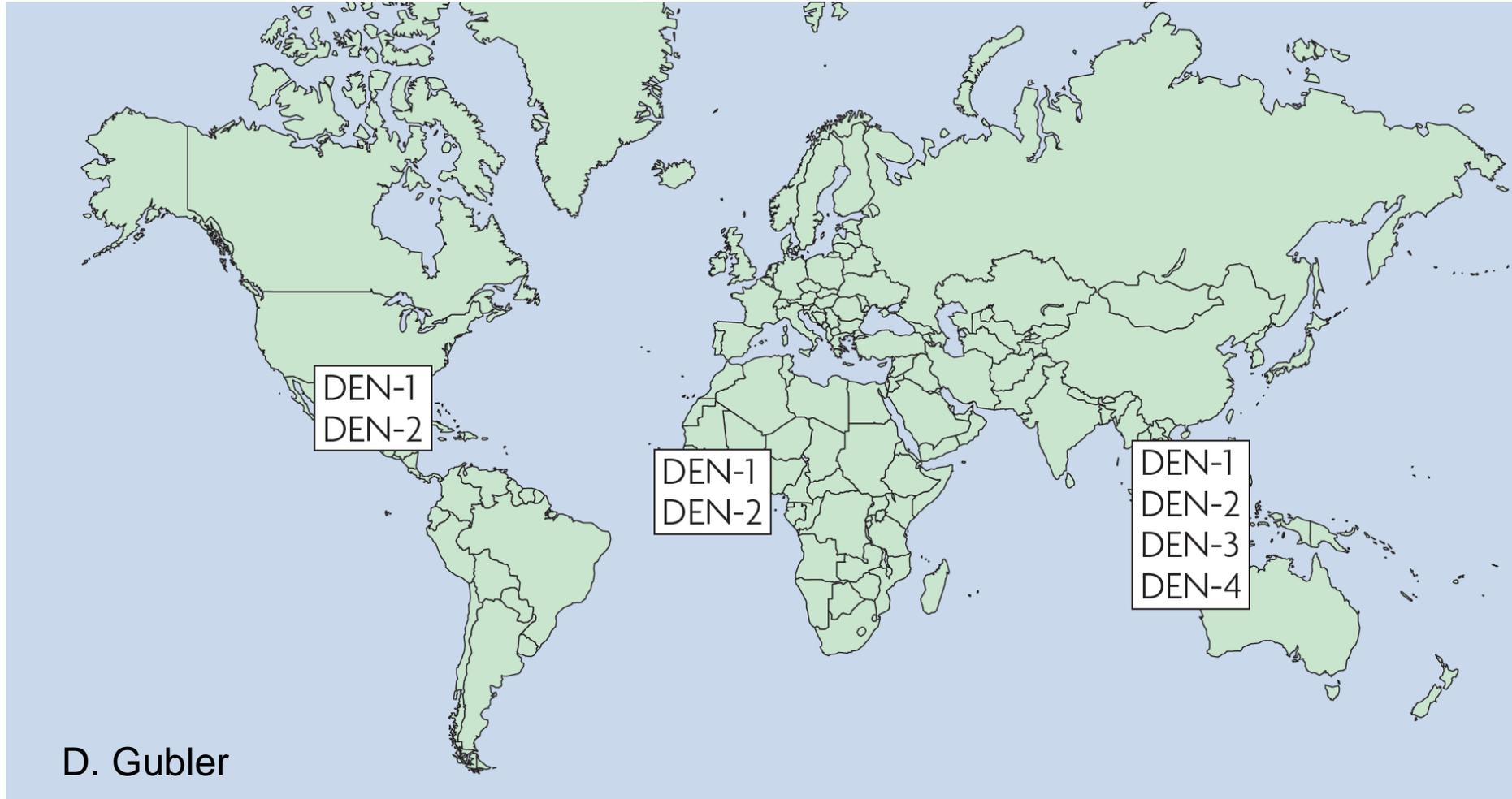


Factors Driving Disease

- There is a significantly increased risk of severe dengue disease (dengue hemorrhagic fever) when **infected a second time with a different DENV type** than what you were infected with during your first infection (i.e. DENV-4 during first infection, DENV-2 during second).
- **Co-circulation of numerous DENV types** in similar time and space increases risk of experiencing multiple infections with different DENV types.



DENV Type Distribution - 1970



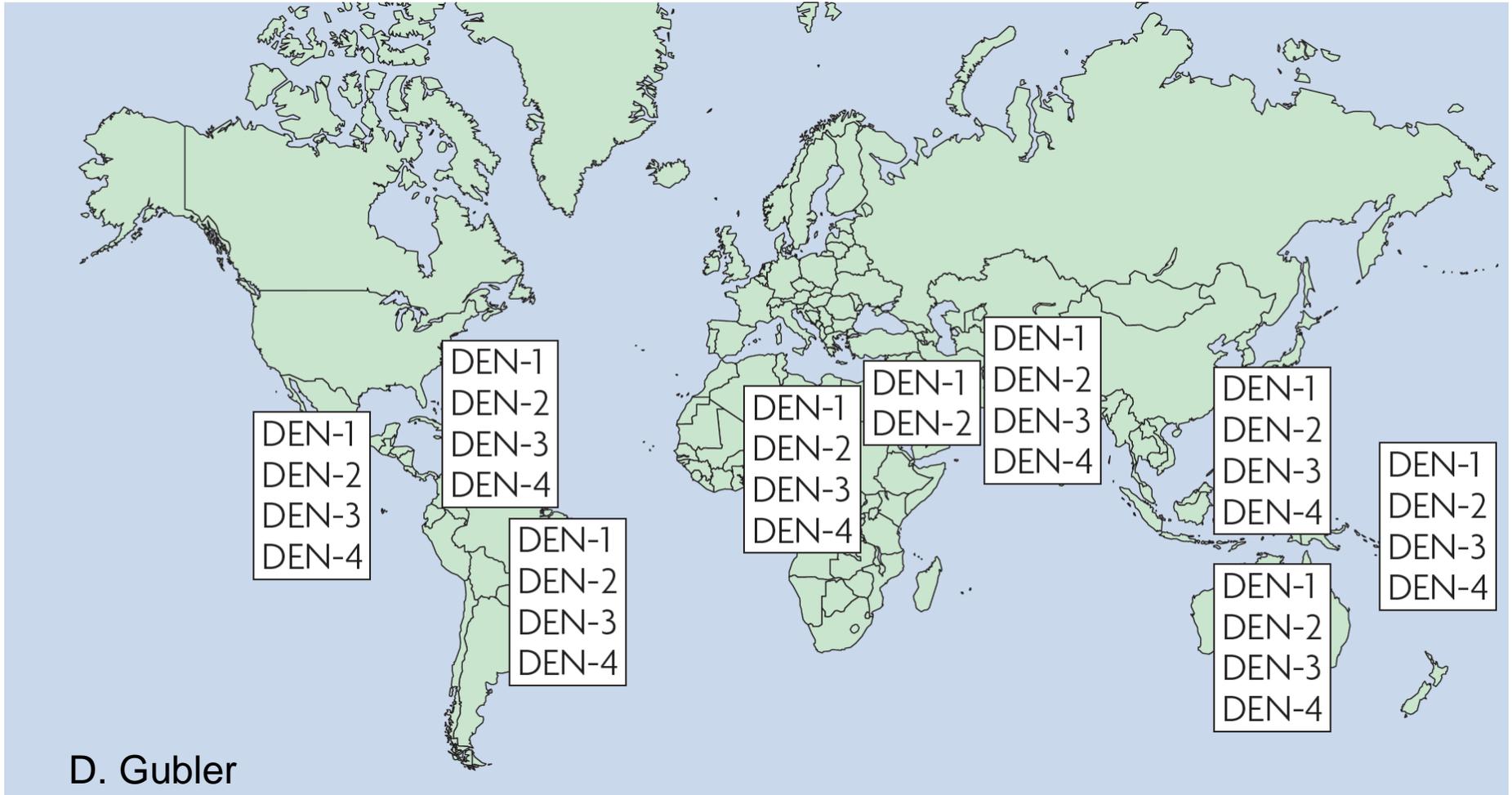
Global Air Travel Flight Patterns



<http://upload.wikimedia.org/wikipedia/commons/a/ac/World-airline-routemap-2009.png>



DENV Type Distribution - 2004

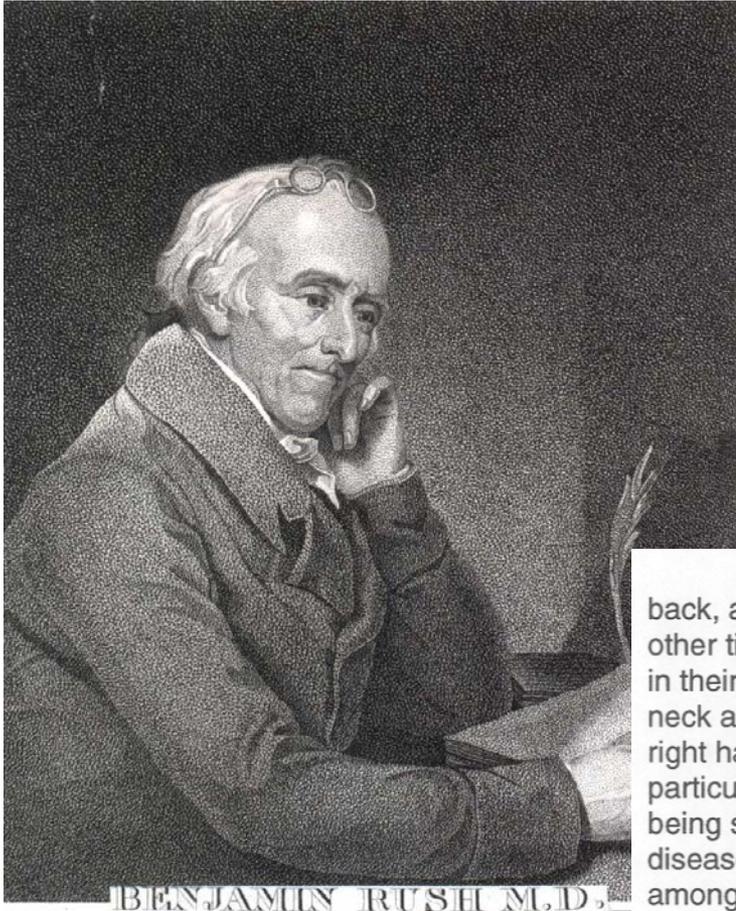


Case Presentation

- 18 year old native from Thailand (moved to US at 10 years of age) presents in August with 2 days of illness including fever, headache, bone pain, and nausea 3 days after returning from a vacation in Puerto Rico. You suspect he has a dengue infection. He is tolerating PO intake without vomiting and is urinating. Vital signs except for temperature (102.5F) are in the range of normal. Mucous membranes are moist, skin turgor is normal, abdominal exam is normal, and lungs are clear. A CBC reveals a low WBC (3.5k) but otherwise is within normal limits. Electrolytes are normal.
- What is the most reasonable initial management strategy?
 - 1. treat as outpt, provide NSAIDS, encourage PO fluids
 - 2. treat as inpt, provide 1L NS bolus, monitor in ICU setting
 - 3. treat as outpt, provide acetaminophen, encourage po fluids, F/U
 - 4. treat as inpt, encourage PO fluids, perform q6 hr HCT evaluations



Clinical Phenotype



AN
ACCOUNT
OF THE

Bilious Remitting Fever,

AS IT APPEARED IN PHILADELPHIA, IN THE SUMMER
AND AUTUMN OF THE YEAR 1780.

The pains which accompanied this fever were exquisitely severe in the head, back, and limbs. The pains in the head were sometimes in the back parts of it, and at other times they occupied only the eyeballs. In some people, the pains were so acute in their backs and hips, that they could not lie in bed. In others, the pains affected the neck and arms, so as to produce in one instance a difficulty of moving the fingers of the right hand. They all complained more or less of a soreness in the seats of these pains, particularly when they occupied the head and eyeballs. A few complained of their flesh being sore to the touch, in every part of the body. From these circumstances, the disease was sometimes believed to be a rheumatism. But its more general name among all classes of people was, the *Break-bone fever*.



Dengue haemorrhagic fever

Diagnosis, treatment, prevention
and control

SECOND EDITION



World Health Organization
Geneva
1997

DENGUE

GUIDELINES FOR DIAGNOSIS,
TREATMENT, PREVENTION AND CONTROL



New edition
2009

TDR

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

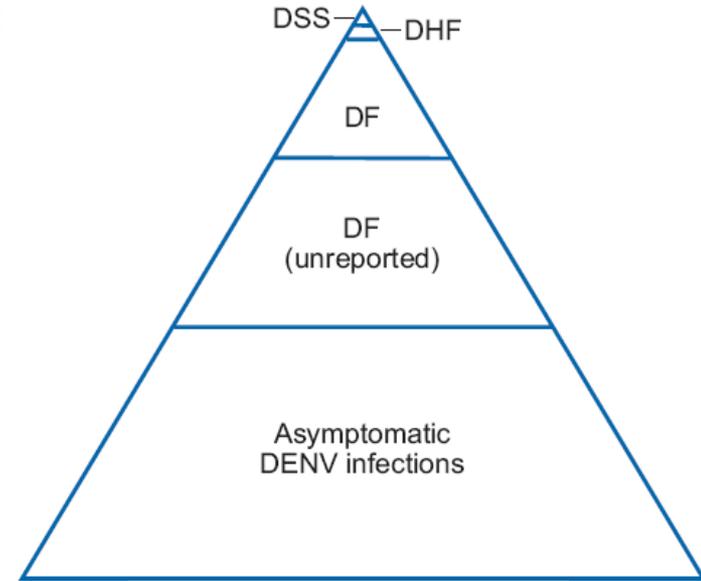


World Health
Organization

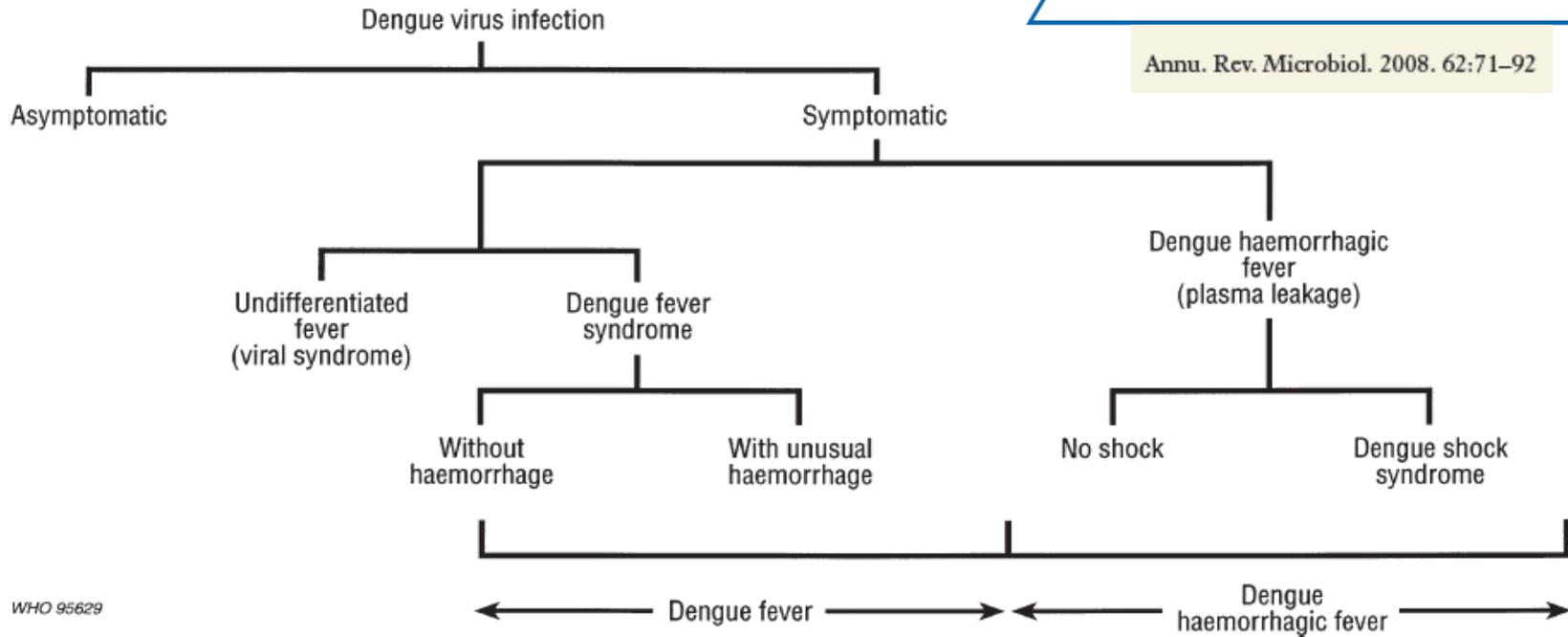
http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf



Dengue Infection Clinical Phenotypes



Annu. Rev. Microbiol. 2008. 62:71-92



WHO 95629



1997 WHO dengue fever case definition

- Probable dengue infection
 - Acute febrile illness and at least 2 of the following:
 - Headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, and leukopenia
- Confirmed dengue infection
 - Above + lab confirmation (at least one method below)
 - DENV isolation (blood, autopsy samples)
 - 4 fold rise in IgM or IgG to any of the four DENV antigens in paired blood samples
 - Demonstration of DENV antigen (tissue, CSF, serum) by ELISA, Immunohistochemistry, immunofluorescence
 - PCR +



1997 WHO case definition for DHF/DSS

TABLE 1

1997 World Health Organization (WHO) case definition for dengue hemorrhagic fever and dengue shock syndrome*

DHF, the following must all be present:

Fever, or history of acute fever, lasting 2–7 days, occasionally biphasic

Hemorrhagic tendencies, evidenced by at least one of the following:

A positive tourniquet test

Petechiae, ecchymoses, or purpura

Bleeding from the mucosa, gastrointestinal tract, injection sites, or other locations

Hematemesis or melaena

Thrombocytopenia (100,000 cells/mm³ or less)

Evidence of plasma leakage caused by increased vascular permeability, manifested by at least one of the following:

A rise in the hematocrit equal to or > 20% above average for age, sex, and population

A drop in the hematocrit following volume replacement treatment equal to or > 20% of baseline

Signs of plasma leakage such as pleural effusion, ascites, and hypoproteinemia

Case definition for dengue shock syndrome:

All of the above four criteria for DHF must be present, plus evidence of circulatory failure manifested by:

Rapid and weak pulse, and

Narrow pulse pressure (< 20 mm Hg)

or manifested by:

Hypotension for age, and

Cold, clammy skin and restlessness.

*HF = dengue hemorrhagic fever.



2009 WHO dengue case definitions

TABLE 2

2009 World Health Organization (WHO) dengue case definitions*¹⁴

Probable dengue

Live in or travel to dengue endemic area, fever and two of the following:
 Nausea, vomiting
 Rash
 Aches and pains
 Tourniquet test positive
 Leucopenia
 Any "Warning Sign"
 Dengue with Warning Signs
 Abdominal pain or tenderness
 Persistent vomiting
 Clinical fluid accumulation
 Mucosal bleed
 Lethargy, restlessness
 Liver enlargement > 2 cm
 Laboratory increase in HCT concurrent with rapid decrease in platelet count

Severe dengue (short form)

Severe plasma leakage
 Shock (DSS)
 Fluid accumulation with respiratory distress
 Severe bleeding (as evaluated by clinician)
 Severe organ involvement
 Liver AST or ALT \geq 1,000
 CNS impaired consciousness
 Heart and other organs

Severe dengue (long form)

There is evidence of plasma leakage, such as:
 High or progressively rising hematocrit;
 Pleural effusions or ascites;
 Circulatory compromise or shock (tachycardia, cold and clammy extremities, capillary refill time greater than 3 seconds, weak or undetectable pulse, narrow pulse pressure or, in late shock, unrecordable blood pressure).
 There is significant bleeding
 There is an altered level of consciousness (lethargy or restlessness, coma, convulsions).
 There is severe gastrointestinal involvement (persistent vomiting, increasing or intense abdominal pain, jaundice).
 There is severe organ impairment (acute liver failure, acute renal failure, encephalopathy or encephalitis, or other unusual manifestations, cardiomyopathy) or other unusual manifestations.

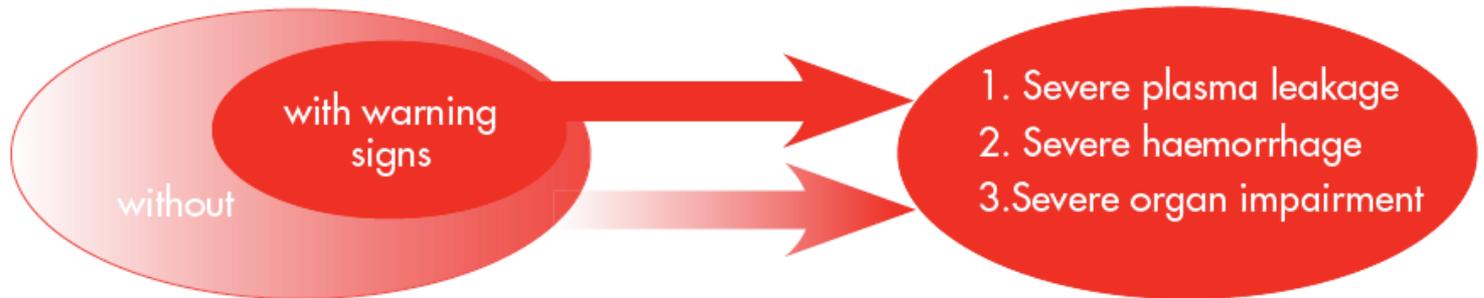
*HCT = hematocrit; DSS = dengue shock syndrome; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CNS = central nervous system.



Figure 1.4 Suggested dengue case classification and levels of severity

DENGUE ± WARNING SIGNS

SEVERE DENGUE



CRITERIA FOR DENGUE ± WARNING SIGNS

CRITERIA FOR SEVERE DENGUE

Probable dengue
 live in /travel to dengue endemic area.
 Fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

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

Warning signs*

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

*(requiring strict observation and medical intervention)

Severe plasma leakage
 leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding
 as evaluated by clinician

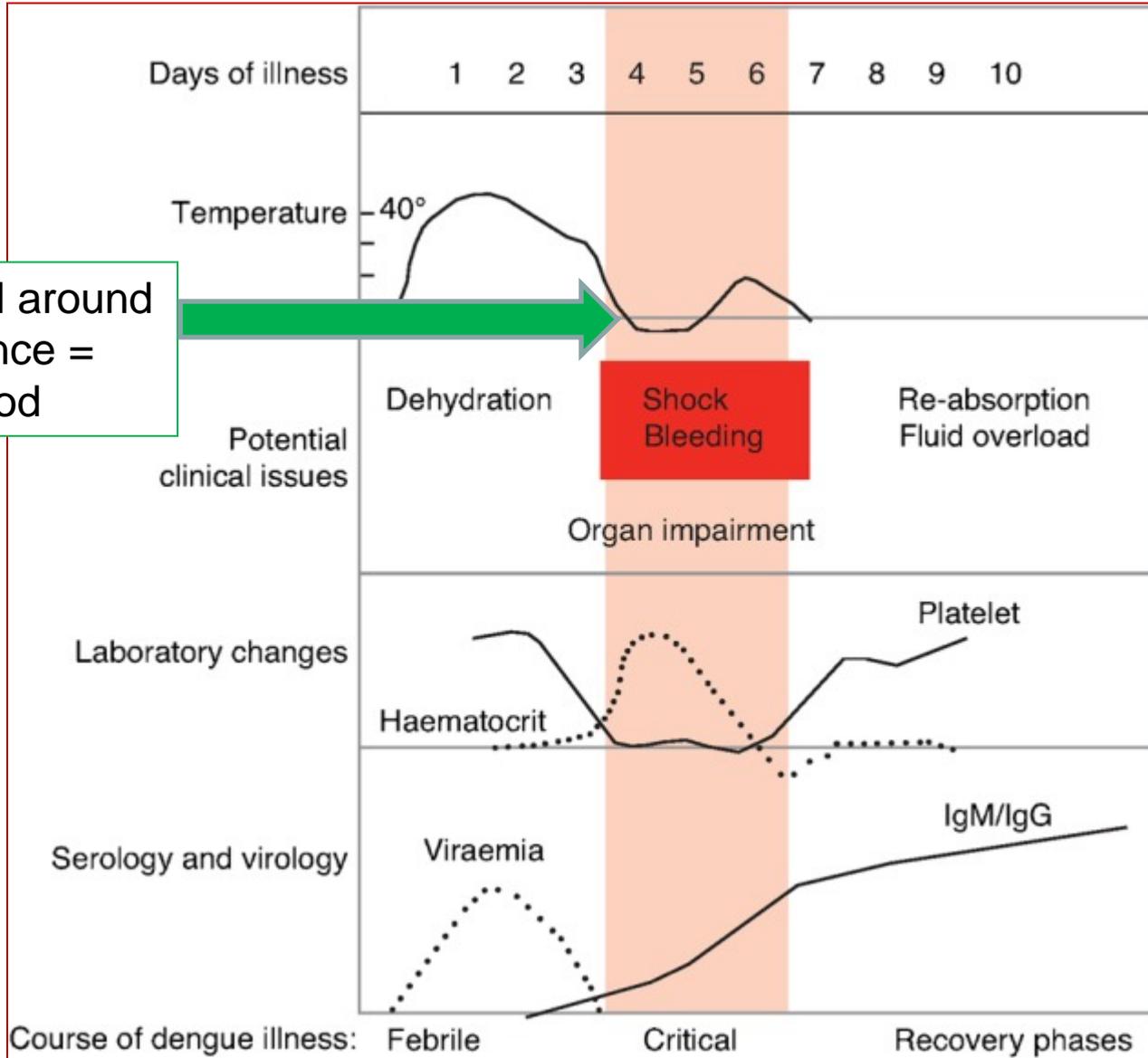
Severe organ involvement

- Liver: AST or ALT \geq 1000
- CNS: Impaired consciousness
- Heart and other organs



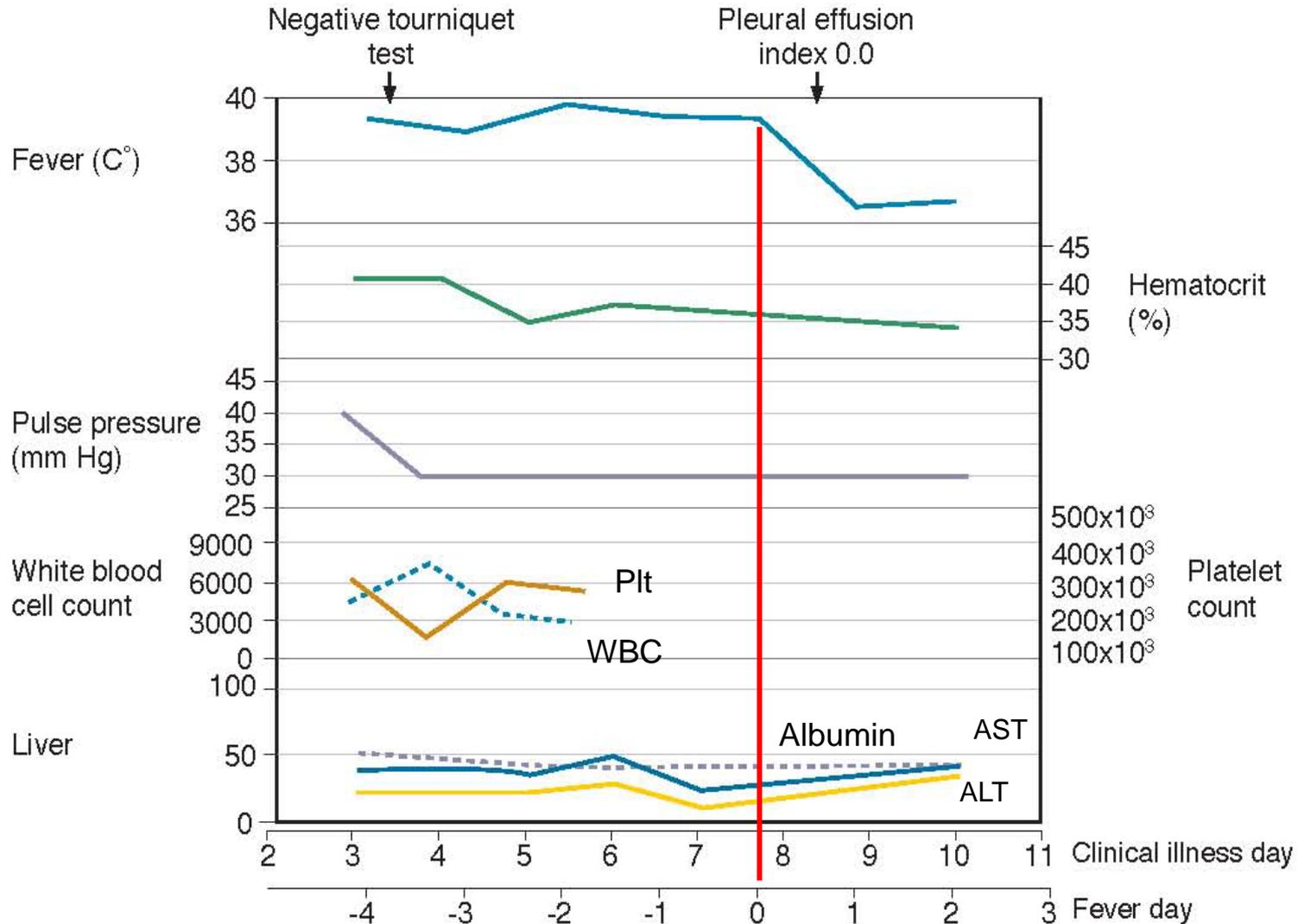
Dengue Clinical and Lab Parameters

24 hr period around defervescence = danger period



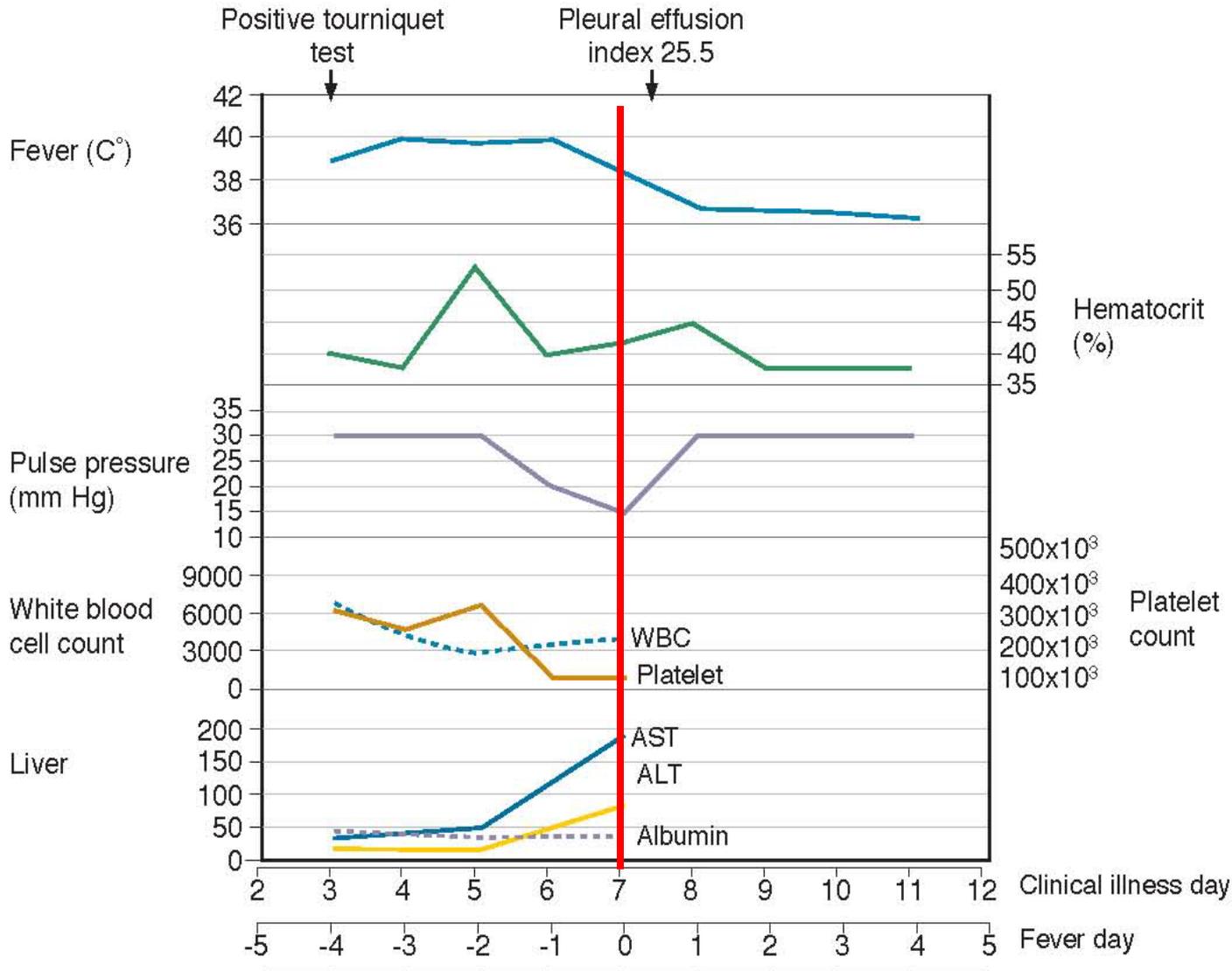
Dengue Fever

6 year old male with acute primary den-1, DF

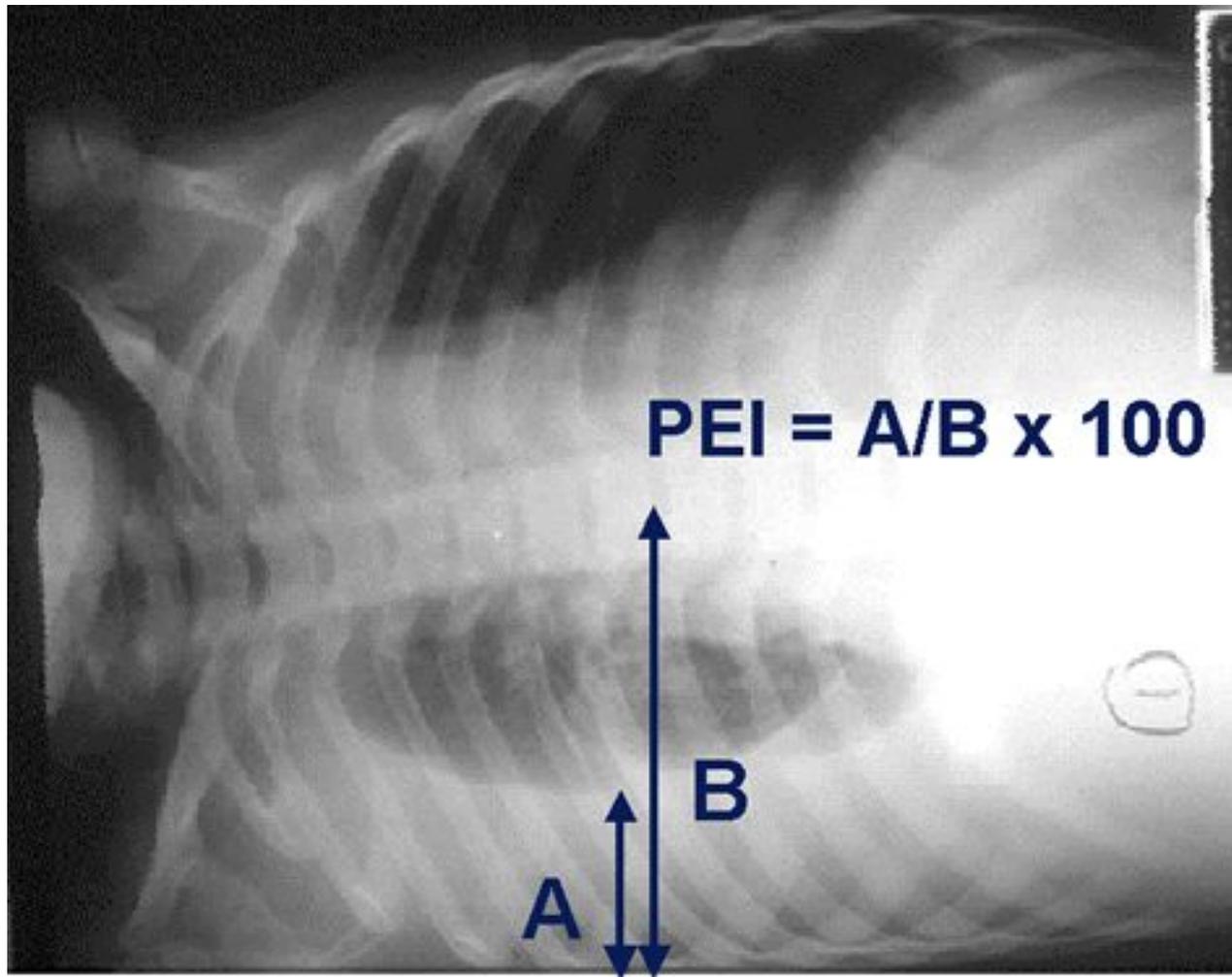


Dengue Hemorrhagic Fever

7 year old male with acute secondary den-1, grade III DHF



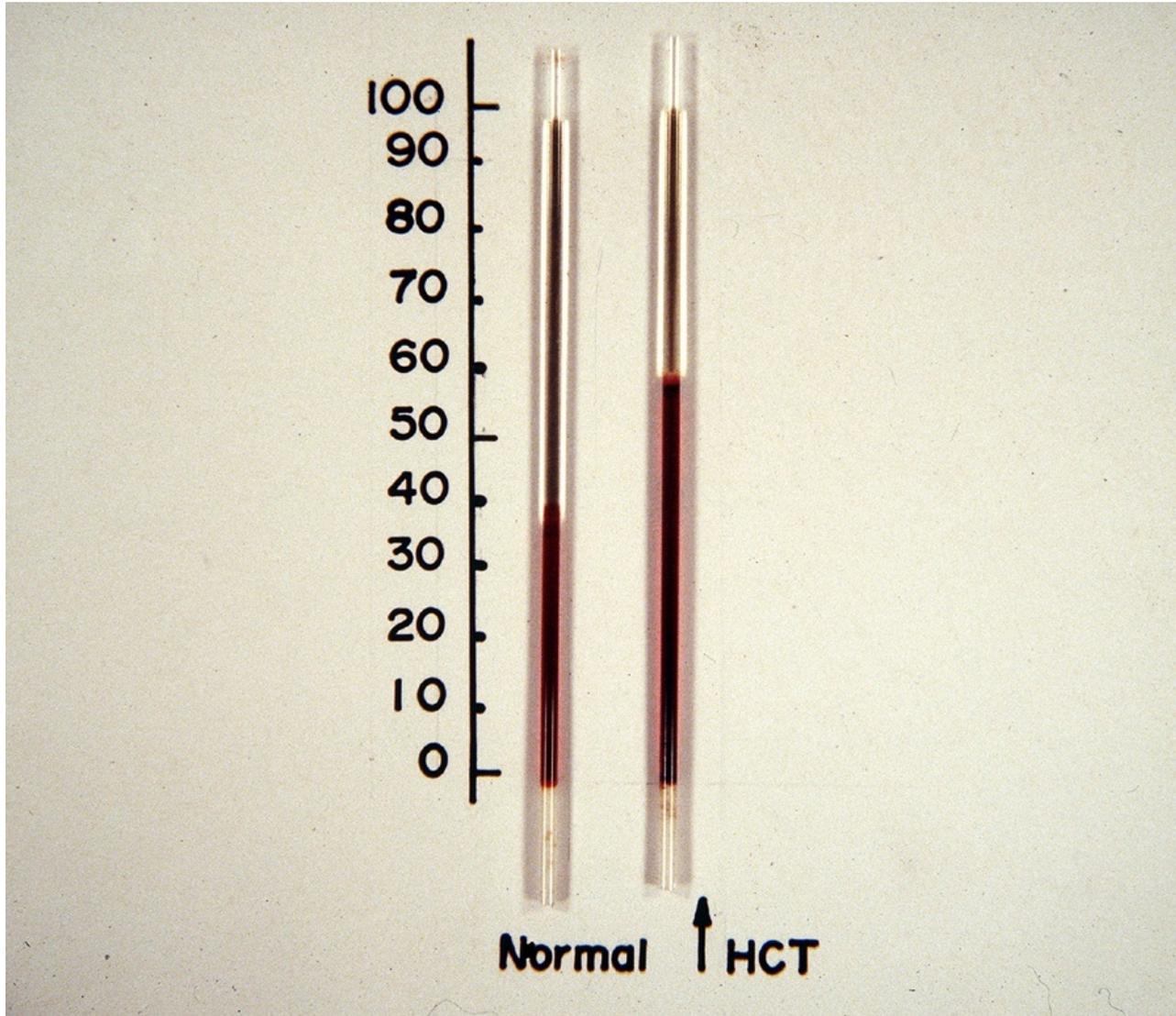
Pleural Effusion Index



R LAT decubitus X-ray showing a large pleural effusion, DHF the day after defervescence. Degree of plasma leakage may be quantified by means of the pleural effusion index. The pleural effusion index is calculated as 100 times the maximum width of the R pleural effusion, divided by the maximal width of the R hemithorax.



Hemoconcentration



Diagnosing Dengue

- Maintain high degree of suspicion
 - Geographic location
 - Clustering of cases
- History and physical
 - Clinical presentation
 - Vital signs (HR, BP, Temp)
 - Dengue tourniquet test (TT)
- Clinical lab assessment
 - CBC (WBC, HCT, PLT), AST/ALT
- Dengue tests in US
 - IgM capture ELISA
 - CDC RT-PCR
- Dengue area, +Clinical, +TT, WBC<5k = High PPV (~70%)



Evaluation of diagnostic tests: dengue

Rosanna W. Peeling, Harvey Artsob, Jose Luis Pelegrino, Philippe Buchy, Mary J. Cardoso, Shamala Devi, Delia A. Enria, Jeremy Farrar, Duane J. Gubler, Maria G. Guzman, Scott B. Halstead, Elizabeth Hunsperger, Susie Kliks, Harold S. Margolis, Carl M. Nathanson, Vinh Chau Nguyen, Nidia Rizzo, Susana Vázquez and Sutee Yoksan

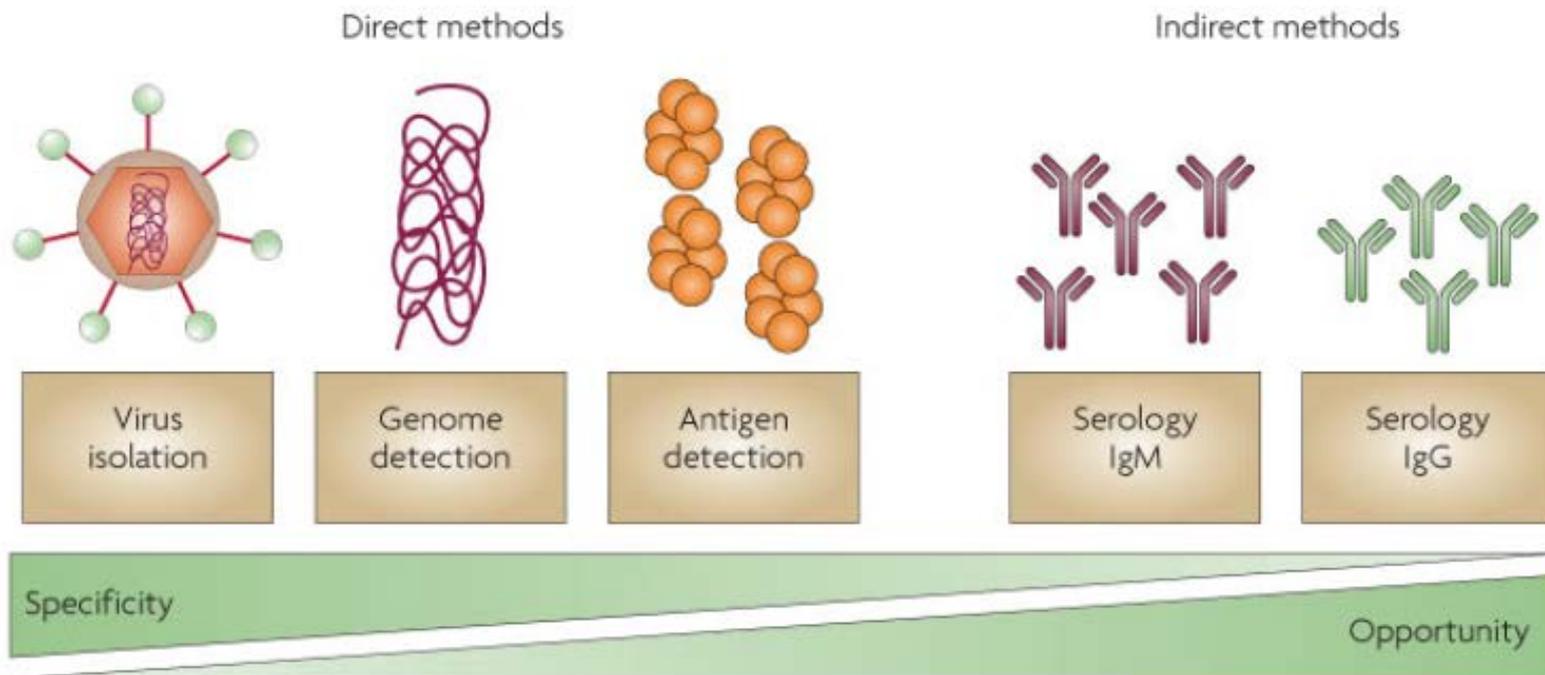


Figure 1 | **Comparative merits of direct and indirect laboratory methods for the diagnosis of dengue infections.** Opportunity refers to the fact that antibody testing is usually the most practical diagnostic option available.

Dengue Tourniquet Test

- Measure BP
- $SBP + DBP / 2 =$ target insufflation pressure for test
- Inspect area near antecubital fossa
 - You will assess delta before / after
- Inflate to target pressure
- Hold for 5 minutes
- Remove cuff
- Reassess antecubital fossa
- Count # of petechiae in 2.5 cm^2 area
- ≥ 10 new petechiae is positive



- **TT measures capillary fragility, severe disease predictor?**



Case Presentation

- 18 year old native from Thailand (moved to US at 10 years of age) presents in August with 2 days of illness including fever, headache, bone pain, and nausea 3 days after returning from a vacation in Puerto Rico. You decide to manage him as an outpatient. He fails to follow up as requested but does return day 6 of his illness afebrile with resolution of some symptoms but he now has abdominal pain, slight shortness of breath, and lethargy.
- What is the most reasonable management strategy at this point?
 - 1. Continue close follow up as outpatient, encourage PO fluid intake, this is the natural history of a resolving dengue infection
 - 2. Admit to the hospital, approach as a critically ill patient, this is a severe dengue virus infection
 - 3. Admit to the hospital, evaluate for another infectious disease process, these new symptoms represent a new medical problem
 - 4. Prescribe doxycycline, he probably has leptospirosis



Dengue Treatment

DENGUE WITHOUT WARNING SIGNS

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 maximum per day in adults and accordingly in children.

Patients with stable HCT can be sent home.

Monitoring

Daily review for disease progression:

- decreasing white blood cell count
- defervescence
- warning signs (until out of critical period).

Advice for immediate return to hospital if development of any warning signs, and

- written advice for management (e.g. home care card for dengue).



For research on
diseases of poverty
UNICEF - UNDP - World Bank - WHO





DENGUE WITH WARNING SIGNS

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, renal failure
- social circumstances such as living alone, living far from hospital

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's Lactate at maintenance rate.

Monitoring

Monitor:

- temperature pattern
- volume of fluid intake and losses
- urine output (volume and frequency)
- warning signs
- HCT, white blood cell and platelet counts.



Figure 2.2 Algorithm for fluid management in compensated shock

- Assess
- Intervene
- Re-assess

Compensated shock (systolic pressure maintained but has signs of reduced perfusion)
 Fluid resuscitation with isotonic crystalloid
 5–10 ml/kg/hr over 1 hour

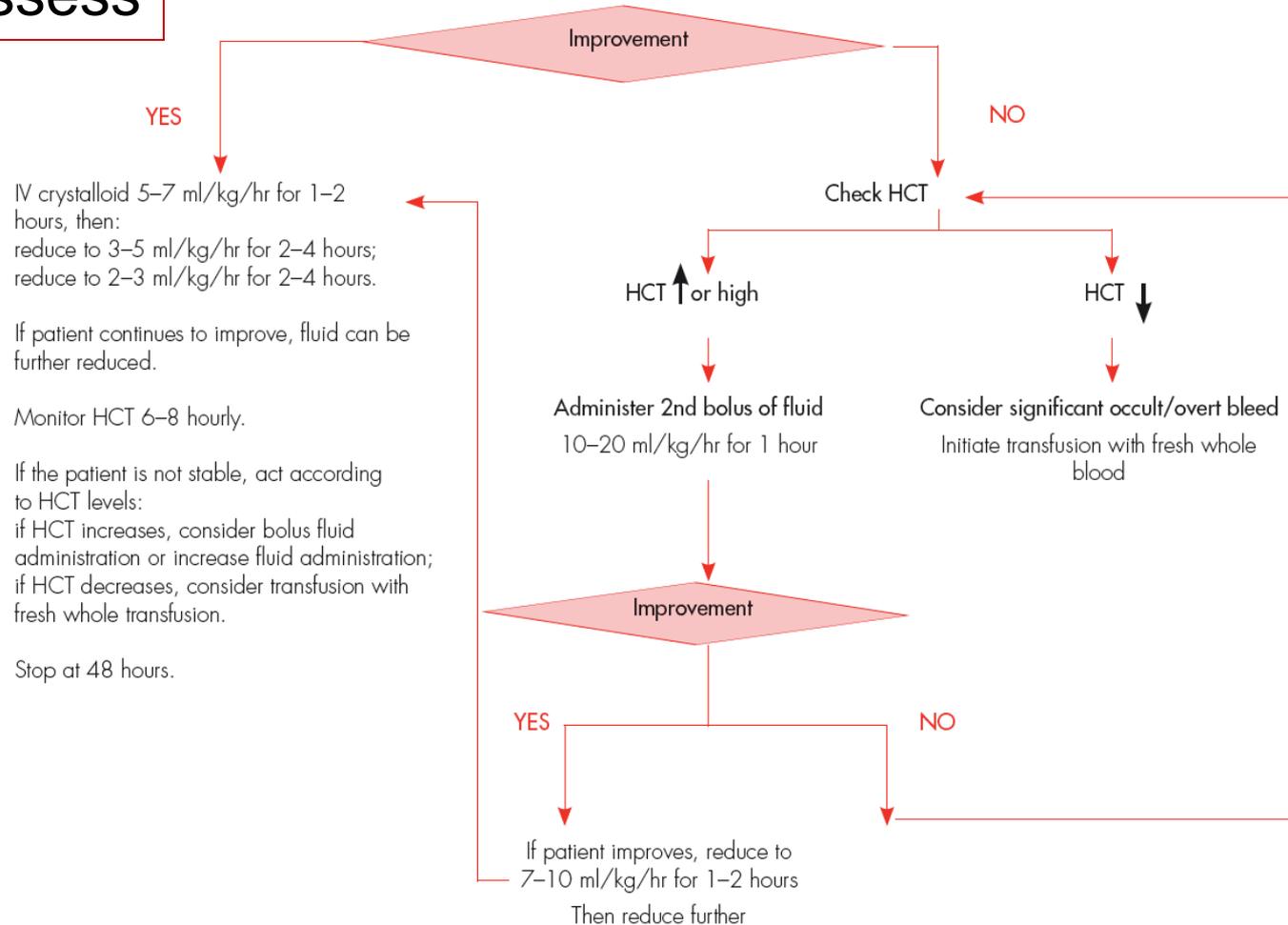
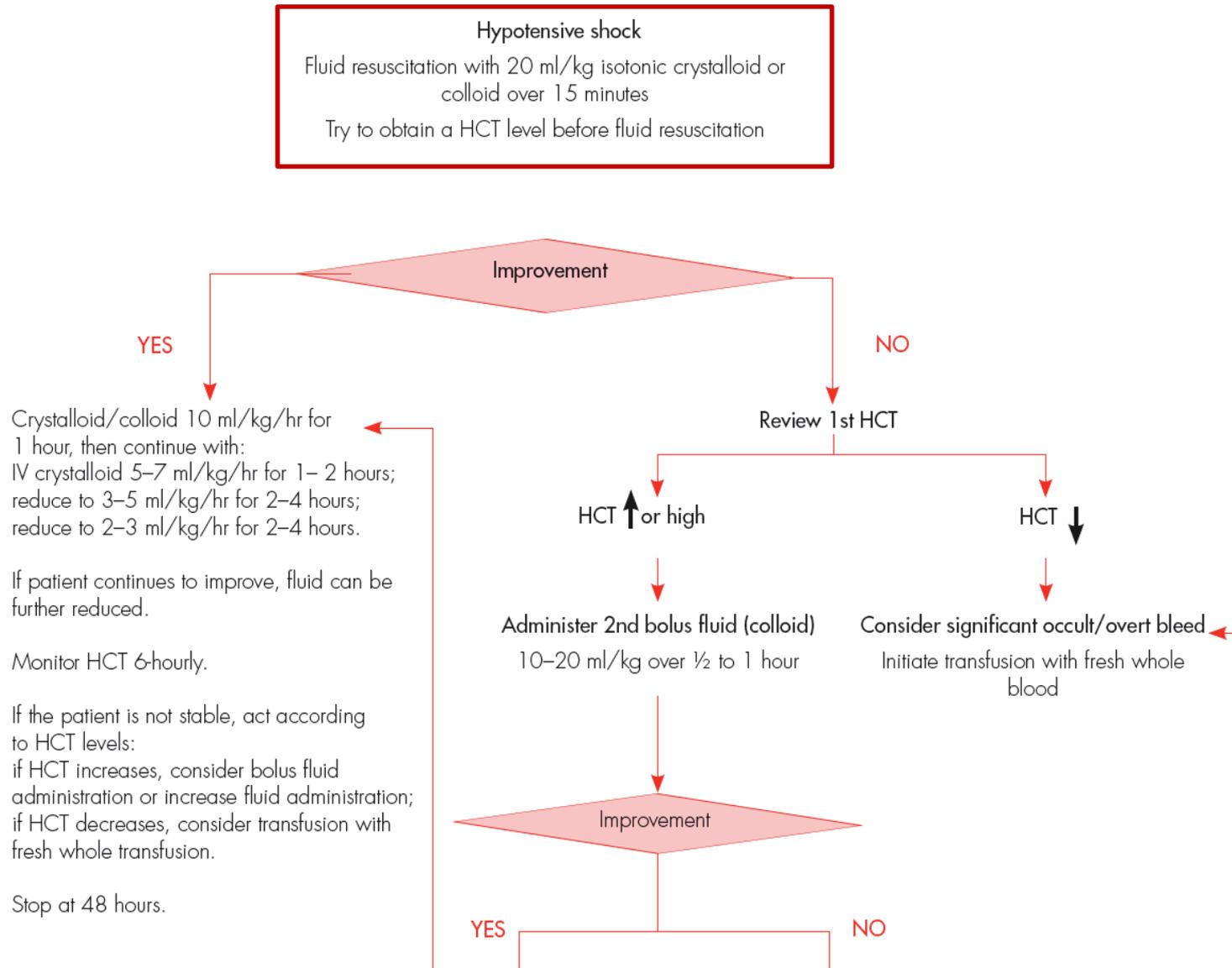
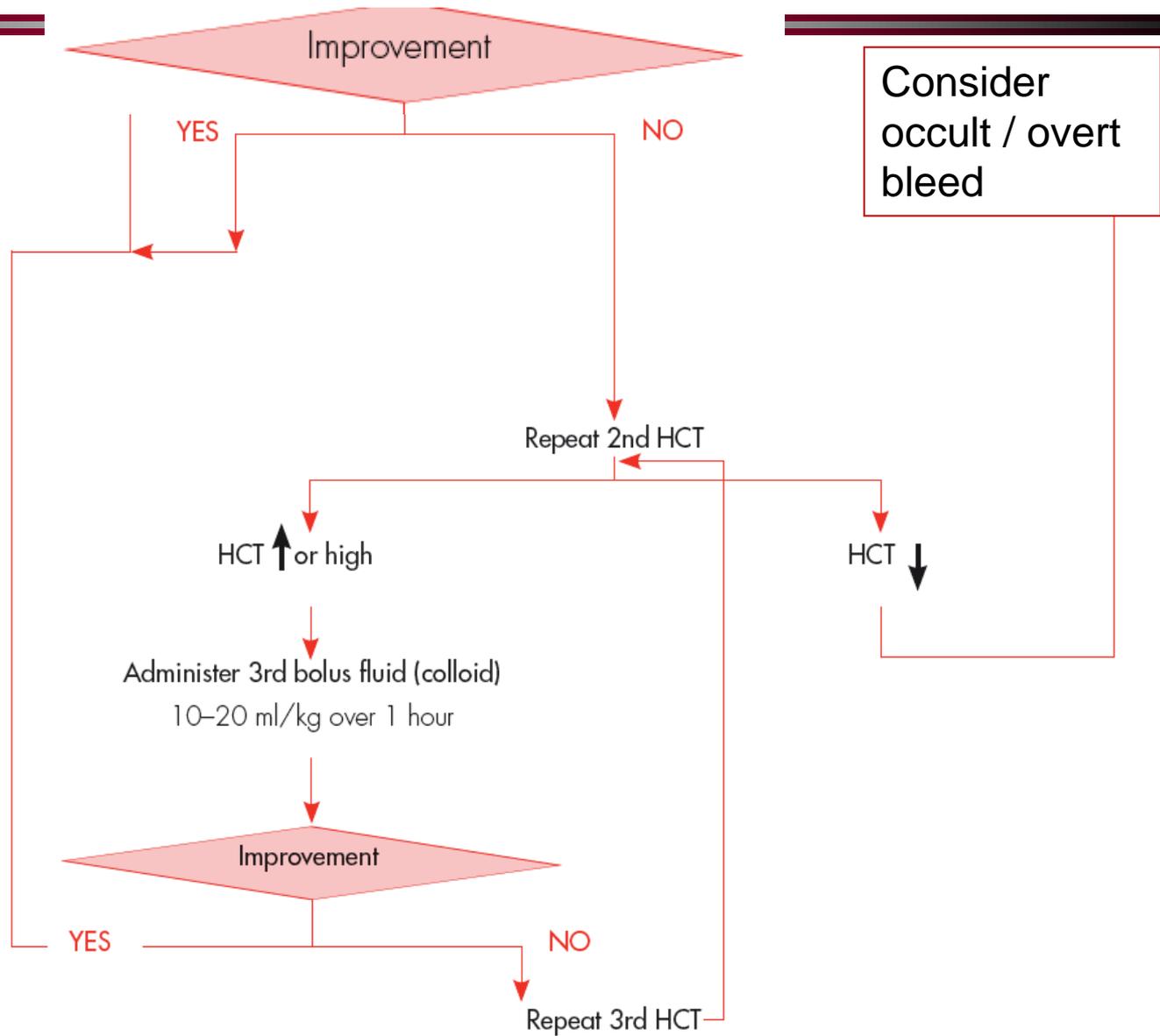


Figure 2.3 Algorithm for fluid management in hypotensive shock



- Assess
- Intervene
- Re-assess



Textbox A. Good clinical practice and bad clinical practice

	Good practice	Bad practice
1	Assessment and follow-up of patients with non-severe dengue and careful instruction of warning signs to watch out for	Sending patients with non-severe dengue home with no follow-up and inadequate instructions
2	Administration of paracetamol for high fever if the patient is uncomfortable	Administration of acetylsalicylic acid (aspirin) or ibuprofen
3	Obtaining a haematocrit level before and after fluid boluses	Not knowing when haematocrit levels are taken with respect to fluid therapy
4	Clinical assessment of the haemodynamic status before and after each fluid bolus	No clinical assessment of patient with respect to fluid therapy
5	Interpretation of haematocrit levels in the context of fluid administered and haemodynamic assessment	Interpretation of haematocrit levels independent of clinical status
6	Administration of intravenous fluids for repeated vomiting or a high or rapidly rising haematocrit	Administration of intravenous fluids to any patient with non-severe dengue
7	Use of isotonic intravenous fluids for severe dengue	Use of hypotonic intravenous fluids for severe dengue
8	Giving intravenous fluid volume just sufficient to maintain effective circulation during the period of plasma leakage for severe dengue	Excessive or prolonged intravenous fluid administration for severe dengue
9	Avoiding intramuscular injections in dengue patients	Giving intramuscular injections to dengue patients
10	Intravenous fluid rate and frequency of monitoring and haematocrit measurement adjusted according to the patient's condition	Fixed intravenous fluid rate and unchanged frequency of monitoring and haematocrit measurement during entire hospitalization for severe dengue
11	Close monitoring of blood glucose, i.e. tight glycaemic control	Not monitoring blood glucose, unaware of the hyperglycaemic effect on osmotic diuresis and confounding hypovolaemia
12	Discontinuation or reducing fluid therapy once haemodynamic status stabilizes	Continuation and no review of intravenous fluid therapy once haemodynamic status stabilizes



Pathophysiology

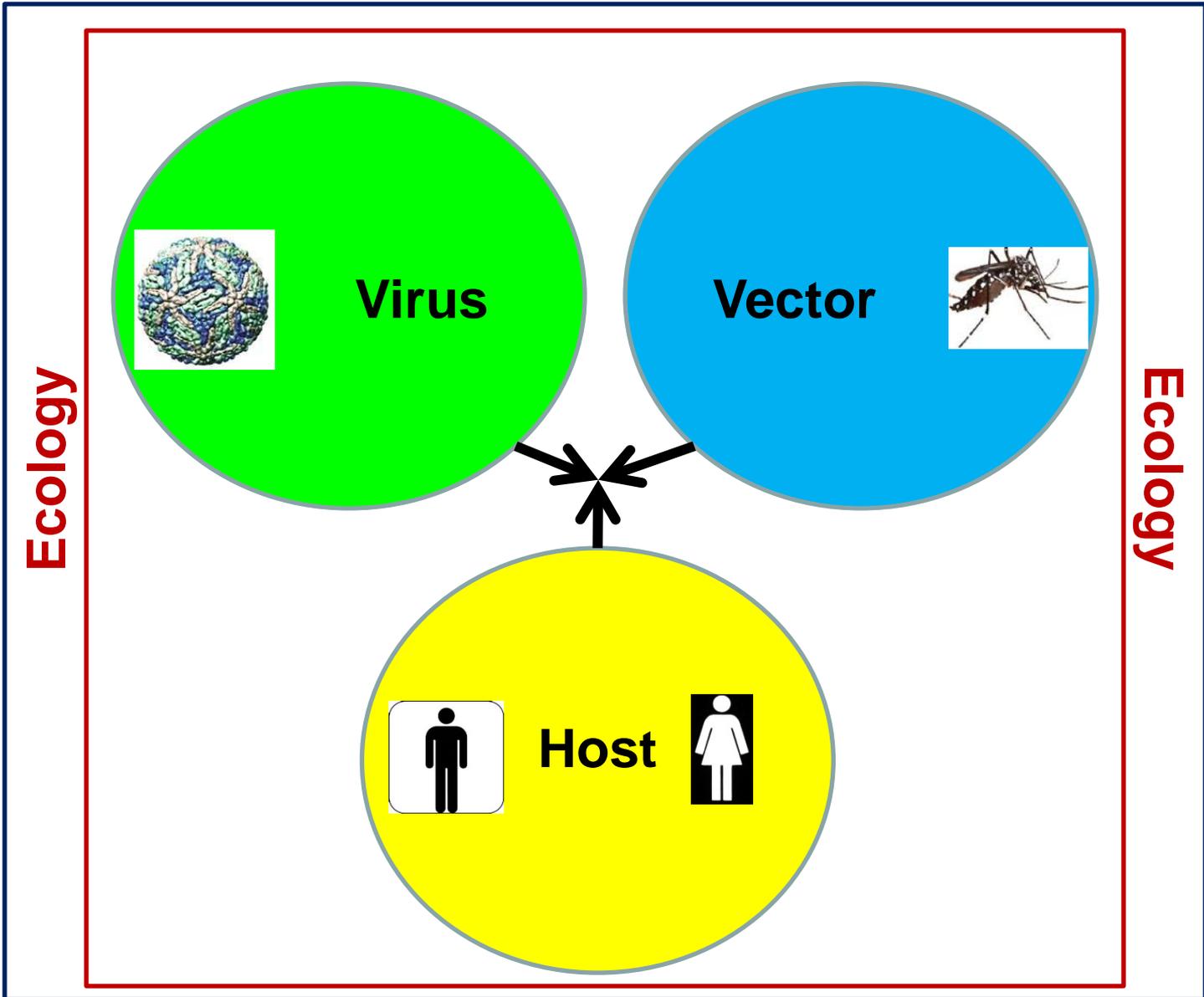


Dengue Ward: QSNICH, Bangkok, Thailand (Photo: Christopher Brown, IHT)



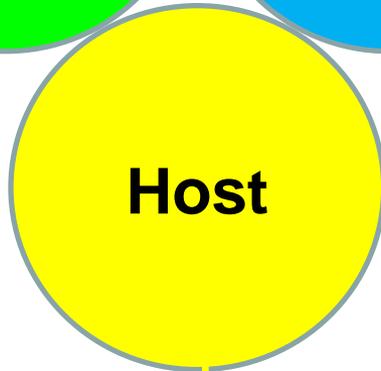
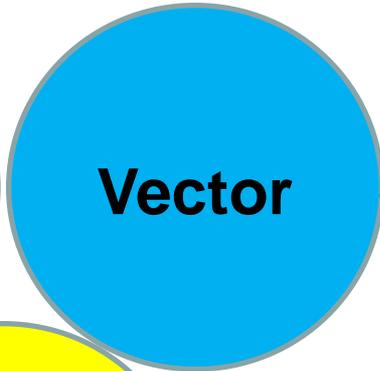
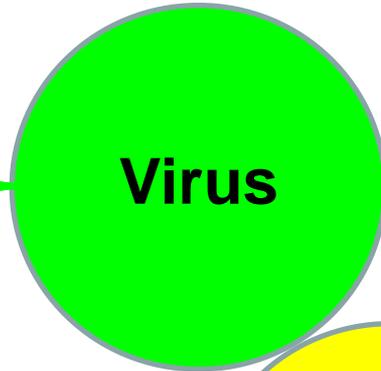
Exposure and Infection Outcome Determinants

Space & Time



Exposure Determinants – Infection Risk

- Tropism for Aedes
 - Tropism for man
- Replicative kinetics
 - Human / Aedes
- “Immune avoidance”
 - Human / Aedes
- Evolutionary capacity

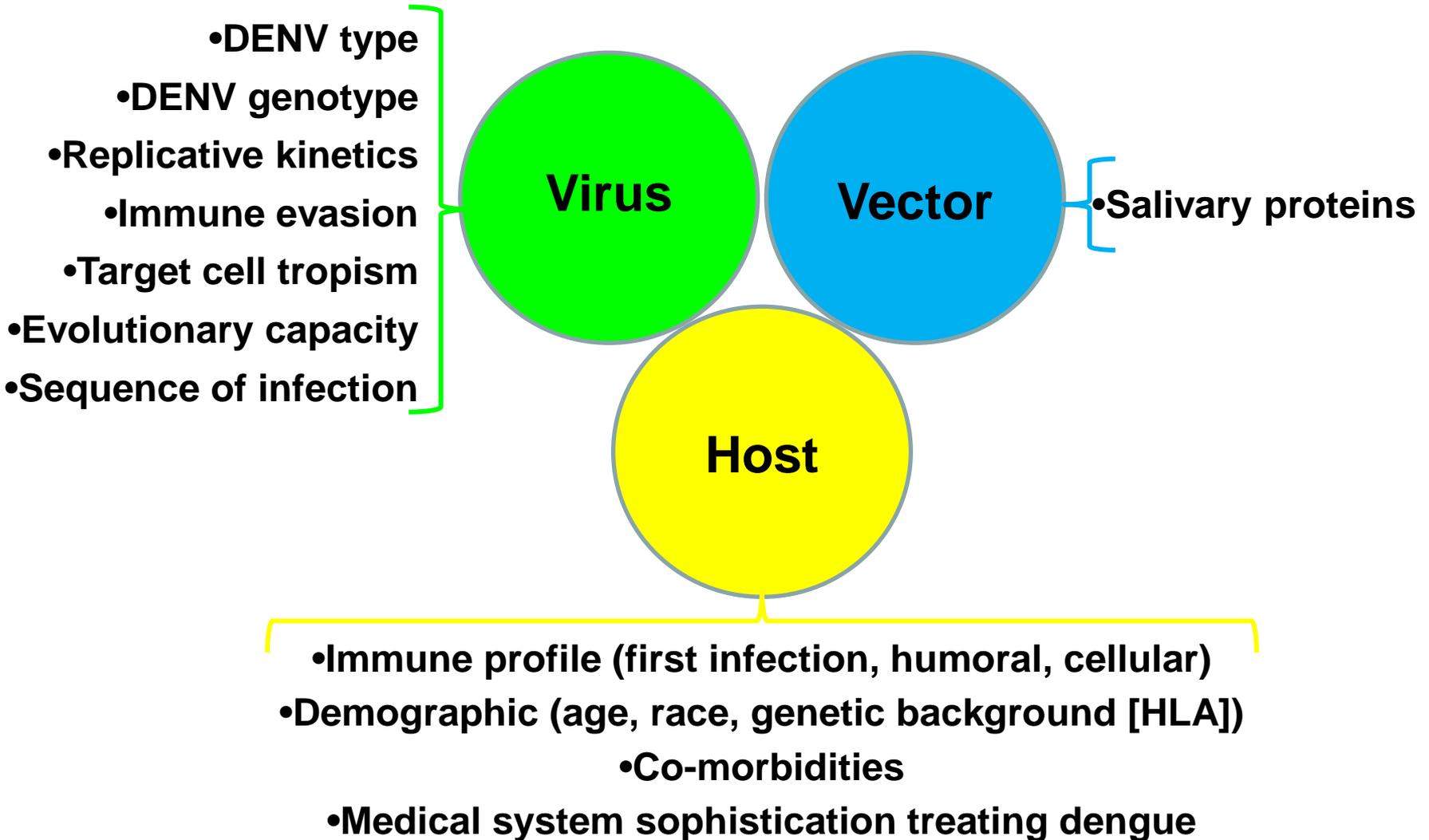


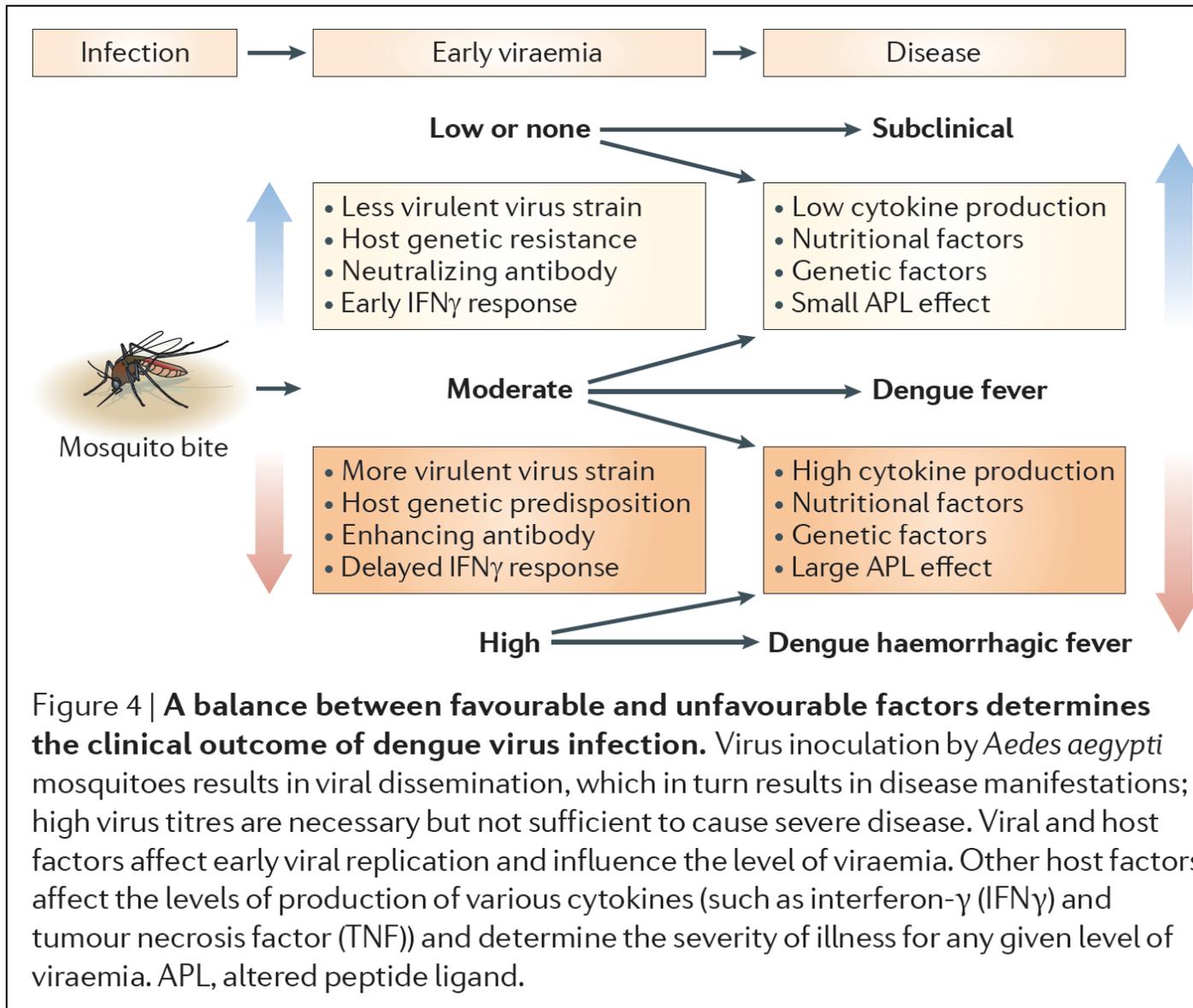
- Response to ecology
 - Temperature
 - Rain
- Infection resistance
 - Co-infection
- Evolutionary capacity

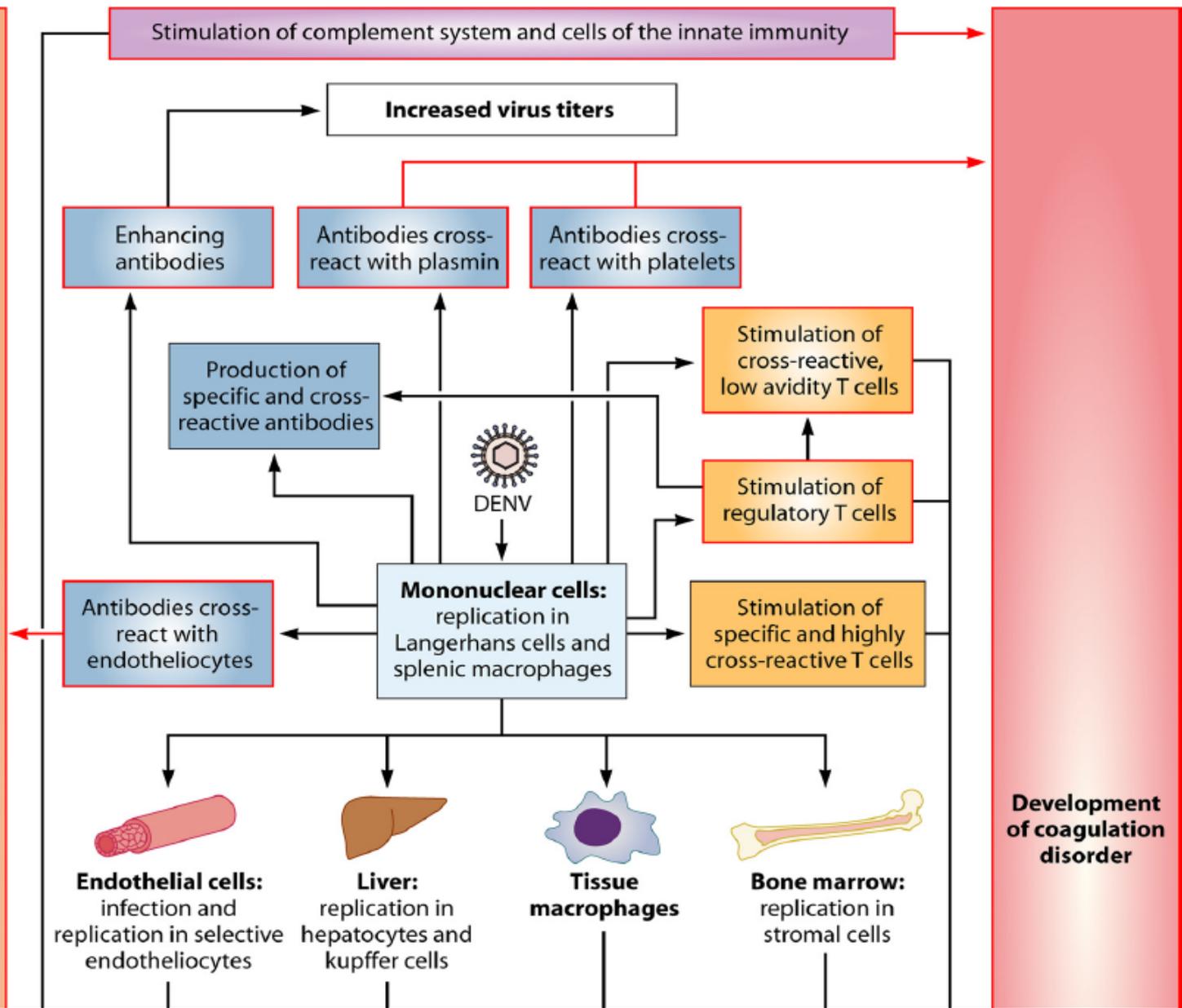
- Immune profile (dengue, other flavivirus)
- Vector exposure dynamics (duration, concentration)
 - “Neighbors” infection status
- Activities of daily living (who, what, where, when)



■ Infection Outcome Determinants – Disease Risk ■







Endothelial cell dysfunction

Endothelial cells:
infection and replication in selective endotheliocytes

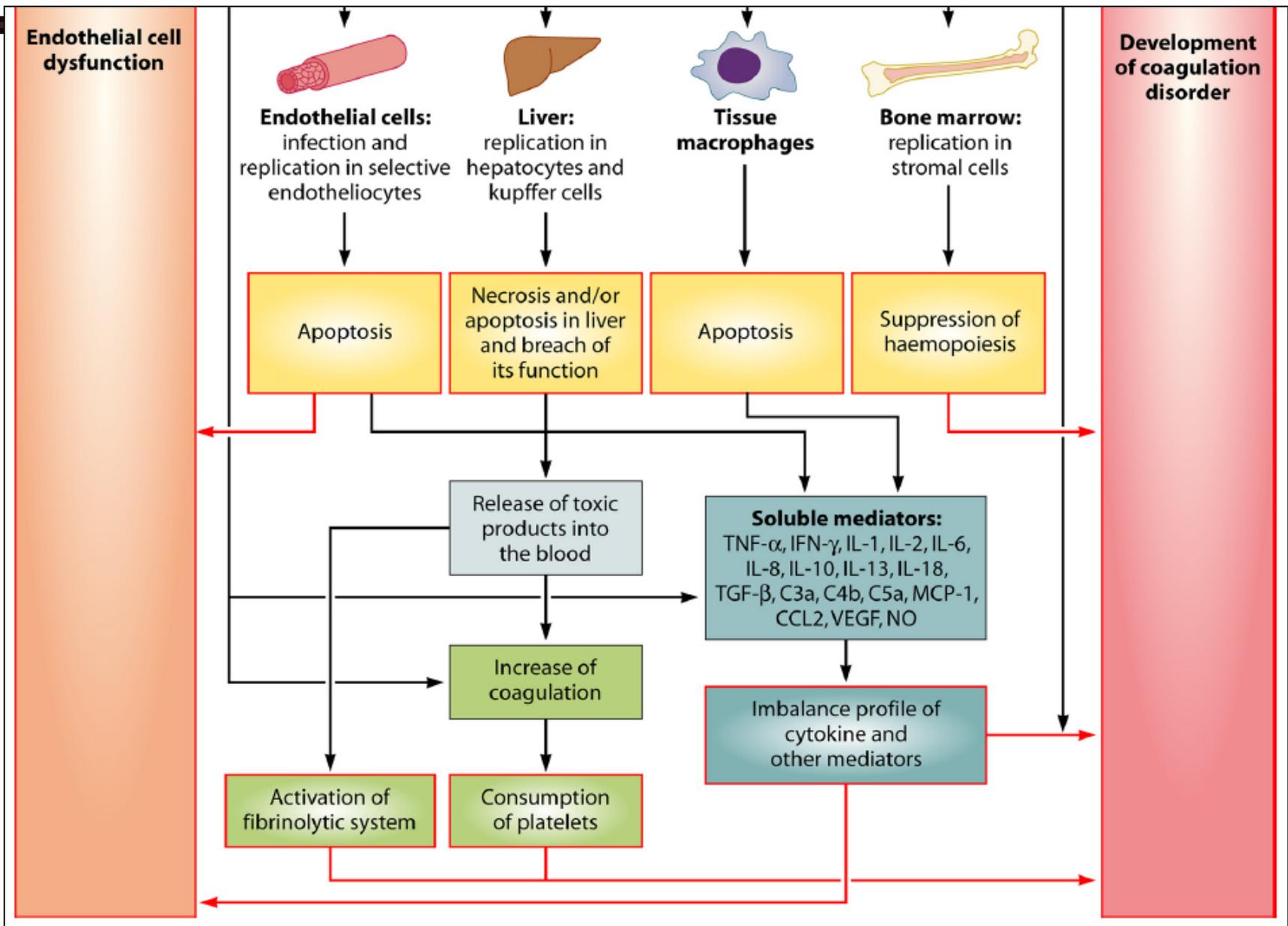
Liver:
replication in hepatocytes and kupfer cells

Tissue macrophages

Bone marrow:
replication in stromal cells

Development of coagulation disorder

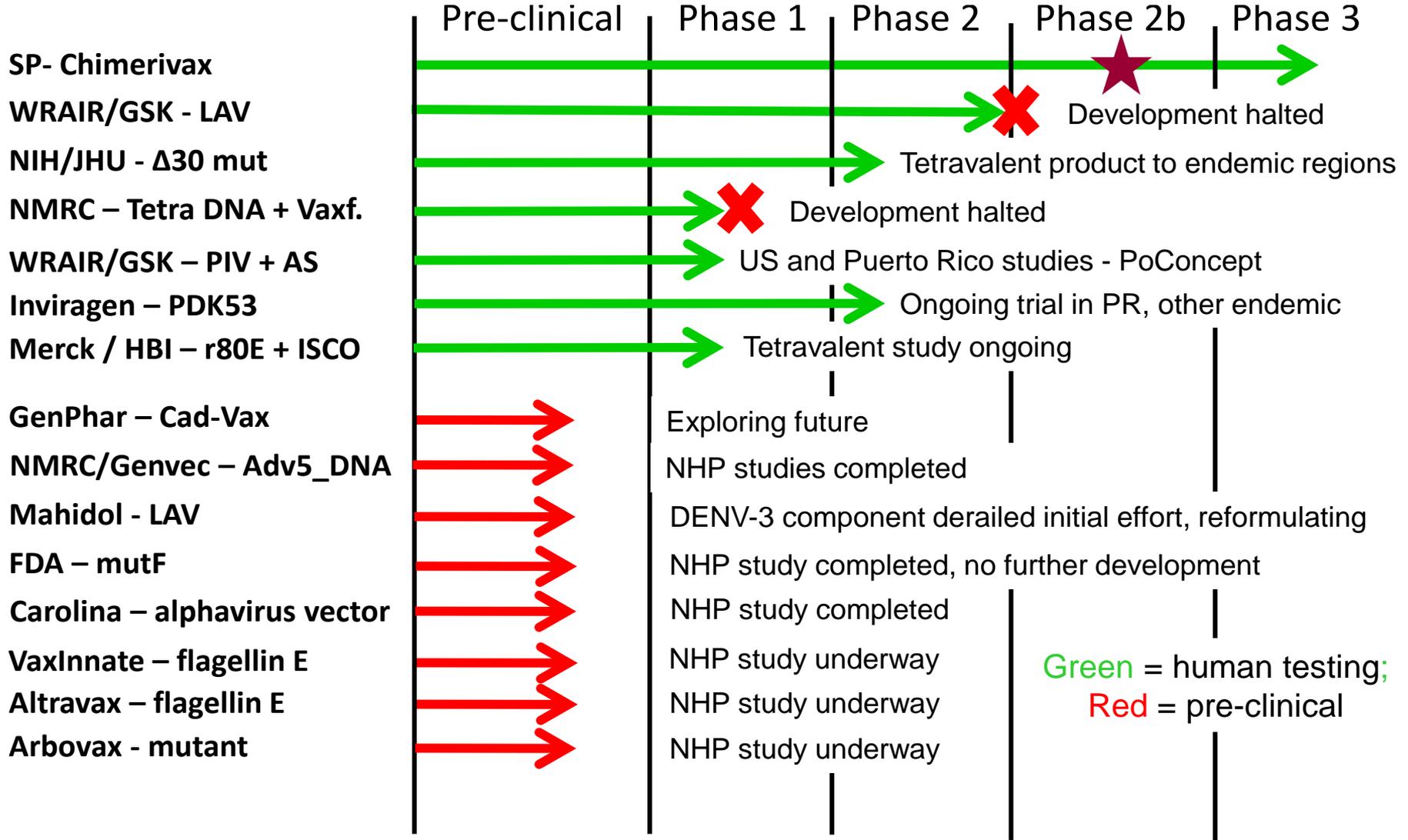




Dengue Vaccine Development

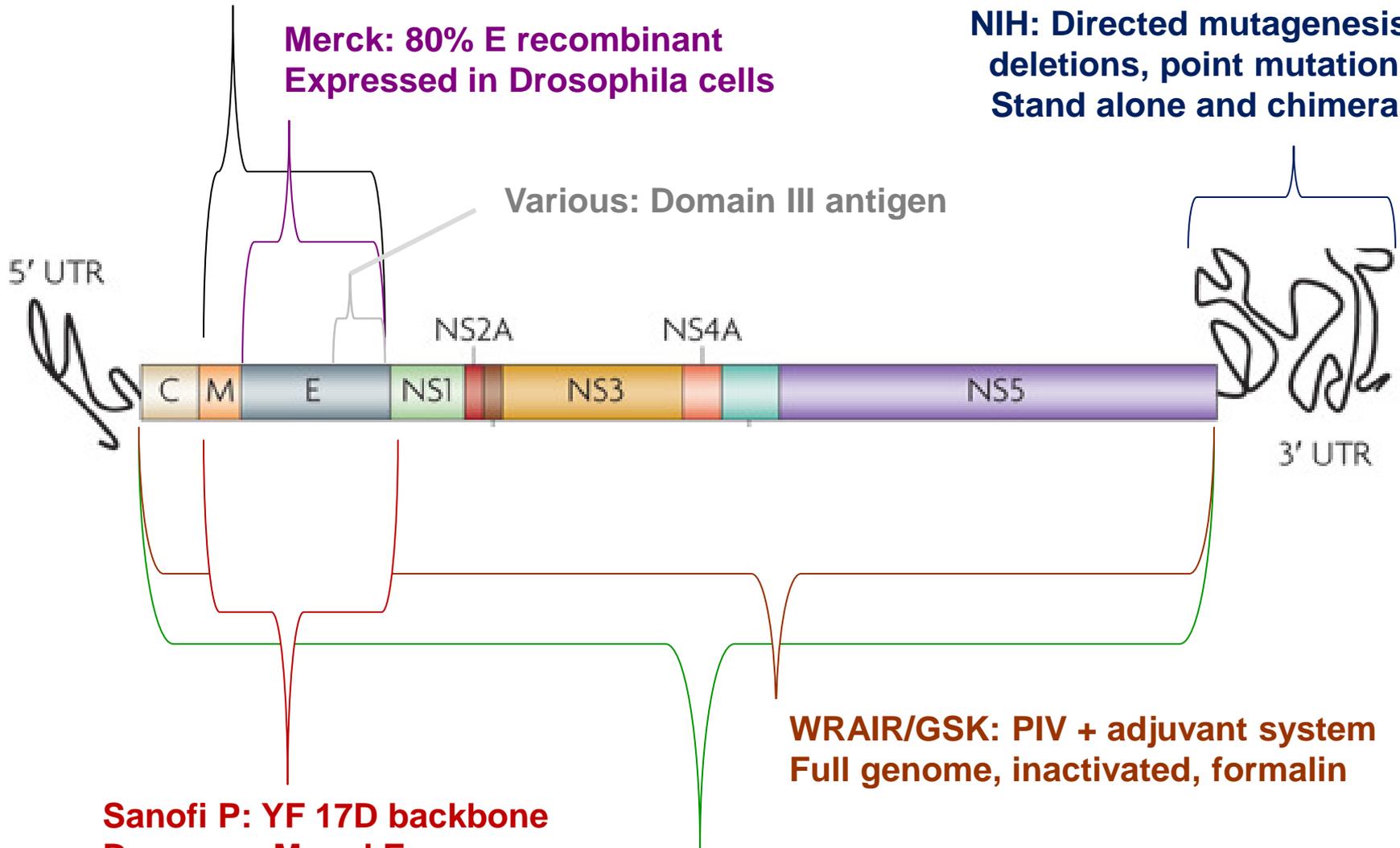


Dengue Vaccine Pipeline 2013



NMRC & others: DNA (preM+E) + adjuvant

**NIH: Directed mutagenesis, deletions, point mutations
Stand alone and chimeras**



**Sanofi P: YF 17D backbone
Dengue prM and E
Monovalents formulated as tetra-**

**WR AIR/GSK: PIV + adjuvant system
Full genome, inactivated, formalin**

**Inviragen: DENV-2 PDK backbone,
Directed mutagenesis, DENV-2/-1, -2/-3, -2/-4**



Development Challenges

- **Each DENV type may cause severe disease/death**
 - Viable vaccine requires efficacy against multiple types
 - Immune interference may prevent balanced response
- **Incomplete understanding of protection / pathology**
 - Will a poor dengue vaccine increase / worsen disease?
 - Extrapolating wild type infection data to immunization?
- **No validated immune correlate of protection**
 - No metrics or benchmarks for vaccine developers
 - Increases need for larger scale clinical trials



Development Challenges

- **No validated animal model of disease**
 - NHPs develop viremia and Nab but not disease
- **No validated human infection model**
 - Advancing vaccines based on Nab and NHP data
 - Efficacy trials may not capture efficacy vs. all DENVs
- **Biologic assays used for endpoint determinations**
 - Inter-assay variability notorious
 - Neutralizing antibody's ability to predict efficacy?
- **Numerous indications with unique challenges**
 - Needs vary at the time, space, and population level



Conclusions

- The world needs a dengue vaccine!
- Global dengue burden is increasing
- Maintain a high index of suspicion in febrile traveler
- High financial and societal cost associated with disease
- Numerous factors continue to drive transmission
- Numerous vaccine development challenges exist
- Dengue vaccine pipeline robust
- Numerous areas for expanded study exist



Questions?

