Dengue Infection

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Objectives

At the end of the session, the participants should be able to:

- ☐ Identify patients who have dengue infection by symptomatology and laboratory results
- ☐ Provide appropriate management for dengue patients based on their classification
- ☐ Advise prevention and control measures for the family and the community
- ☐ Recognize updated evidence-based management of Dengue

Case vignette

- Junior, a 5-year-old boy, previously healthy, was brought to Ambulatory Care Unit for the following
  - **High grade fever (Tmax 39.5˚C) for 2 days**
  - **Poor appetite**, **vomiting** and **body pains**

- Pertinent PE
  - VS: HR: 110 bpm, RR: 24 bpm, T **39.2˚C**
    BP: 90/60 mmHg, Weight: 15kg
  - **(+) flushed skin**
  - Hyperemic throat but no exudates
  - Rest of PE normal
  - **(-) tourniquet test**

Initial CBC

Hgb 110 G/L
Hct 0.33
WBC 4.0 x 10^9/L
Neutrophils 0.25
Lymphocytes 0.70
Platelet 160,000 U/L

Is this patient a Dengue Suspect?

Yes

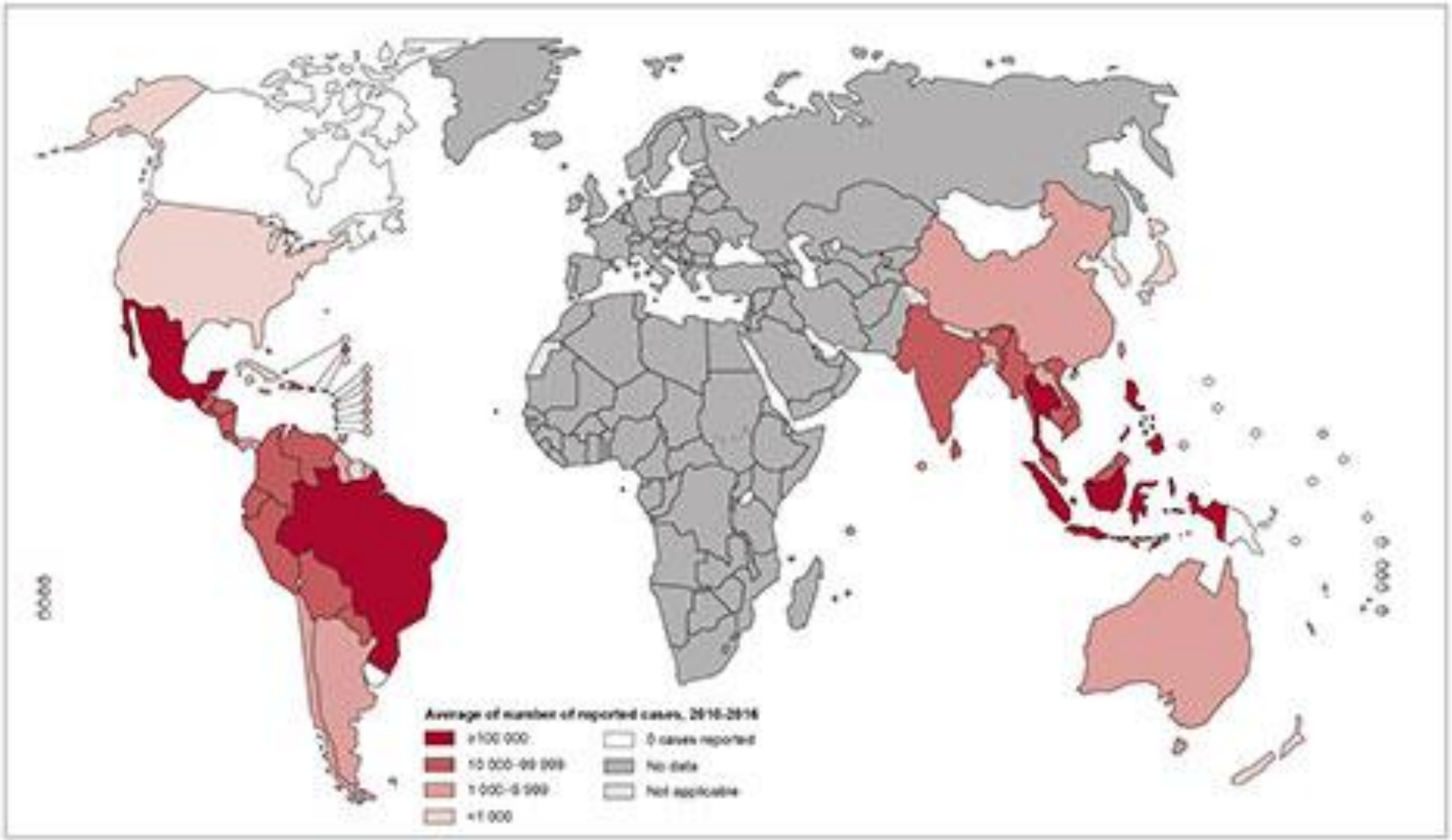
No

Table 4A.1 - Ten Leading Causes of Morbidity

Philippines, 2018

	Disease	Number of case	Rate per 100,000 population
1	Acute Respiratory Tract Infection	1,209,821	1,139.53
2	Hypertension	602,811	567.79
3	ALRTI and Pneumonia	503,884	474.61
4	Urinary Tract Infection	280,687	264.38
5	Bronchitis	130,057	122.50
6	Acute Watery Diarrhea	112,543	106.00
7	Influenza	91,681	86.35
8	Diseases of the Heart	66,688	62.81
9	Dengue Fever	51,361	48.38
10	TB Respiratory	39,923	37.60

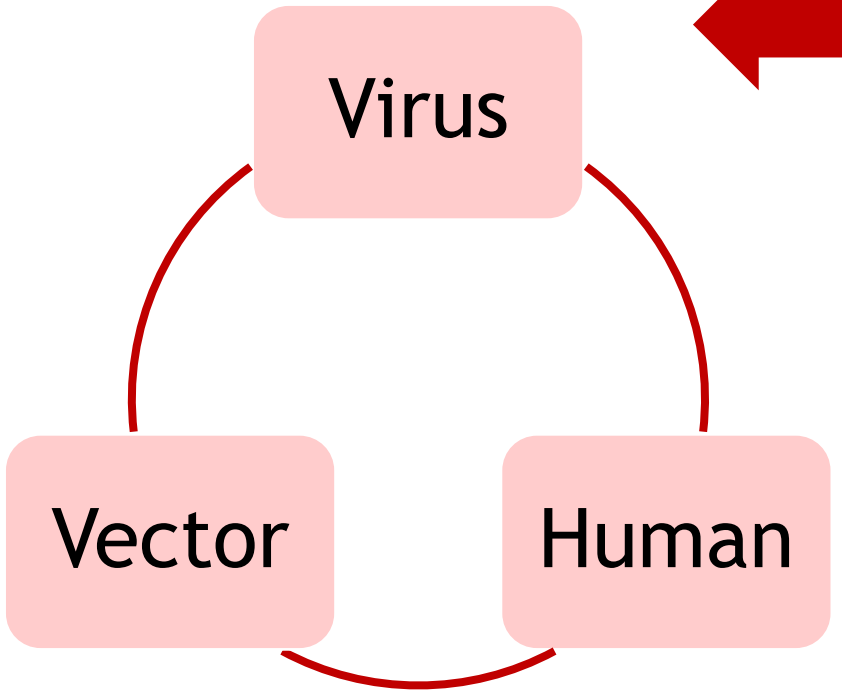
Distribution of dengue, worldwide, 2016



Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization

Dengue



Four distinct serotypes

DEN-1
DEN-2
DEN-3
DEN-4

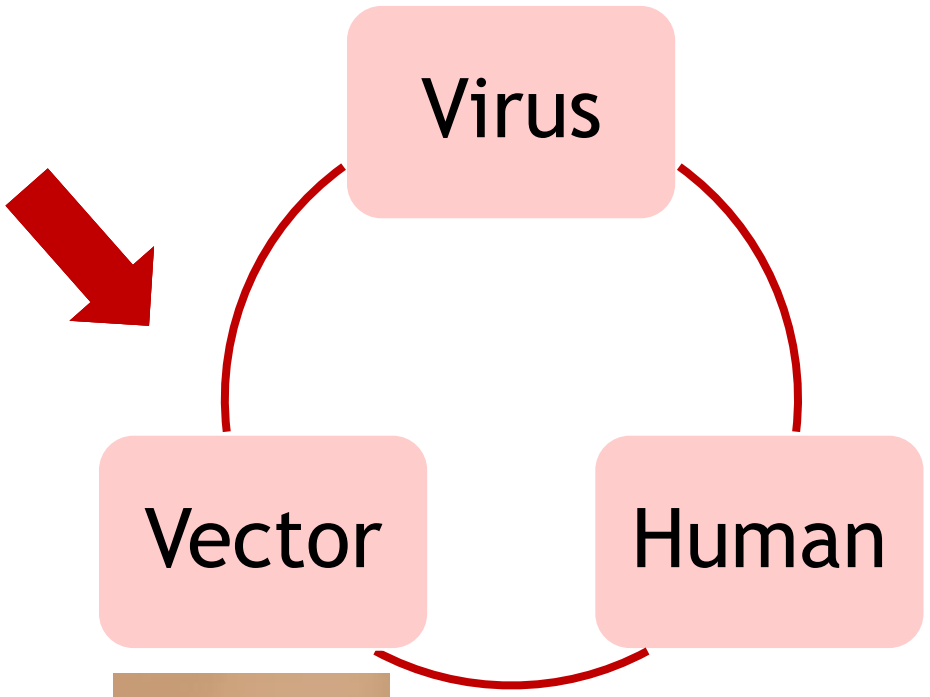
} "Asian"

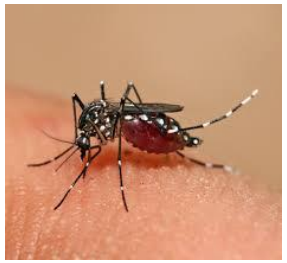
Genus: Flavivirus
Family: Flaviviridae

Dengue

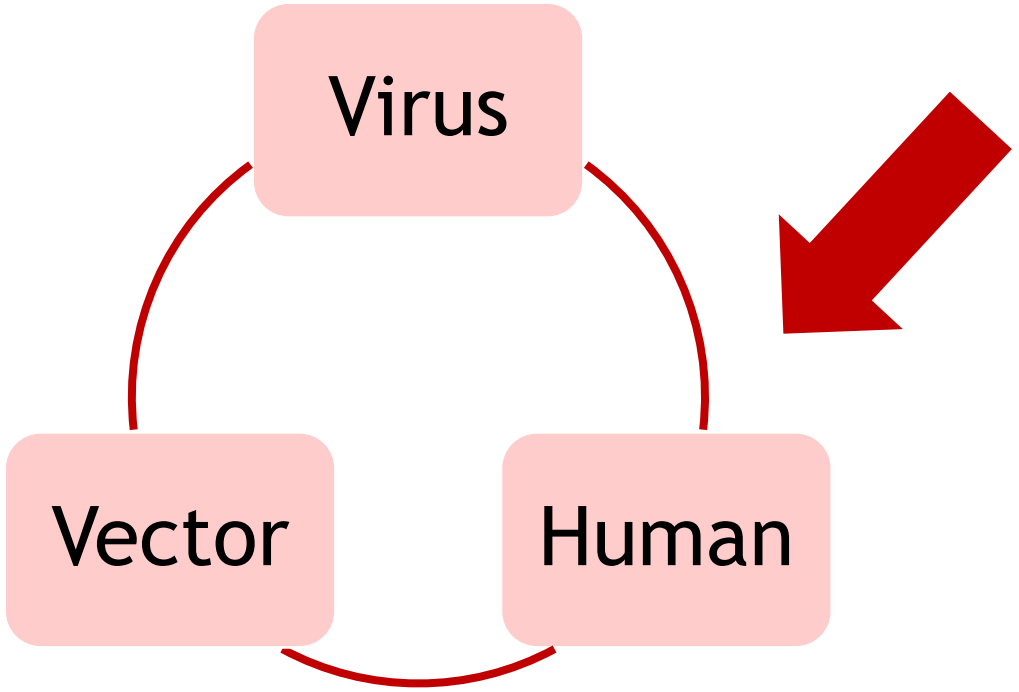
Aedes aegypti
- Tropical and subtropical areas
- Breed close to houses
- Daytime feeders
- Take multiple blood meals in a single breeding

Aedes albopictus
- More tolerant of cold
- Daytime and night time feeder





Dengue



Once infected, human become the main carriers and multipliers of the virus

Incubation time: 2-7 days

Symptom onset: 4-5 day; maximum 12

Recovery from one serotype provides lifelong immunity against that serotype

+ partial and transient protection against the other 3 serotypes

Case vignette

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  - **High grade fever (Tmax 39.5˚C) for 2 days**
  - **Poor appetite**, **vomiting** and **body pains**

- Pertinent PE
  - VS: HR: 110 bpm, RR: 24 bpm, T **39.2˚C**
    BP: 90/60 mmHg, Weight: 15kg
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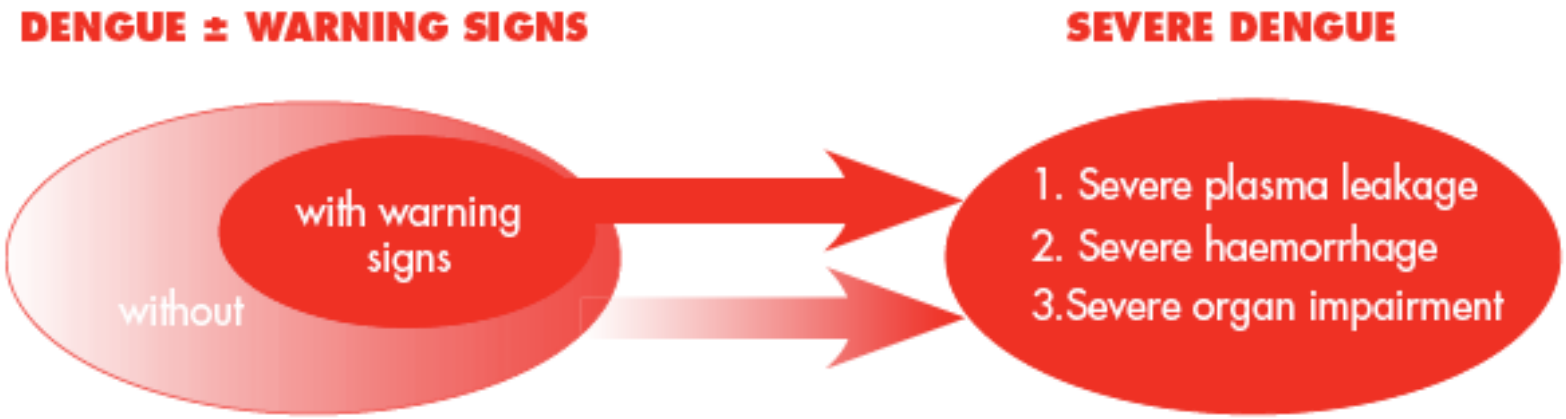
  - Rest of PE normal
  - **(-) tourniquet test**

Initial CBC

Hgb 110 G/L
Hct 0.33
WBC 4.0 x 10^9/L
Neutrophils 0.25
Lymphocytes 0.70
Platelet 160,000 U/L

Is it a dengue case? How is it classified?

WHO Case classification



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
- 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 enlargment >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

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 >=1000
- CNS: Impaired consciousness
- Heart and other organs

Dengue Case Classification

Probable Dengue Fever

Lives in or travels to dengue-endemic area, with fever, plus ANY TWO of the following

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

<u>Any warning sign</u>

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

Case vignette

- Junior, a 5-year-old boy, previously healthy, was brought to Ambulatory Care Unit for the following
  - ☑ **High grade fever** (Tmax 39.5°C) for 2 days
  - Poor appetite, **vomiting** and **body pains**

- Pertinent PE
  - VS: HR: 116 bpm, RR: 24 bpm, T **39.2°C**
    BP: 90/60 mmHg, Weight: 15kg
  - (+) flushed skin
  - Hyperemic throat but no exudates
  - Rest of PE normal
  - (-) tourniquet test

Initial CBC

Hgb 110 G/L
Hct 0.33
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Neutrophils 0.25
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Platelet 160,000 U/L

Dengue Case Classification

Probable Dengue Fever

Lives in or travels to dengue-endemic area, with fever, plus ANY TWO of the following

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

DENGUE WITH NO WARNING SIGNS

Dengue Case Classification

Laboratory-confirmed dengue

- Viral culture **and/or**
- Polymerase Chain Reaction (PCR) **and/or**
- Nucleic Acid Amplification Test- Loop Mediated Amplification Assay (NAAT-LAMP) **and/ or**
- Plaque Reduction Neutralization Test (PRNT)

Dengue Case Classification

Severe dengue

Severe plasma leakage

- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe hemorrhage

- As evaluated by clinician

Severe organ impairment

- Liver: AST or ALT >=1000
- CNS: impaired consciousness
- Heart and other organs

How do we manage a dengue case?

Stepwise approach to dengue management

Overall assessment

- History
- Physical examination
- Investigation, laboratories

Diagnosis, assessment of disease phase & severity

Management

- Disease notification
- Management decisions based on severity

Stepwise approach to dengue management

STEP 1:
Overall Assessment

HISTORY

- Onset of fever/illness
- Oral intake
- Assess for warning signs
- Diarrhea
- Seizures, impaired consciousness, behavioral changes
- Urine output
- Other relevant history:
  - Dengue in other family members
  - Travel to dengue-endemic area
  - Co-existing conditions

Stepwise approach to dengue management

STEP 1:
Overall Assessment

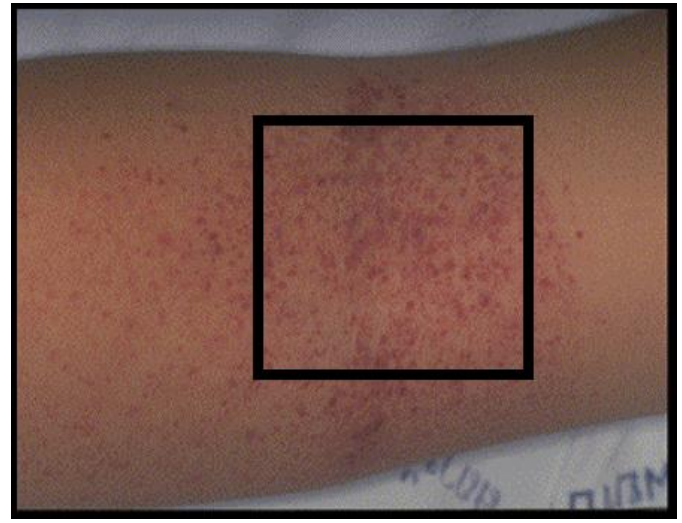
Physical examination

- Mental state & GCS score
- Hydration status
- Hemodynamic status
- Tachypnea/ acidotic breathing/ pleural effusion
- Abdominal tenderness/hepatomegaly/ascites
- Rash and bleeding manifestations
- Tourniquet test*

Tourniquet test

- Marker of capillary fragility

- How to do it?
  - Take the BP, and record (e.g. BP 100/70)
  - Inflate the cuff to a point midway between SBP and DBP (e.g. (100+70)/2 = 85)
  - Reduce and wait 2 minutes
  - Count petechiae below antecubital fossa



A positive test is ≥ **10** or more petechiae per 1 square inch

Stepwise approach to dengue management

STEP 1:
Overall Assessment

Investigation

- Full blood count
- A hematocrit to establish baseline
- Laboratory tests to confirm is optional
- Additional tests , if indicated: tests of liver function, creatinine, bicarbonate, urine specific gravity etc.

Stepwise approach to dengue management

STEP 2:
Diagnosis, Assessment of Disease Phase and Severity

Determine

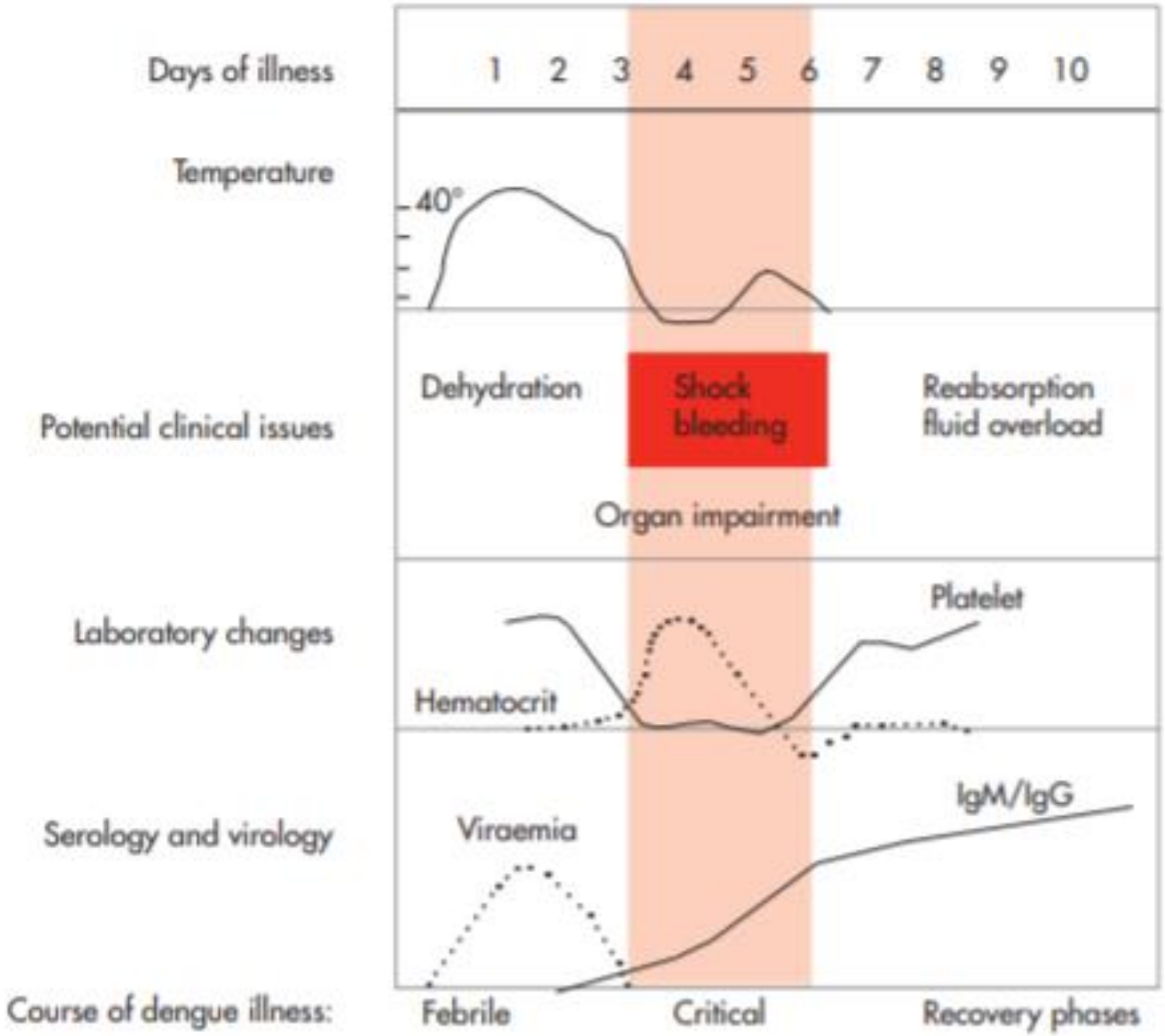
- Is this dengue?
- Phase of dengue (febrile/critical/recovery)
- Presence of warnings signs
- Hydration and hemodynamic status
- Does the patient require admission

The course of dengue illness

Febrile

Critical

Recovery



Laboratory test

DENGUE NS1 RDT

- Requested between 1-5 days of illness
- Used to detect dengue virus antigen during early phase of acute dengue infection

DENGUE IgM/IgG

- Requested beyond 5 days of illness
- Used to detect antibodies during the acute late stage of infection (IgM) and previous infection (IgG)
- May cross-react with other arboviral diseases (e.g. Chikungunya, Zika)

Question: Junior is likely in what disease phase?

✓ Febrile

Critical

Recovery

- ☐ Junior, a 5-year-old boy, previously healthy, was brought to Ambulatory Care Unit for the following
  - ☐ High grade fever (Tmax 39.5°C) for 2 days
  - ☐ Poor appetite, vomiting and body pains
- ☐ Pertinent PE
  - ☐ VS: HR: 128 bpm, RR: 28 bpm, T 39.2°C
    BP: 90/60 mmHg, Weight: 15kg
  - ☐ (+) flushed skin
  - ☐ Hyperemic throat but no exudates
  - ☐ Rest of PE normal
  - ☐ (-) tourniquet test

Initial CBC

Hgb 110 G/L
Hct 0.33
WBC 4.0 x 10^9/L
Neutrophils 0.25
Lymphocytes 0.70
Platelet 160,000 U/L

Question: Which test should be ordered in Junior's test? (check all that applies)

✓ CBC w/pc

✓Dengue NS1Ag

Dengue IgM/IgG

Various clinical problems during the different phases

Febrile phase	Critical phase	Recovery phase
• Dehydration • High fever may cause neurologic disturbances and febrile seizures in young children	• Shock from plasma leakage • Severe hemorrhage • Organ impairment	• Hypervolemia (only if intravenous fluid therapy has been excessive and/or has extended into this period)

Stepwise approach to dengue management

STEP 3:
Management

Disease Notification

Management Decisions

GROUP A → send home

GROUP B → refer for in-hospital management

GROUP C → require emergency treatment and urgent referral

Management decisions

- Patients may be sent home
- Adequate bed rest
- Adequate fluid intake
- Paracetamol for fever

GROUP A

Without warning signs

- In-hospital care
- Encourage oral fluid intake
- Initiate IV fluids with crystalloids if oral intake is not tolerated

GROUP B

With warning sings

- Requires emergency treatment
- IV fluid resuscitation
- Blood transfusion, when necessary

GROUP C

Severe Dengue

What will be your disposition for Junior?

A. Send home and monitor ✓

B. Refer for in-hospital management

C. Refer for emergency treatment

Group A:
Patients who may be sent home

Patients with all of the following:

- Able to tolerate adequate volumes of oral fluids
- Pass urine at least once every 6 hours
- Does not have any of the warning signs, particularly when fever subsides
- Stable hematocrit

Ambulatory patients should be monitored daily for disease progression (decreasing WBC, defervescence, and warning signs)

Advice to return to the hospital immediately if any warning signs develop

ACTION PLAN: GROUP A (Home Care)

ORS

- Encourage oral intake of ORS, fruit juice and other fluids containing electrolytes and sugar
- Caution: fluids containing sugar/ glucose among diabetics

Paracetamol

- Give paracetamol for high fever
- Tepid sponge if patient still has high fever
- Do not give aspirin, NSAIDs (may aggravate bleeding/gastritis)

Dengue home care & advice

- Ideally, monitor daily for temperature pattern, volume intake and losses, & urine output
- Instruct care-givers to bring the patient if with any warning sign

Calculation of Oral Rehydration Fluids

Body Weight (kg)	ORS to be given
> 3-10	100 ml/kg/day
> 10-20	75 ml/kg/day
> 20-30	50-60 ml/kg/day
> 30-60	40-50 ml/kg/day

Ludan A. Chapter 41: Pediatric Fluid and Electrolyte Therapy. In *Textbook of Pediatrics and Child Health*. del Mundo F, Estrada FA, Santos-Ocampo PD, Navarro XR, editors. Manila: JMC Press. Fourth edition. 2000:1485-1499

What is the minimum amount of fluids for Junior?

Weight: 15kg

1000mL

✓ 1125mL

1500mL

Group B:
Patients for In-patient management

These includes the following:

- with warning signs
- with co-existing conditions that make dengue or its management more complicated (e.g. pregnant, infant, old age, DM, hemolytic disease)
- with social circumstances (living alone, living far from a health facility)

ACTION PLAN: DENGUE WITHOUT WARNING SIGNS (IN-HOSPITAL)

Encourage ORS

IVF 0.9% saline or LR ± dextrose at maintenance rate, if ORS not tolerated

ORS after a few hours after IVF therapy

ACTION PLAN: DENGUE WITHOUT WARNING SIGNS (IN-HOSPITAL)

- ☐ Periodic assessment needed for appropriate fluid adjustment
- ☐ Monitor clinical parameters and correlate with hematocrit
- ☐ Avoid over- and under hydration
- ☐ Decrease IVF anytime based on clinical assessment
- ☐ If with signs of deterioration → manage for compensated or hypotensive shock

Monitor:

- Temperature pattern
- Volume of fluid intake and losses
- Urine output (volume & frequency)
- Warning signs
- Hct, WBC, platelet count

Group C:
Patients for emergency treatment & urgent referral

These patients have:

- Severe plasma leakage leading to dengue shock and/or fluid accumulation with respiratory distress
- Severe hemorrhages
- Severe organ impairment (hepatic, renal, cardiomyopathy, encephalopathy or encephalitis)

Is prophylactic platelet transfusion warranted among dengue patients with thrombocytopenia?

- There is **insufficient evidence** to say that prophylactic platelet transfusion in patients with minimal or no active bleeding will improve platelet counts, prevent hemorrhage and reduce mortality

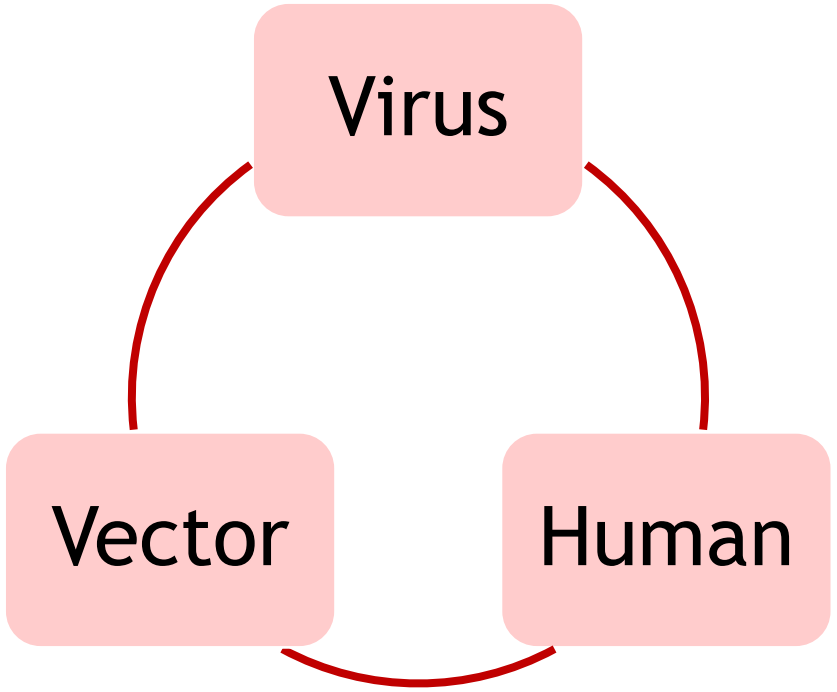
- Children with dengue who have platelet count <50,000 mm3 with minimal or no active bleeding should NOT be give prophylactic platelet transfusion

Strong recommendation, based on moderate to very low-quality evidence

PPS-PIDSP. (2017). Clinical Practice Guidelines on Dengue in Children.

How do we prevent and control the infection?

Dengue



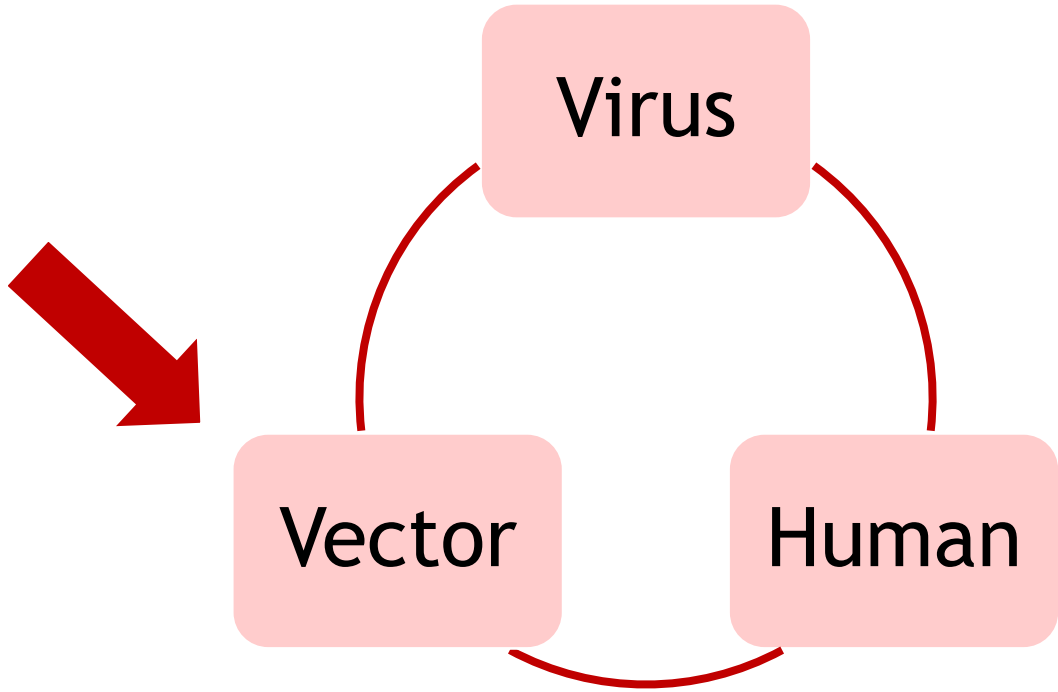
Avoid getting further mosquito bites if you know you are infected

Dengue

Main method:
Prevent mosquito breeding sites

- Environmental management and modification
- Dispose of solid waste properly
- Covering domestic water storage
- Apply insecticides

Community engagement
- Educate the community on the risks of mosquito-borne diseases
- Engage the community for mobilization in sustained vector control



National Dengue Prevention and Control Program

Objective: reduce dengue morbidity by at least 25% by 2022

Program components:

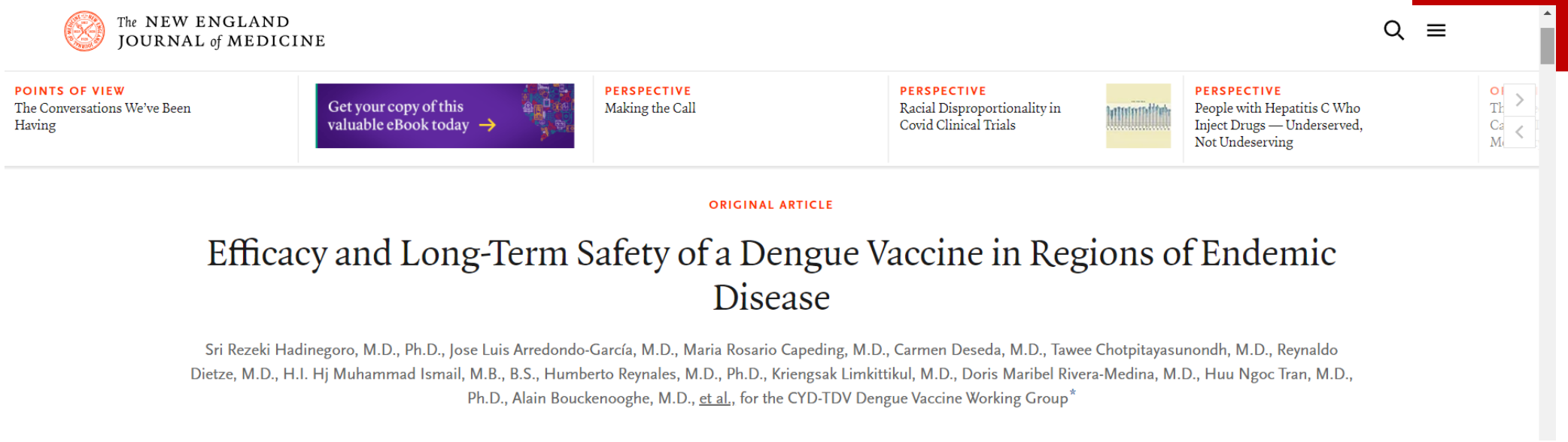
- ☐ Surveillance
- ☐ Case management and Diagnosis
- ☐ Integrated Vector Management (IVM)
- ☐ Outbreak response
- ☐ Health promotion & advocacy
- ☐ Research

4S strategy:

- Search and destroy
- Seek early consultation
- Self-protection measures
- Say yes to fogging only during outbreaks

Is the dengue vaccine effective? Is it safe?

Efficacy



Based on 2 phase III clinical trials, the pooled efficacy showed:

- 65.6% reduction in symptomatic dengue
- 80.8% reduction in hospitalized dengue
- 93.2% reduction in severe

There is a higher reduction of symptomatic dengue among DENV seropositive individuals (81.9%; 95%CI: 67.2 90) compared to those who are seronegative (52.5%, 95% CI 5.9-76.1%)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy

S. Sridhar, A. Luedtke, E. Langevin, M. Zhu, M. Bonaparte, T. Machabert, S. Savarino, B. Zambrano, A. Moureau, A. Khromava, Z. Moodie, T. Westling, C. Mascareñas, C. Frago, M. Cortés, D. Chansinghakul, F. Noriega, A. Bouckenooghe, J. Chen, S.-P. Ng, P.B. Gilbert, S. Gurunathan, and C.A. DiazGranados

ABSTRACT

BACKGROUND

In efficacy trials of a tetravalent dengue vaccine (CYD-TDV), excess hospitalizations for dengue were observed among vaccine recipients 2 to 5 years of age. Precise risk estimates according to observed dengue serostatus could not be ascertained because of the limited numbers of samples collected at baseline. We developed a dengue anti–nonstructural protein 1 (NS1) IgG enzyme-linked immunosorbent assay and used samples from month 13 to infer serostatus for a post hoc analysis of safety and efficacy.

METHODS

In a case–cohort study, we reanalyzed data from three efficacy trials. For the principal analyses, we used baseline serostatus determined on the basis of measured (when baseline values were available) or imputed (when baseline values were missing) titers from a 50% plaque-reduction neutralization test ($PRNT_{50}$), with imputation conducted with the use of covariates that included the month 13 anti-NS1 assay results. The risk of hospitalization for virologically confirmed dengue (VCD), of severe VCD, and of symptomatic VCD according to dengue serostatus was estimated by weighted Cox regression and targeted minimum loss–based estimation.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Sridhar at Sanofi Pasteur, 1541 Ave. Marcel Mérieux, 69280, Marcy l'Etoile, France, or at saranya.sridhar@sanofi.com.

Dr. Luedtke, Ms. Langevin, and Dr. Zhu contributed equally to this article.

This article was published on June 13, 2018, at NEJM.org.

N Engl J Med 2018;379:327-40.
DOI: 10.1056/NEJMoa1800820

Post-hoc analysis on safety

Dengue-seronegative participants:
HR for hospitalization:
1.75 (95% CI 1.14-2.70) among 2-16 years

HR 1.41 (95%CI 0.74-2.68) among 9-16 years

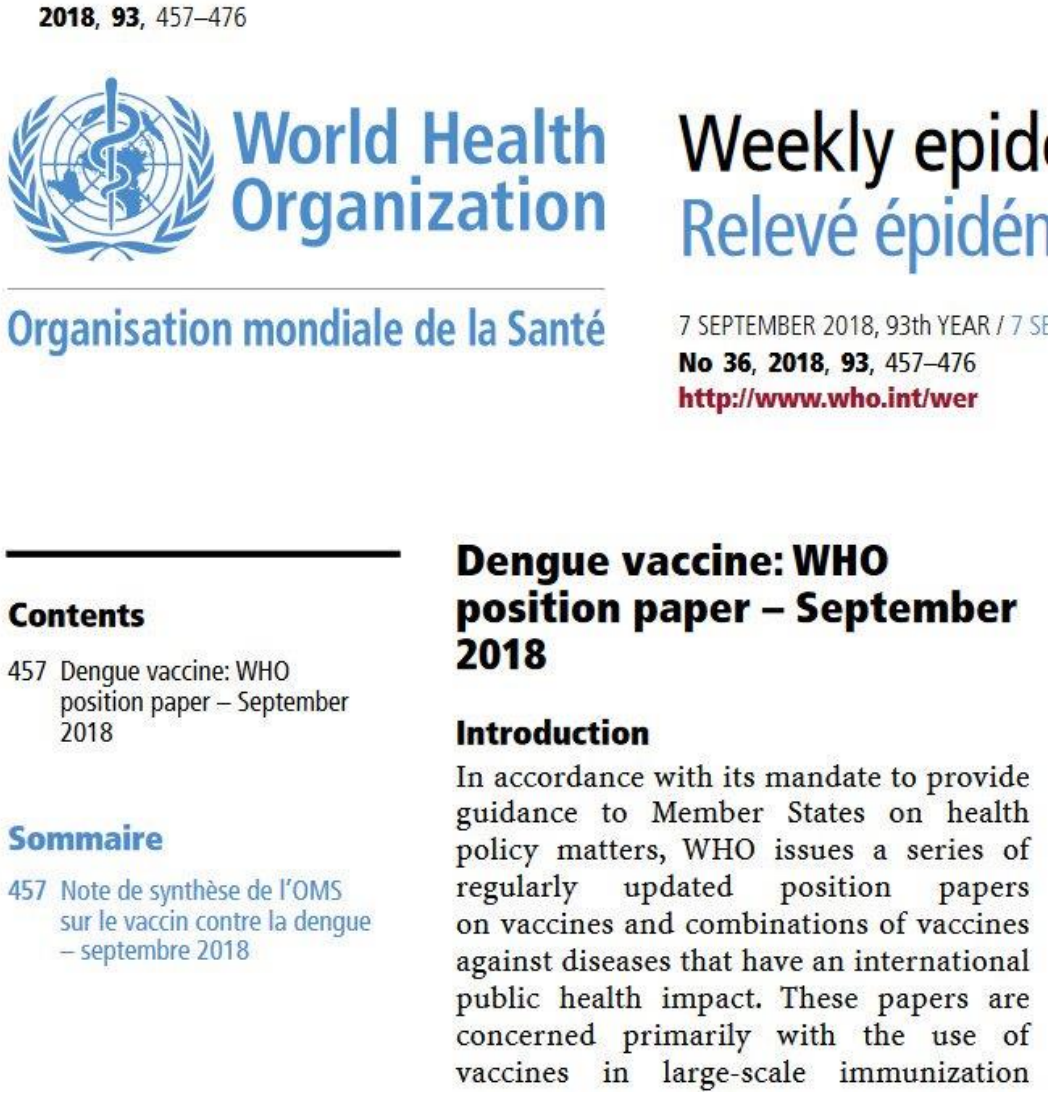
The risk of severe dengue was lower among seropositive vaccine recipients

WHO Position

the live attenuated dengue vaccine CYD-TDV has been shown in clinical trials to be *efficacious and safe in persons who have had a previous dengue virus infection* (seropositive individuals).

However, it *carries an increased risk of severe dengue in those who experience their first natural dengue infection after vaccination* (seronegative individuals)

For countries considering vaccination as part of their dengue control programme, *pre-vaccination screening is the recommended strategy*. With this strategy, only persons with evidence of a past dengue infection would be vaccinated



2018, 93, 457–476

World Health Organization

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No 36, 2018, 93, 457–476
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Dengue vaccine: WHO position paper – September 2018

Introduction

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization

Is there a role of “Tawa-tawa” in the management of dengue fever?

Hindawi
Journal of Tropical Medicine
Volume 2018, Article ID 2048530, 7 pages
https://doi.org/10.1155/2018/2048530

Review Article

Potential Use of *Euphorbia hirta* for Dengue: A Systematic Review of Scientific Evidence

Sashini D. Perera, Uthpala A. Jayawardena, and Chanika D. Jayasinghe

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Received 20 December 2017; Accepted 12 March 2018; Published 16 April 2018

Academic Editor: Marcel Tanner

Euphorbia hirta commonly known as *Tawa-Tawa* is a plant used in folklore medicine in the Philippines for the treatment of dengue. Though, *E. hirta* has been extensively investigated for numerous bioactivities, limited studies have been conducted on the antidengue activity. Thus, the present study provides a comprehensive review of studies conducted on the antidengue activity of *E. hirta*. A systematic literature survey was carried out in scientific databases, PubMed®, Scopus, and Google Scholar, for research carried on the antidengue activity of *E. hirta*. The literature search identified a total of 867 articles: databases PubMed = 6, Scopus SciVerse® = 423, and Google Scholar = 437; one additional article was identified by searching reference lists. Eight full papers were entitled to the review; out of those, two studies focused on ethnobotanical surveys, three on animal experiments, one on human trial, and two on *in vitro* antiviral activities, and one was computational study. The available evidence conclusively demonstrates the potential of *E. hirta* against dengue as it holds significant antiviral and platelet increasing activities. However, the number of studies conducted to validate its antidengue activity was found to be inadequate. Hence, well-controlled clinical trials and contemporary pharmacological approaches including activity guided fractionation and elucidation of the mode of action are encouraged to establish the use of *E. hirta* for dengue.

"The available evidence conclusively demonstrates the potential of *E. hirta* against dengue"

Critic:
8 full papers
Low quality studies

→ Need for clinical trials

Summary

- Recognize patients who are presenting with dengue by symptomatology
- Manage the patients accordingly by proper classification, triaging, ordering of laboratories as necessary, and ensure adequate hydration
- Recommend preventive and control measures to families and communities

Thank you!

References

- Department of Health. (nd). Dengue Health Advisory. Retrieved from: https://www.doh.gov.ph/Health-Advisory/Dengue
- Perera SD et al. (2018). Potential Use of Euphorbia hirta for Dengue: A Systematic Review of Scientific Evidence. DOI: 10.1155/2018/2048530
- Sridhar S *et al*. (2018). *Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy*. N Engl J Med 379:327-40
- Thomas SJ *et al*. (2019). Dengue Virus Infection: Clinical Manifestations and Diagnosis. Retrieved from UptoDate
- Thomas SJ *et al*. (2019). Dengue Virus Infection: Prevention and Treatment. Retrieved from UptoDate
- World Health Organization. (2020). *Dengue and Severe Dengue*. Retrieved from WHO: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue
- World Health Organization. (nd). *Dengue Control*. Retrieved from: https://www.who.int/denguecontrol/disease/en/
- World Health Organization. (2009). *Dengue Guidelines for Diagnosis, Treatment, Prevention and Control*