Why should you care about dengue?
Situational update and key concepts of clinical presentation and management

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Disclaimer

The findings and conclusions of this presentation are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Dengue Epidemiological Situation

Dengue Global Situation

AP AP News

Historic dengue fever outbreak hits Argentina

Hospital emergency rooms in Buenos Aires are overflowing with patients during a historic dengue fever outbreak.

26 mar 2024

World Health Organization (WHO)

WHO takes action against increasing dengue outbreaks in the Western Pacific Region

In April this year, the small Pacific island country of Samoa declared a dengue outbreak, reflecting a concerning trend of escalating rates...

29 may 2024

NPR NPR

Travelers beware: It's a big year for dengue

It's already a record-breaking year for dengue infections in Central and South America, with almost 10 million cases diagnosed so far.

29 jun 2024

Agência Brasil

Brazil reports 6.1 mi cases of dengue in six months

Brazil ended the first half of 2024 with 6,159,160 probable cases of dengue and 4,250 deaths from the disease. A total of 2,730 deaths are...
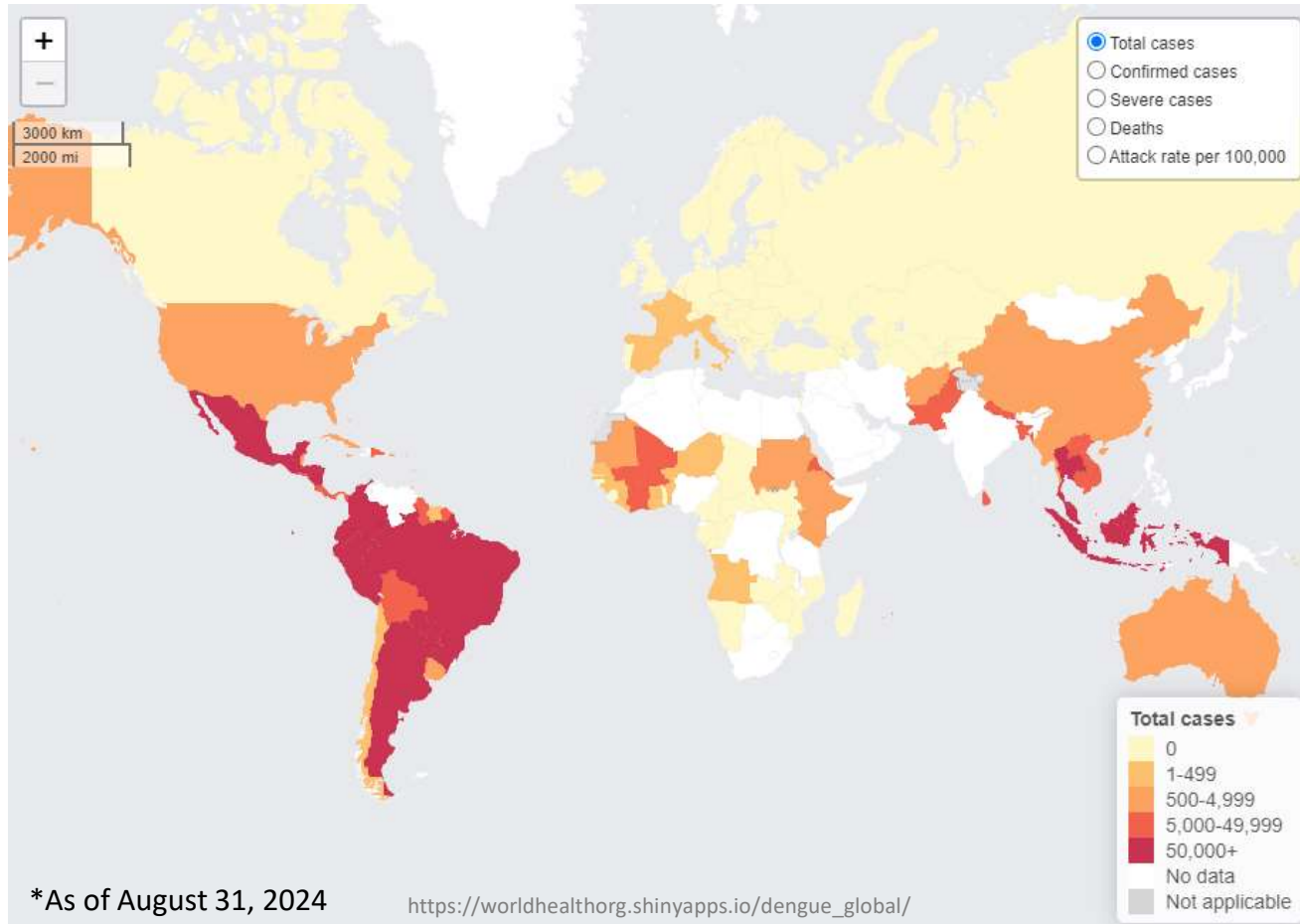
Africanews

Burkina Faso: more than 350 deaths from dengue fever in a month

An epidemic of dengue fever, a mosquito-borne disease, claimed 356 lives in Burkina Faso between mid-October and mid-November, bringing the...
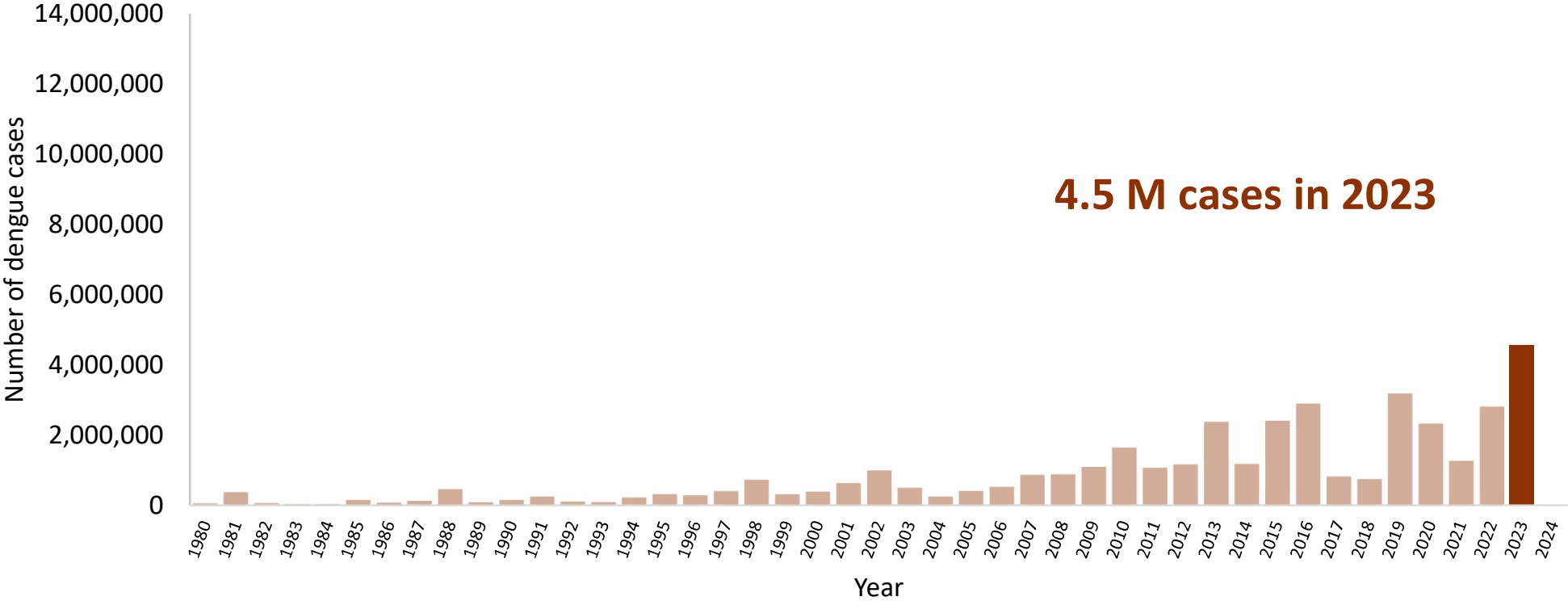
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Dengue Global Situation
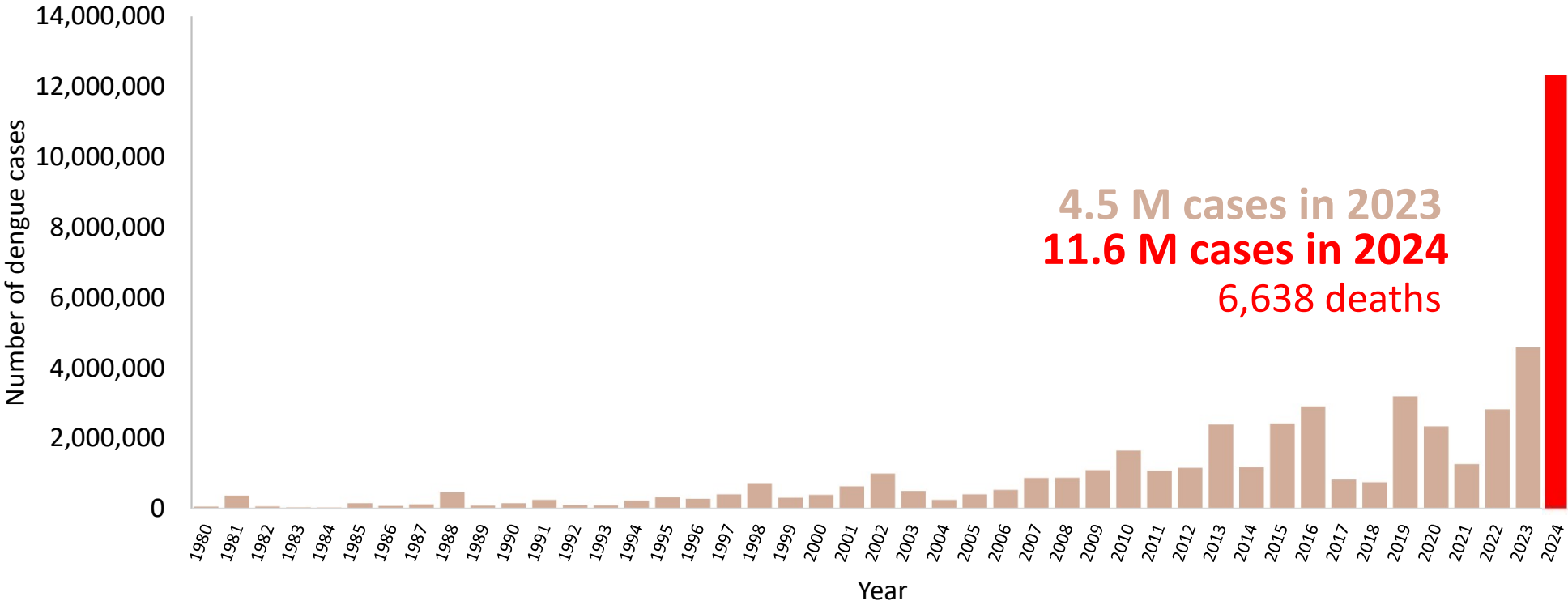## More than **12.3 M cases** reported in 2024*

*As of August 31, 2024

https://worldhealthorg.shinyapps.io/dengue_global/

Dengue in the Americas, 1980-2023

4.5 M cases in 2023

Dengue in the Americas, 1980-2024

Number of dengue cases (y-axis): 0 to 14,000,000

Year (x-axis): 1980 to 2024

4.5 M cases in 2023
11.6 M cases in 2024
6,638 deaths

Data from PAHO PLISA Health Information Platform for the Americas

Dengue Travel Health Notices, CDC
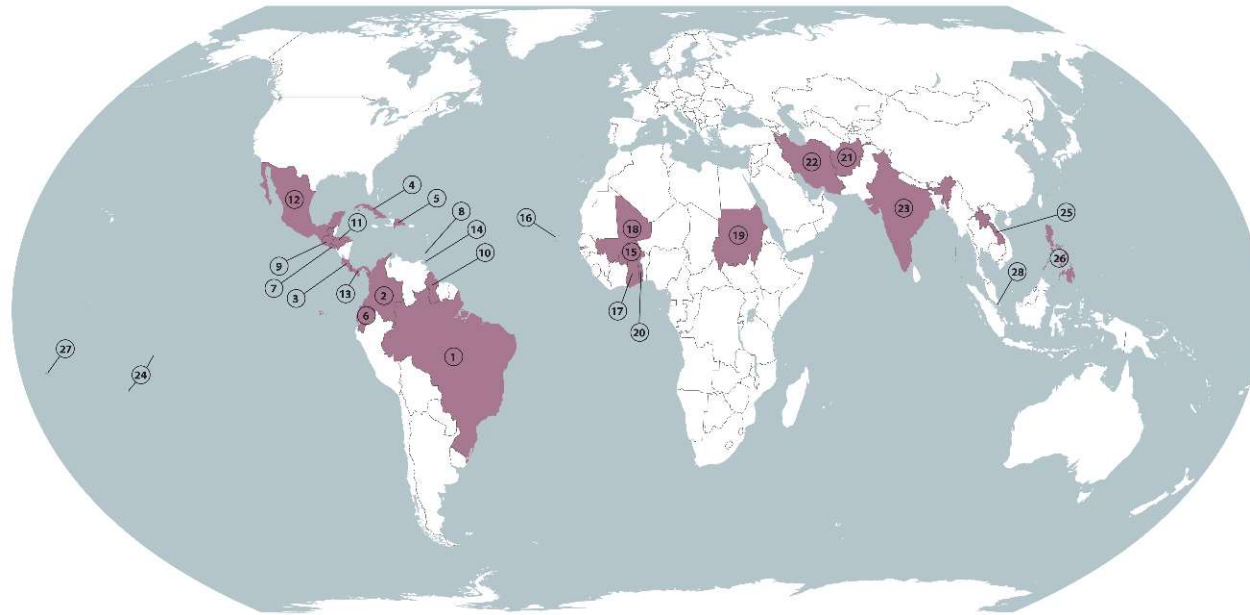
Dengue THN by WHO Region

AMERICAS
1. Brazil
2. Colombia
3. Costa Rica
4. Cuba
5. Dominican Republic
6. Ecuador
7. El Salvador
8. Grenada
9. Guatemala
10. Guyana
11. Honduras
12. Mexico
13. Panama
14. Trinidad and Tobago

AFRICA
15. Burkina Faso
16. Cape Verde
17. Ghana
18. Mali
19. Sudan
20. Togo

EASTERN MEDITERRANEAN
21. Afghanistan
22. Iran

SOUTH-EAST ASIA
23. India

WESTERN PACIFIC
24. French Polynesia
25. Laos
26. Philippines
27. Samoa
28. Singapore

Countries reporting higher-than-usual numbers of dengue cases

Names and boundary representation are not necessarily authoritative.

https://wwwnc.cdc.gov/travel/notices/level1/dengue-global

Dengue in the United States
Travel associated cases

- Most dengue cases in US states are related to travel

- In 2024, **1,750 cases** reported in 50 jurisdictions (1,890 in all 2023)

- Highest case numbers:
  - Florida (n=410)
  - New York (n=235)
  - California (n=177)
  - Massachusetts (n=102)
  - Illinois (n=71)

AS GU PR VI MP FM PW MH

No reported cases   1 to 4   5 to 49   50 to 249   250+
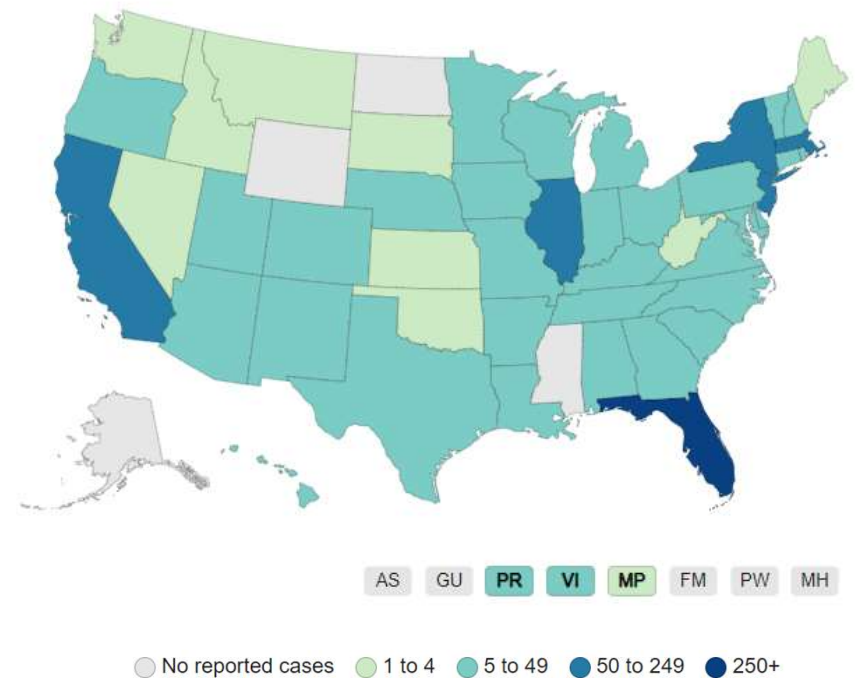
Dengue in the United States
Endemic areas

- Dengue is endemic in six US territories and freely associated states*
- Puerto Rico declared a public health emergency due to dengue in March 2024
- Total 3,332 cases, 194 (5.8%) severe
- Predominance of DENV-3
- Five dengue related deaths

Salud declara epidemia de dengue en Puerto Rico

El secretario de Salud, Carlos Mellado, firmó un orden administrativa, declarando una emergencia de salud pública.

Por **TELEMUNDO PR** y **The Associated Press** • Publicado el 25 de marzo del 2024 •

Increased Risk of Dengue Virus Infections in the United States

Print

HAN HEALTH ALERT NETWORK

This is an official **CDC** HEALTH ADVISORY

Distributed via the CDC Health Alert Network
June 25, 2024, 2:30 PM ET
CDCHAN-00511

DECLARAN EPIDEMIA DE DENGUE EN PUERTO RICO

https://www.telemundopr.com/noticias/puerto-rico/salud-declara-epidemia-de-dengue-en-puerto-rico/2591931/

*Puerto Rico, US Virgin Islands, American Samoa, Federated States of Micronesia, Marshall Islands, Palau
** Data as of Sept 8 https://www.salud.pr.gov/CMS/DOWNLOAD/9277

Dengue in the United States
Locally acquired cases
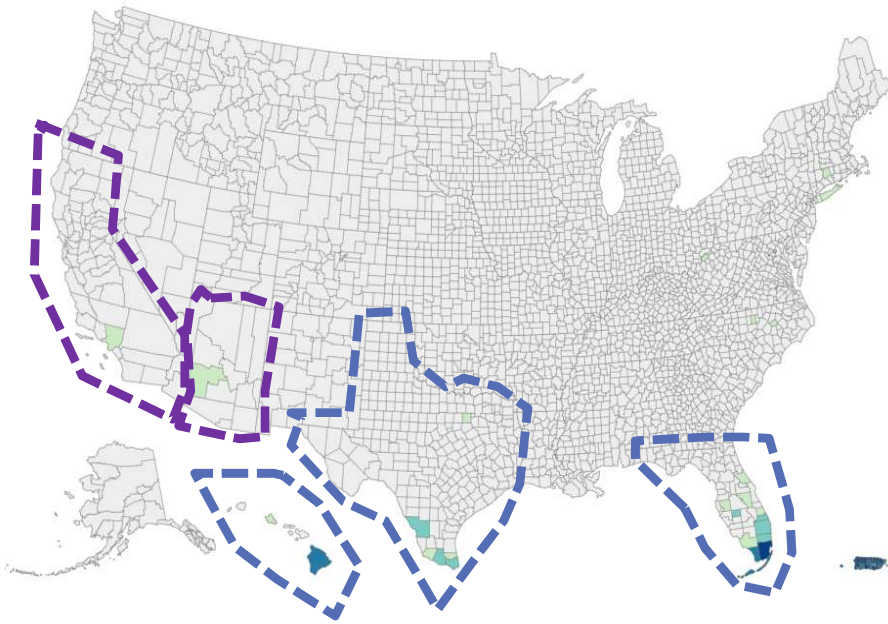
- Sporadic cases to limited oubreaks
  - Florida, Hawaii, Texas

- First evidence of local transmission
  - Arizona, n=2 (2022)
  - California, n=2 (2023)

In 2024:
35 cases in Florida and
3 in California

Dengue Clinical Presentation

Dengue Clinical Classification – WHO (2009)

Dengue

Dengue with warning signs

Severe dengue

Probable Dengue

Live in/travel to endemic area within the last **14 days**

Fever and **two** of the following criteria:

- Nausea/vomiting
- Rash
- Aches and pains (headache, retro-orbital pain, myalgia, arthralgia)
- Tourniquet test positive/petechiae
- Leukopenia

One or more of the following warning signs:

- Abdominal pain or tenderness
- Persistent vomiting (≥3/h, or ≥4/6 h)
- Clinical fluid accumulation (ascites, pleural effusion)
- Mucosal bleeding
- Lethargy, restlessness
- Postural hypotension
- Liver enlargement >2 cm
- Progressive increase in hematocrit

One or more of the following manifestations:

- Severe plasma leakage leading to
  Shock
  Respiratory distress
- Severe bleeding
- Severe organ involvement
  Liver (AST or ALT >1,000)
  Brain
  Heart

AST: Aspartate Aminotransferase
ALT: Alanine Aminotransferase

Dengue Clinical Course

Mosquito bite

3 - 14 days

2 - 7 days

1 - 2 da

Incubation

Febrile

Critica

Viremic

-7

0

7

Days
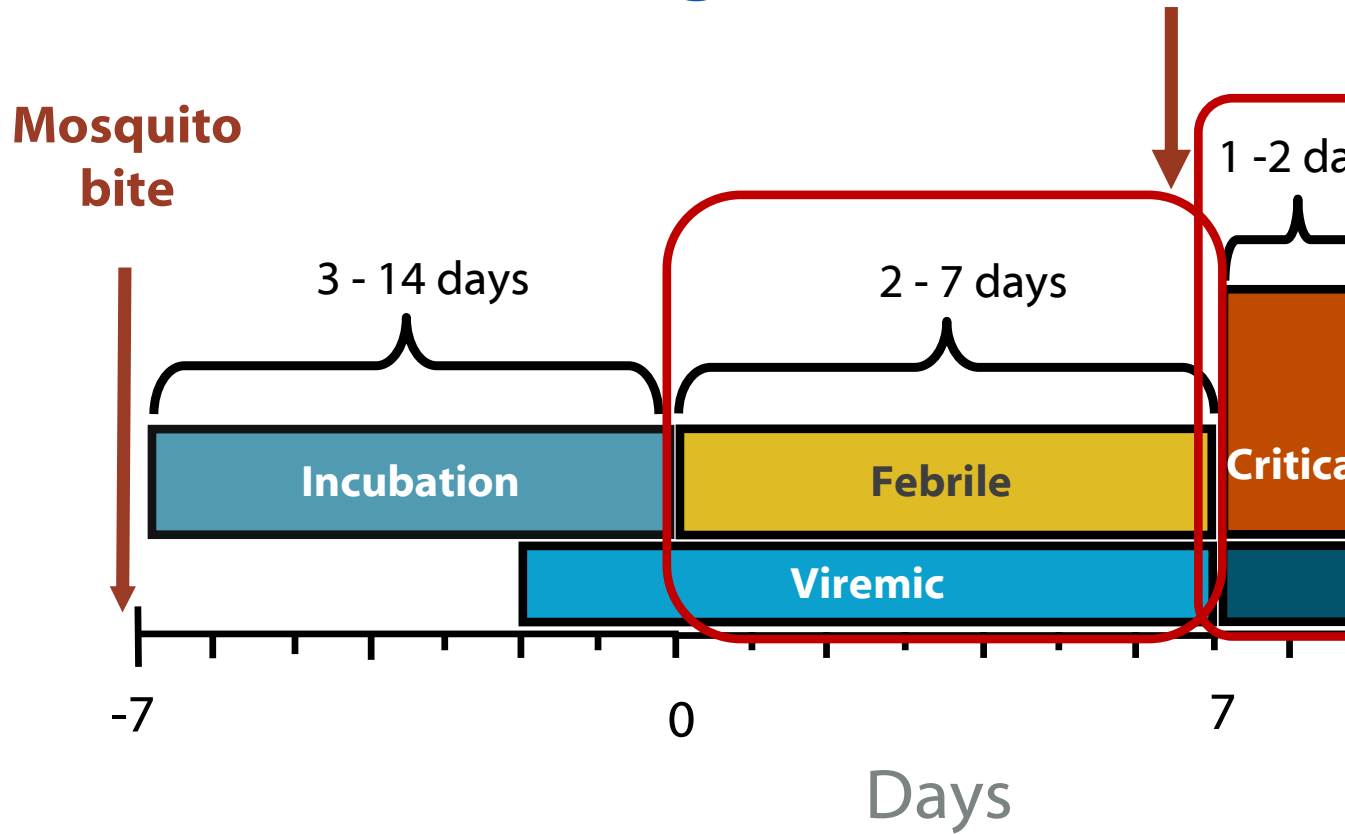
Dengue Clinical Management

Clinical management

- **Management of dengue should be based on clinical evaluation, not on lab confirmation**
  Test with PCR and IgM **or** NS1 and IgM

- Progression to severity is possible in all patients

- Determine:

  - Clinical severity classification

  - Phase of disease

  - Comorbidities

  And classify patient in group A, B1, B2, or C

- Most patients can be managed at home

  Bed rest, oral hydration, acetaminophen

- Pregnant patients should be hospitalized

Intravenous fluid therapy

Dengue Case Management

Presumptive Diagnosis

YES / NO

Repeat IV crystalloid solution at 10mL/kg up to two times§

Reduce IV crystalloid solution progressively§
- 5-7mL/kg/hr for 2-4 hrs
- if improving decrease to 3-5mL/kg/hr for 2-4 hrs
- if improving decrease to 2-4mL/kg/hr

YES — Improvement in clinical status, urine output >1mL/kg/hr, stable or minimal change in hematocrit?¶

NO — Treat as group C (dengue with shock) Transfer to a higher level of care

and social risk on a case-by-case basis* / or AST>1000 IU] encephalitis)

| Group A Outpatient management | Group B Inpatient management | Group C Inpatient management |

*For co-existing conditions and social risk see page 6, item #9.

- There are no antivirals available
- Management is supportive
- Obtain a reference hematocrit
- Limit IV fluids in febrile phase – if patient can drink, encourage oral hydration
- IV fluids usually needed for only 24-48 hours
- Give minimum IV fluids required to restore IV volume, maintain good perfusion and urine output
- IV fluids are increased and decreased in a step-wise manner

Clinical management

- Monitor and reassess frequently
- Look for early signs of shock in all patients

  Narrow pulse pressure, delayed capillary refill, tachycardia

- Shock (not bleeding) is the most common severe dengue manifestation
- Patients with severe dengue should be placed in intensive care

- Do not use steroids routinely
- Do not give prophylactic transfusions
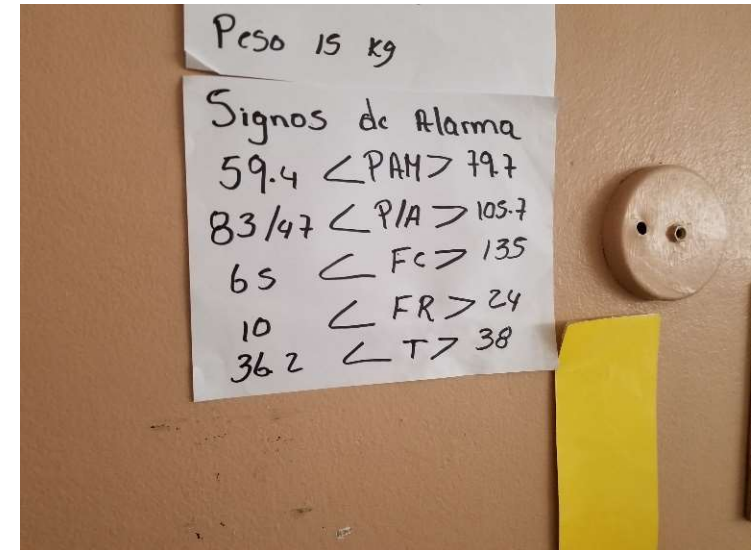
Normal vital signs ranges posted on the bed of a patient with dengue in a hospital in Honduras

Think dengue!

- Unrecognized disease is a common cause of death
- Early recognition of disease and appropriate clinical management with IV fluids can be life-saving

CDC Dengue Branch
dengue@cdc.gov
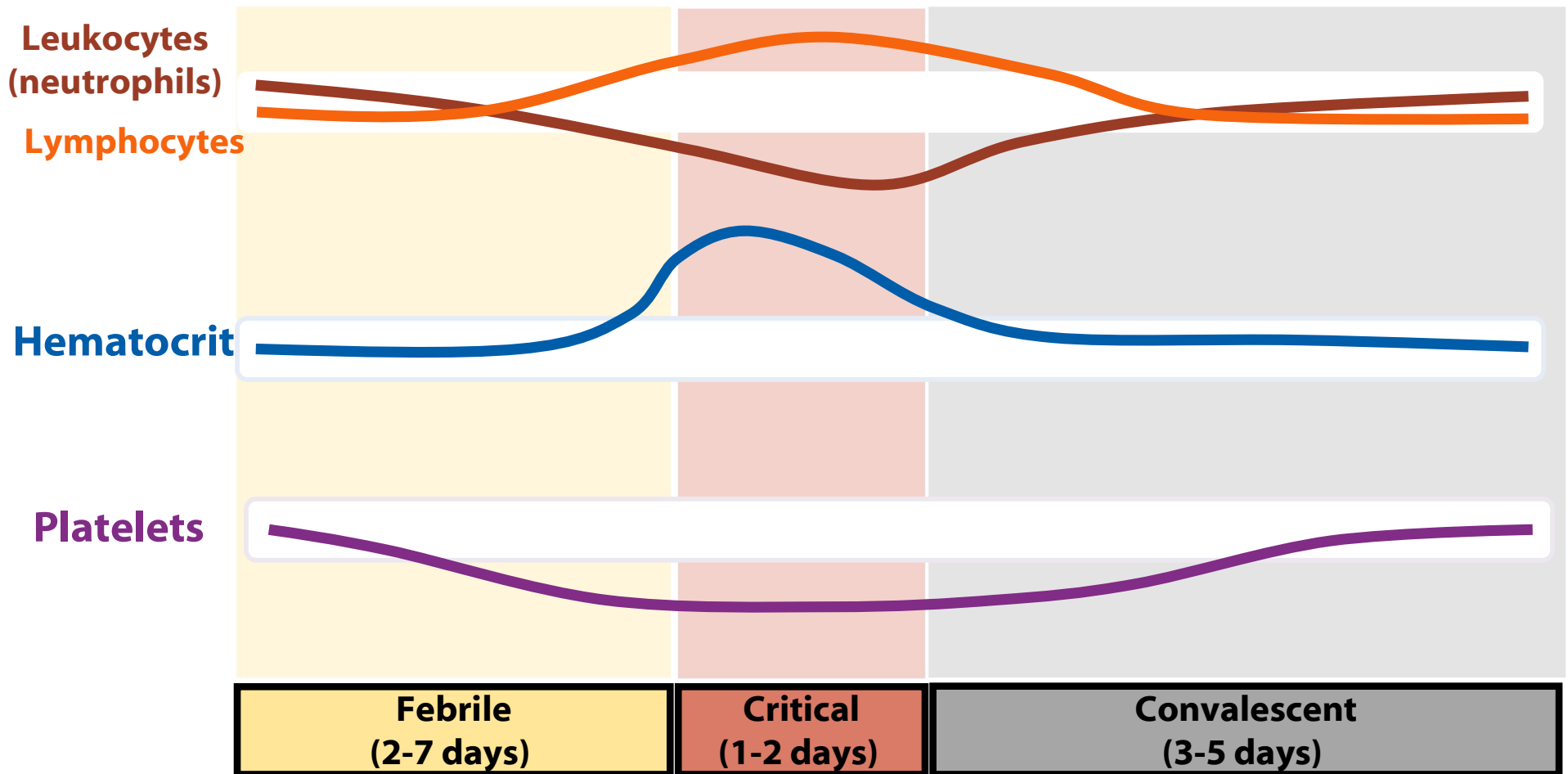
Liliana Sánchez-González
naq5@cdc.gov

Additional slides

Risk factors for severe disease

- Obesity, asthma, hypertension/heart disease, diabetes, kidney disease, chronic liver disease, coagulopathies, hemolytic diseases

- Pregnancy, infancy, elderly patients

- Secondary infection
  - Higher risk in secondary infection, compared to 1st, 3rd, and 4th
  - Dengue can progress to severe disease with any infection

Common laboratory findings

Leukocytes (neutrophils)

Lymphocytes

Hematocrit

Platelets

| Febrile (2-7 days) | Critical (1-2 days) | Convalescent (3-5 days) |

Tourniquet Test

- Take patients blood pressure and record (e.g. 100/70)

- Inflate blood pressure cuff to a point midway between systolic and diastolic pressure and maintain for 5 minutes.

  $([100 + 70] / 2 = 85$ mmHg$)$

- Reduce and wait 2 minutes.

- Count petechiae below antecubital fossa.

- Positive test: 10 or more petechiae per 1 inch^2

Dengue in pregnancy

- No established link with birth defects

  Has been associated with low birth weight, miscarriage, stillbirth

- Pregnancy is a risk factor for severe dengue, higher risk for maternal death
- Clinical presentation in the critical phase can be very similar to preeclampsia – delayed diagnosis
- Vertical transmission – uncommon

  Symptomatic infection in newborn
  Infants exposed in utero/at birth, may be at increased risk of severe dengue if infected during infancy, due to the presence of heterologous anti-dengue antibodies (from primary infection or maternal antibodies)

- Pregnant women with dengue should always be hospitalized

  If in labor, medical care should be provided in a tertiary hospital, increased risk of hemorrhage

  Route of delivery – based on individual circumstances, Cesarean section should be avoided if possible

Discharge Criteria

- No fever for 48 hours

- Improvement in clinical status (general well-being, appetite, hemodynamic status, urine output, no respiratory distress)

- Increasing trend of platelet count

- Stable hematocrit without IV fluids

Dengue Differential Diagnosis

- **Febrile phase**

  Malaria, typhoid fever, influenza, chikungunya, rubella, measles, leptospirosis, meningococcal infection, Zika, yellow fever, mononucleosis, rickettsia infections, COVID-19

- **Critical phase**

  Malaria, typhoid fever, leptospirosis, viral hepatitis, bacterial sepsis, acute abdomen, diabetic ketoacidosis, preeclampsia, platelet disorders, COVID-19

Dengue vaccines

Dengvaxia

US ACIP recommends **3 doses** (six months apart) for the prevention of dengue in:

- People **9–16** years old <u>with</u>
    - laboratory confirmation of previous dengue virus infection <u>and</u>
    - living in endemic areas

Dengue vaccines

Qdenga (TAK-003)

WHO-SAGE has recommended **2 doses** (three months apart) in

- People **6–16** years old
    - Settings with high dengue disease burden and high transmission intensity
    - Introduced 1-2 years prior to age-specific peak incidence of hospitalizations
- Authorized by the European Medicine Agency, approved in several countries (UK, Argentina, Indonesia, Thailand, Brasil)
- FDA application was voluntarily withdrawn in the United States

There are currently no dengue vaccines recommended for **travelers** in the United States

Dengue Prevention

- Use EPA-registered insect repellents:
  - DEET, picaridin, IR3535, oil of lemon eucalyptus, para-menthane-diol, 2-undecanone

- Wear long-sleeved shirts and long pants

- Select accommodations with well-screened windows and doors, or air conditioning, when possible

Potential Range of *Ae. aegypti* and *Ae. albopictus* in the United States, 2017

Estimated Potential Range of *Aedes aegypti* in the United States, 2017
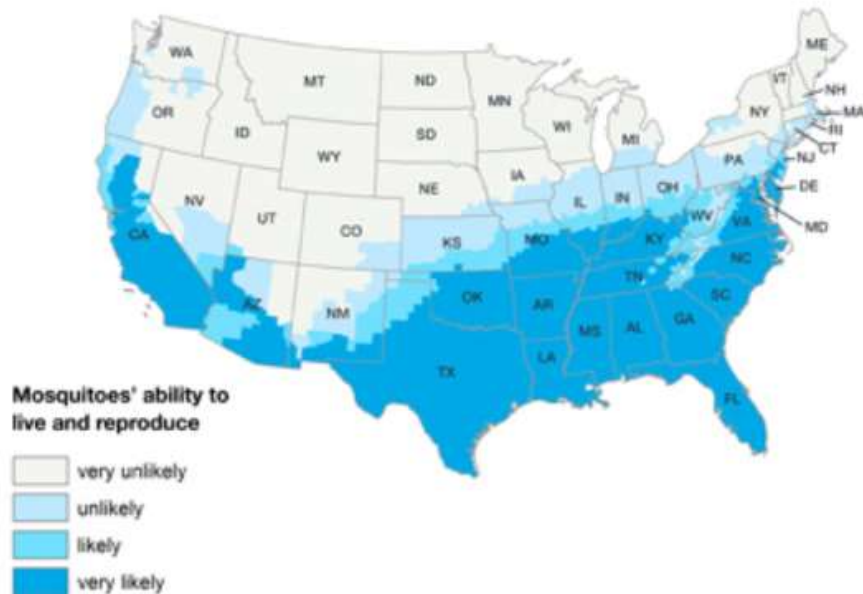
Estimated Potential Range of *Aedes albopictus* in the United States, 2017

Mosquitoes' ability to live and reproduce
- very unlikely
- unlikely
- likely
- very likely

*These maps represent CDC's best estimate of the potential range of *Aedes aegypti* and *Ae. albopictus* in the United States. Maps do not represent risk for spread of disease.

Dengue rashes

Picture 3 reproduced from *Matsuura H, Kishida M, Nakata Y, et al Dengue rash: white islands in a sea of red Postgraduate Medical Journal 2019;95;676* with permission from BMJ Publishing Group Ltd

History and Physical Exam

Criteria	Assessment
Fever	Onset, defervescence
Other symptoms	Cough, runny nose, sore throat, anorexia, diarrhea, dysgeusia, lymphadenopathy, conjunctival injection
Hydration status	Oral intake, urine output
Warning signs	**Abdominal pain/tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, postural hypotension, hepatomegaly, hemoconcentration**
Rash and bleeding manifestations	Examine skin for rashes, mild mucosal bleeding. Melena and hematuria
Change in mental status	Dizziness, seizures, restlessness
Comorbidities/other conditions	Chronic conditions, pregnancy, infants, social conditions

Dengue Classification, WHO 1997

Dengue Hemorrhagic Fever

A case must meet all 4 the following criteria:

- Fever or history of fever lasting 2–7 days,

- Hemorrhagic tendency:

  At least one: a positive tourniquet test; petechiae, ecchymoses or purpura; bleeding from the mucosa, gastro-intestinal tract, injection sites or other locations; or hematemesis or melena.

- Thrombocytopenia [⩽100,000 cells/mm3]

- Evidence of plasma leakage due to increased vascular permeability:

  An increase in hematocrit ⩾20% above average for age, sex and population; a decrease in the hematocrit after intervention ⩾20% of baseline; signs of plasma leakage such as pleural effusion, ascites or hypoproteinemia

Dengue Shock Syndrome

All four criteria for DHF must be met, in addition to evidence of circulatory failure manifested by:

- Rapid and weak pulse and

- Narrow pulse pressure (<20 mmHg)

  or manifested by

- Hypotension for age and

- Cold, clammy skin and restlessness

Current trials of dengue therapeutics

Drug name	Target	Pre-clinical data	Clinical Data
JNJ-64281802	NS4B inhibitor that inhibits viral replication	Antiviral activity in vitro was shown for its analog, JNJ-A07. Decrease in viremia, viral burden, and inflammatory cytokines, and improved survival in immunocompromised mouse model of DENV infection	Clinical trials for dengue prophylaxis in healthy individuals (NCT05201794) as well as for dengue therapy in patients with confirmed dengue fever (NCT04906980) are in progress
VIS513	Pan-serotype anti-DENV monoclonal antibody	Diminished circulating infectious DENV in NHPs, and reduced viral load with improved survival in immunocompromised mice models of DENV infection	Clinical trial in progress (CTRI/2021/07/035290)
Zanamivir	Neuraminidase inhibitor to block desialylation on platelet membrane	Reduction in DENV2 NS1-induced endothelial hyperpermeability and vascular leakage in vitro	Clinical trial to test efficacy against vascular leakage (NCT04597437) is currently on-going

Current trials of dengue therapeutics (2)

Drug name	Target	Pre-clinical data	Clinical Data
Metformin	Oral anti-hyperglycemic agent, AMPK activator	Antiviral effect in DENV infected cells in vitro	A retrospective study (n = 223) showed decreased risk of severe dengue with metformin use in dengue patients with diabetes. NCT04377451 open-label safety and tolerability study recently completed.
Vitamin D	Unclear mechanism. Can increase calcium availability for immune cell activation	Reduced viral replication and inflammatory cytokines production in vitro	Randomized clinical trial ongoing (NCT06071481). Effect on progression to severe dengue.
EYU688	NS4B + SSTR (Nonstructural protein 4B + Somatostatin receptor)		Randomized placebo-controlled trial (NCT06006559, not yet recruiting) Outcome: Viral load reduction at 48 hours post treatment.

Adapted from: Palanichamy Kala, M., St. John, A.L. & Rathore, A.P.S. Dengue: Update on Clinically Relevant Therapeutic Strategies and Vaccines. Curr Treat Options Infect Dis 15, 27–52 (2023)