INMED Humanitarian Health Conference

Tropical Diseases of Significance

Duane R Spaulding, MD, FACP
International Consultant, Advisor, and Medical Educator
Email: NGO.Medical.Advisor@gmail.com

Tropical Diseases of Significance

Dengue

The Potential Lull Before The Storm

Background and Experience *(1 of 5)*

- Internal Medicine practice / Hospitalist for 26 years in Colorado Springs
  - Opted for early retirement to pursue more international medical volunteerism as a medical educator, advisor, and consultant

Background and Experience *(2 of 5)*

- 12 years (2010–2022) as Medical Director/Senior Advisor for 10-21 clinics in Haiti after the catastrophic Earthquake
  - Mentored and trained our employed Haitian Medical Teams
  - Supervised the deployment of hundreds of expat Medical Volunteers
  - *Heart to Heart International*, Lenexa, Kansas

BACKGROUND AND EXPERIENCE *(3 OF 5)*

- Lecturer addressing 4 Tropical Diseases for Global First Responders preparing to deploy to Disaster Zones worldwide (2016–2022)
  - Including Dengue presentations
  - *Heart to Heart International*, Lenexa, Kansas

Background and Experience *(4 of 5)*

- Consulting and Teaching in 13 sub-Saharan African countries
  - *Project C.U.R.E.*, Centennial, Colorado, & Kansas City
  - *Nazarene Compassionate Ministries International*, Lenexa, Kansas
  - *Water for Generations,* Denver, Colorado

BACKGROUND AND EXPERIENCE *(5 OF 5)*

- Facilitating the preparations of Medical Volunteers for deployments to clinics on **4** continents with these entities:
  - *Project C.U.R.E.,* Centennial, Colorado, & Kansas City
  - *Rocky Vista University College of Osteopathic Medicine*, Parker, Colo.
  - *Resurrection, A United Methodist Church*, Leawood, Kansas

SESSION OBJECTIVES

- Understand the Epidemiology and some Pathophysiology
- Know the criteria for Diagnosing this widespread tropical disease
- Know the Triage Criteria for patients who risk suddenly decompensating while seemingly recovering
- Implement only appropriate Treatment Options to avoid iatrogenic complications
- Know the Preventive Measures available for yourself and the local population
- [Given the limited time we have tonight, your Handout is much more complete]

DISCLOSURE

There are no relevant financial relationships with ineligible companies to disclose.

OVERVIEW *(1 OF 2)*

- Dengue also called "Break-Bone Fever"
  - Caused by one of the 4 Dengue Viruses (DENV)
  - Spread by mosquitoes during the taking of a blood meal
  - May be asymptomatic or present with a broad range of clinical manifestations – even a life-threatening Shock Syndrome

OVERVIEW *(2 OF 2)*

- Numerous viral, host, and vector factors impact the risk of infection and disease severity
- Dengue is the most widespread mosquito-borne disease among humans
- ~4 Billion people – nearly half the world's population – live where at risk
  - ✧ Thus, Dengue is an important arthropod-borne viral illness from medical and public health perspectives

WORLDWIDE DISEASE BURDEN *(1 OF 3)*

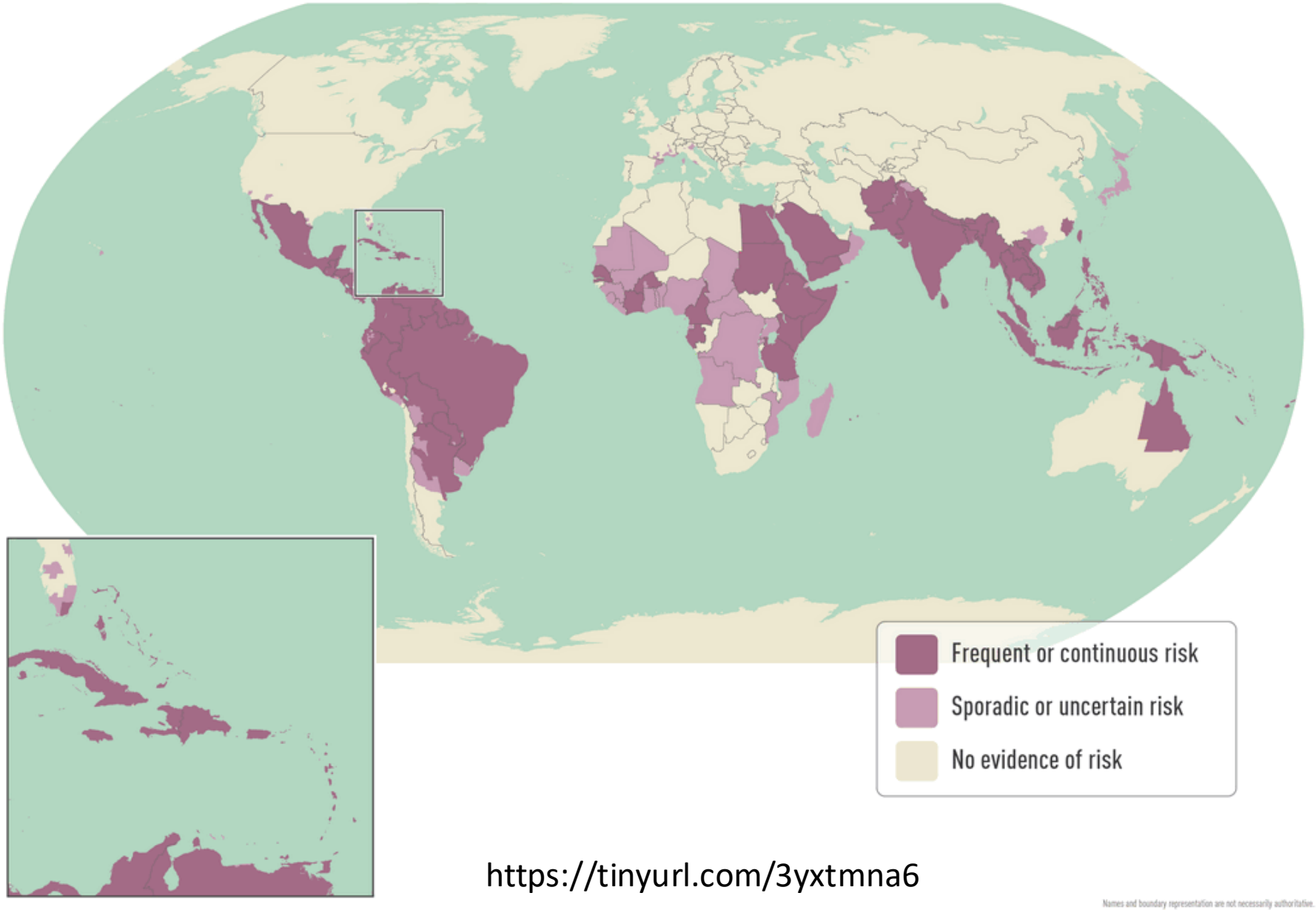
- Dengue is endemic in >130 countries in all 6 WHO regions
  - 70% of the disease burden is in Asia according to the WHO
  - In 2024 (the WORST Dengue year ever): reported 14.4 Million cases; ~53,000 SEVERE cases; 11,200 deaths…roughly double 2023
  - WHO declared "Grade 3 Emergency" (highest tier) in 2024…which continues to the present…

WORLDWIDE DISEASE BURDEN *(2 OF 3)*

- Worldwide incidence & geographic distribution of both Dengue and its more severe manifestation, Severe Dengue, are increasing in recent decades
  - Severe Dengue is highest in parts of Asia and South America

WORLDWIDE DISEASE BURDEN *(3 OF 3)*

- The emergence of Severe Dengue as a public health problem has largely been a result of human behaviors, especially due to:
  - Population growth
  - Poor urban planning (with overcrowding and poor sanitation)
  - Modern transportation
  - Lack of effective mosquito control
  - **SEE:** Page 11 of your Handout



https://tinyurl.com/3yxtmna6

World map highlighting areas of dengue risk.

EPIDEMIOLOGY *(1 OF 3)*

- The distribution of DENGUE overlaps with Yellow Fever, West Nile, Chikungunya, & Zika
  - All carried by the *Aedes* mosquitoes *(More to come)*
- "Dengue-endemic" regions
  - Where DENV transmission occurs year-round with seasonal surges
  - More densely populated urban areas are particularly affected

EPIDEMIOLOGY *(2 OF 3)*

- Including: Tropical Asia, Central & South America, sub-Saharan Africa, and Western Pacific
- And now, with better data across sub-Saharan Africa (where Malaria had masked it), a sharp rise in Dengue was reported in 2024
- Of significance, Dengue is now ALSO seasonally present in the southern U.S., its territories, and southern Europe!

EPIDEMIOLOGY *(3 OF 3)*

- "Epidemic Dengue": when a **single** DENV strain is introduced to a region
  - If many susceptible hosts + mosquitoes, transmission may be explosive
    - Infection incidence exceeding 25–50%
- "Hyperendemic" transmission refers to continuous circulation of **multiple** DENV serotypes in the same area
- No evidence that non-human primates are an important reservoir for transmission to humans

Etiologic Agents

- DENV are members of the genus *Orthoflavivirus*
  - Small, enveloped viruses containing a single-stranded RNA genome
- The DENV include 4 antigenically related but distinct virus "serotypes"
  - Designated DENV-1; DENV-2; DENV-3; DENV-4
- All DENV serotypes are mosquito-borne human pathogens

The Vector – *Aedes* Mosquitoes *(1 of 3)*

- Both epidemic and endemic transmissions of DENV are maintained through a human–female mosquito–human cycle involving genus *Aedes*
  - *Aedes aegypti* mosquitoes: widely distributed in tropical and subtropical areas
  - *Aedes albopictus* mosquitoes: more tolerant of the cold and have a wider geographic distribution, although a less efficient vector

The Vector – *Aedes* Mosquitoes *(2 of 3)*

- An uninfected female *Aedes* mosquito acquires the virus by feeding while the human's viremia titer is sufficient
  - After the necessary "extrinsic" incubation period (i.e., inside the mosquito for 8–12 days) the mosquito remains infectious for its lifetime

THE VECTOR – *AEDES* MOSQUITOES *(3 OF 3)*

- *Aedes* mosquitoes bite throughout the daytime and at twilight, esp. indoors/near houses where they also easily reproduce
  - Prefer to bite humans (notorious "ankle-biters"), frequently go unnoticed, are easily interrupted in their feeding, often moving on to another host
    - Thus, a single infected *Ae. aegypti* mosquito may transmit DENV to several individuals within the same household

Other Modes of Transmission

- Nosocomial DENV transmission
  - Is possible via blood products, needlestick injury, and mucocutaneous exposure
- Vertical transmission between mother and preborn or newborn baby
- Congenital Dengue if maternal infection occurs near term
  - With potentially serious complications

PATHOGENESIS

- The risk of Severe Dengue is highest among individuals with a second Dengue infection caused by another DENV serotype
  - I.e., where there is "hyperendemicity" with multiple DENV serotypes circulating concurrently
  - Probably mediated via a "Cytokine Storm" triggered by the patient's immune system

IMMUNITY

- Long-lasting protection does occur against a DENV infection of the same serotype
  - Cross-immunity against the other 3 DENV serotypes wanes within months
- In the setting of "Hyperendemic" transmission, the prevalence of antibody against the several local DENV serotypes rises with age
  - However, multiple circulating serotypes is a major factor contributing to the occurrence of Severe Dengue

HUMAN INCUBATION PERIOD

- The incubation period of DENV infection has a broad range: 3–14 days
- Symptoms onset is typically 4–7 days after infected *Aedes* mosquito bite
- Viremia (thereby able to infect new biting mosquitoes) closely mirrors the onset of symptoms
  - Then persists until the fever abates

CLINICAL PRESENTATION *(1 OF 3)*

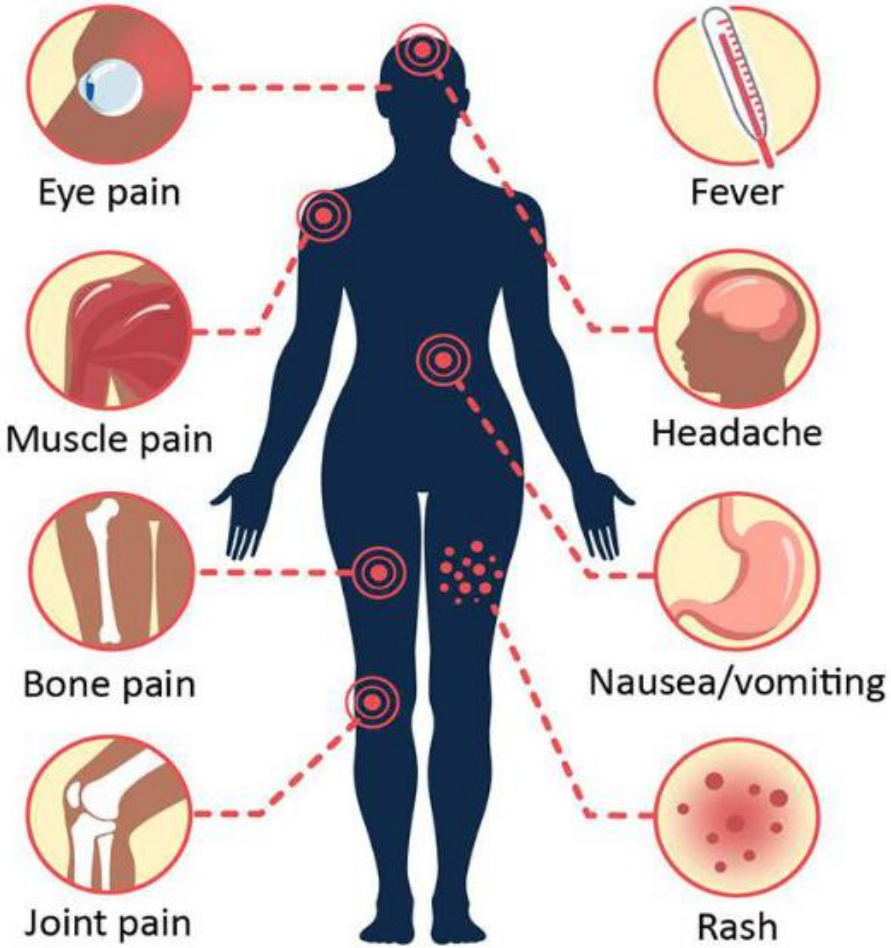
- Overall, ~25% of those infected with DENV will become symptomatic
  - Only ~5% of symptomatic patients (i.e., ~1% of all infections) will develop Severe Dengue
- Children and Adolescents
  - May have high fever but are generally less symptomatic

CLINICAL PRESENTATION *(2 OF 3)*

- "Classic Dengue" is an acute **febrile** illness sometimes known as "Break-Bone Fever" accompanied by these hallmark symptoms:
  - Marked bone, joint, muscle pains
  - Retro-orbital pain
  - Headache
- **SEE:** Page 12 in your Handout

Dengue Symptoms

Fever with any of the following



https://www.cdc.gov/dengue/symptoms/index.html

SIGNIFICANCE OF "PRIMARY" AND "SECONDARY"

- A "primary DENV infection" is the first wild-type infection for that patient
- A "secondary DENV infection" is the second wild-type infection
  - Typically caused by a different DENV serotype
- Secondary infections occurring >18 months later represent the highest risk for SEVERE clinical outcomes

WHO's Revised "Severity Classification" and "Clinical Phases" *(1 of 2)*

- In an effort to improve case management, in 2009 the WHO published a revised Clinical Classification Scheme (replacing the 1997 scheme):
- The Dengue Severity Classification is used as a Clinical Triage Tool
  - Answers the question: **"How sick is this patient RIGHT NOW"**
- The Clinical Phases of the Dengue illness provides a Disease Timeline
  - Answers the question: **"Where is this patient in the course of illness?"**

WHO's Revised "Severity Classification" and "Clinical Phases" *(2 of 2)*

- The best way to think of these:
  - "The Classification tells you **WHAT** to do; the Phase tells you **WHEN** to worry the most."
- However, be advised that some authors still use the outdated terminology – which can be confusing
  - E.g., "Dengue Hemorrhagic Fever", "Dengue Shock Syndrome"…

WHO "Severity Classification" Scheme *(1 of 2)*

- WHO's revisions describe these 3 clinical categories:
  - Dengue Without Warning Signs
  - Dengue With Warning Signs
  - Severe Dengue
- **SEE:** your Handout for the extensive list of criteria for each of these

WHO "Severity Classification" Scheme *(2 of 2)*

- In terms of the "Severe Dengue" category, the salient features include:
  - Dengue infection (as described above) PLUS one or more of these:
    - Severe plasma leakage leading to:
      - Shock
      - Fluid accumulation with Respiratory Distress
    - Severe hemorrhaging
    - Severe organ involvement:
      - Liver with markedly elevated AST/ALT
      - Impaired consciousness
      - Organ failure

Risk Factors for Severe Dengue

- Immunity: History of a prior episode of Dengue
- Pregnant women
- Babies, esp. ages 6m – 12m (described below)
- Adults
- Obesity
- Diabetes
- Kidney failure

WHO "Clinical Phases" of Infection *(1 of 9)*

- According to the WHO 2009 scheme, there are 3 "Clinical Phases" of Dengue:
  - [#1]Febrile Phase
  - [#2]Critical Phase
  - [#3]Convalescent Phase
- **SEE:** your Handout for the extensive lists of criteria for each of these

WHO "Clinical Phases" of Infection *(2 of 9)*

- All 3 Phases occur with "Dengue With Warning Signs" and "Severe Dengue"
- However, most patients have "Dengue Without Warning Signs" including:
  - ONLY [#1]Febrile & [#3]Convalescent Phases – but **not** the [#2]Critical Phase

WHO "Clinical Phases" of Infection *(3 of 9)*

- [#1]FEBRILE PHASE includes a special test:
  - **Tourniquet Test** should be performed:
    - Examine the volar forearm skin just below the antecubital fossa making note of any pre-existing petechiae
    - Inflate a blood pressure cuff on the upper arm to midway between systolic and diastolic blood pressures and hold for 5 minutes
    - 1–2 minutes after deflating, examine below the cuff for new petechiae
      - Presence of ≥10 new petechiae in a square inch = positive test

WHO "Clinical Phases" of Infection *(4 of 9)*

- [#2]CRITICAL PHASE
  - DENV infections that progress to a Critical Phase are a secondary infection
    - As noted, usually occurring >18 months after the primary infection

WHO "Clinical Phases" of Infection *(5 of 9)*

- [#2]CRITICAL PHASE *(Cont'd)*
  - However, a subset of Critical Phase infections occurs in Infants ages 6m–12m in endemic areas
    - Having acquired DENV-specific antibodies passively transplacentally, they are at greater risk as these antibodies decline over time
    - If these infants are then bitten by a DENV-infected mosquito, they may develop a Severe (secondary) Dengue infection

WHO "Clinical Phases" of Infection *(6 of 9)*

- [#2]CRITICAL PHASE *(Cont'd)*
  - ALL symptomatic patients – between days 3–7 of the illness:
    - Must be monitored for signs of vascular leakage of plasma
      - The most specific and life-threatening feature of Severe Dengue
      - Usually occurs during the 24 hours pre/post time of defervescence!
      - Reduces intravascular volume and decreases organ perfusion

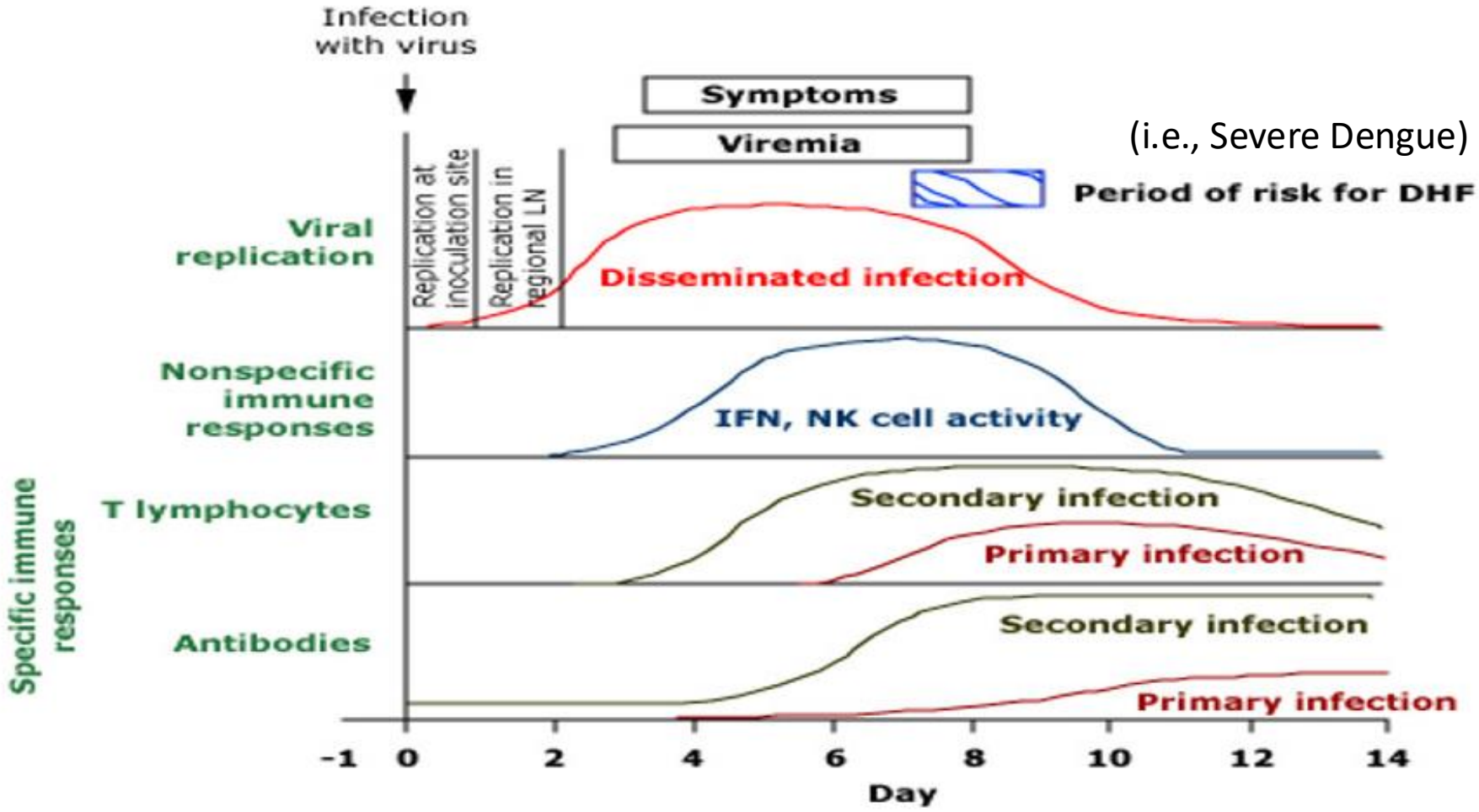
WHO "Clinical Phases" of Infection *(7 of 9)*

- [#2]CRITICAL PHASE *(Cont'd)*
  - Clinical symptoms of the Critical Phase may include:
    - Persistent vomiting
    - Severe abdominal pain
    - Tender hepatomegaly
    - Lethargy or restlessness
  - Possible scenarios: Severe plasma leakage with minimal hemorrhaging… OR **vice versa**
  - This Critical Phase typically lasts 24–48 hours

WHO "Clinical Phases" of Infection *(8 of 9)*

- [#3]CONVALESCENT PHASE
  - Usual duration is 2–4 days
    - Although Adults may experience profound fatigue for even weeks thereafter
- **SEE:** Page 13 in your Handout

ACUTE DENGUE VIRUS INFECTION

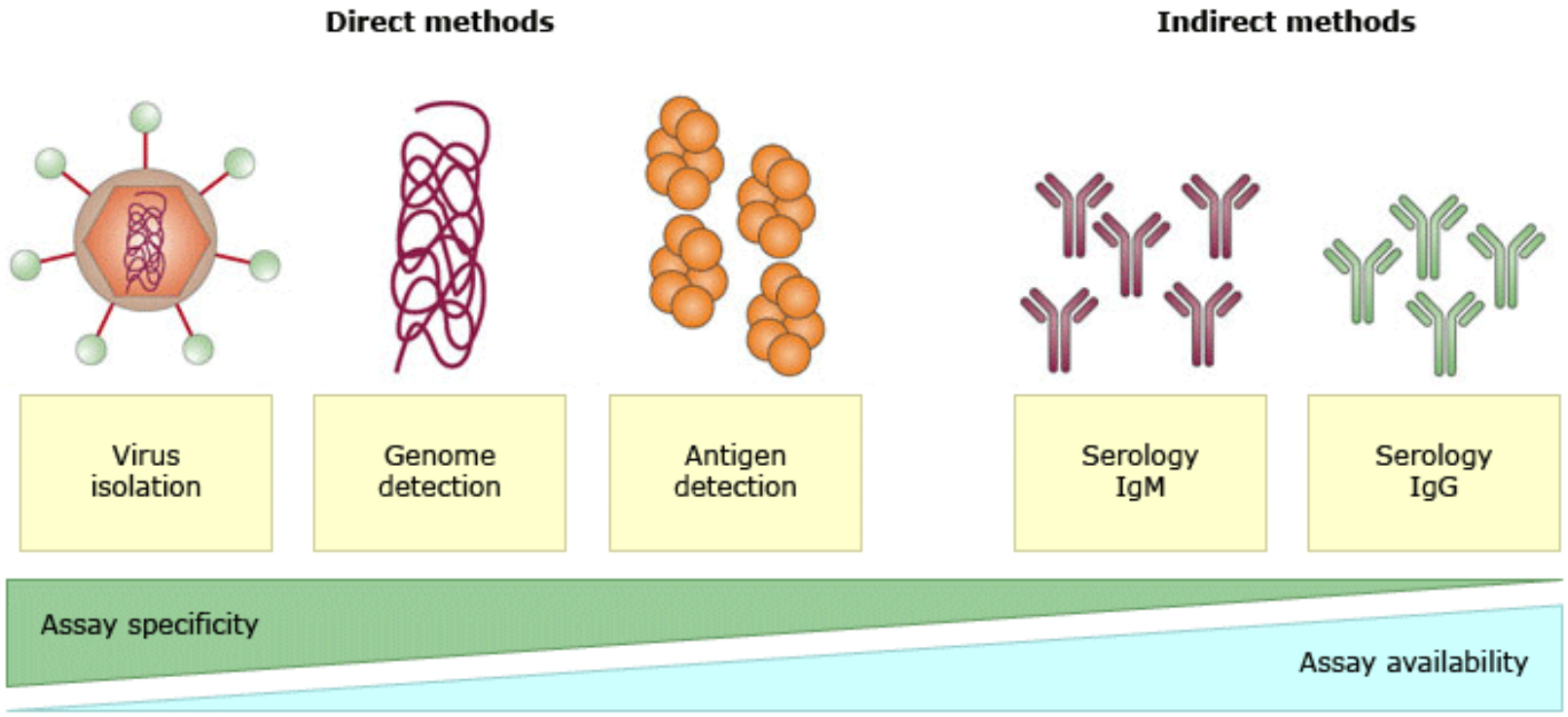


UpToDate, Inc. and/or its affiliates. All Rights Reserved.

Diagnostic Laboratory Tests

- FYI: Laboratory diagnostic tests are available for Dengue
  - Directly: detecting viral components in the serum
  - Indirectly: by serology
- In settings where serologic assays are available:
  - An (Ig)M immunoassay is the test of choice
- Of course, these tests may not be available in the Majority World
- **SEE:** Page 14 in your Handout

Laboratory tests for diagnosis of dengue virus infection



Comparative merits of laboratory methods for diagnosis of dengue infection.

Ig: immunoglobulin.

Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Microbiology. Peeling RW, Artsob H, Pelegrino JL, et al. Evaluation of diagnostic tests: Dengue. Nat Rev Microbiol 2010; 8:S30. Copyright © 2010. www.nature.com/nrmicro.

UpToDate®

Differential Diagnosis *(1 of 3)*

- Early clinical presentations of:
  - Dengue, Chikungunya, and Zika virus infections may be indistinguishable
  - Oropouche virus infection majorly emerged in 2023-2024
    - Likewise, is nearly indistinguishable from Dengue acutely

Differential Diagnosis *(2 of 3)*

- Additional possibilities (depending on the region of the world) include:
  - Other viral hemorrhagic fevers, e.g., Ebola, Marburg, Lassa, Yellow Fever, etc.
  - Malaria
  - Typhoid Fever
  - Leptospirosis
  - Rickettsial infection – including African Tick Bite Fever and Relapsing Fever

Differential Diagnosis *(3 of 3)*

- Viral Hepatitis – including Hepatitis A, B, C, D, and E
- Mayaro virus – in South American settings
- Acute HIV Infection
- COVID-19

TREATMENTS

- General Management
  - Primarily supportive – and sometimes even aggressive
    - E.g., maintaining adequate intravascular volume when indicated
- Antiviral Drugs
  - None YET licensed
    - However, after Johnson & Johnson recently abandoned Mosnodenvir
      - Novartis has another molecule (NITD-688) that shows promise

OUTPATIENT MANAGEMENT OF DENGUE *(1 OF 5)*

- Appropriate for patients with presumptive Dengue diagnosis in the **absence** of **Warning Signs** (listed in your Handout) AND **absence** of ALL **"Coexisting Condition(s)"** including:
  - Pregnancy
  - Infancy
  - Old age
  - Diabetes
  - Obesity
  - Renal failure
  - Poor social situation…

Outpatient Management of Dengue *(2 of 5)*

- HOMECARE Instructions should include:
  - An outpatient must be taking oral fluids and urinating at least Q6 hours
  - Plenty of rest; only light activities
    - Avoid any exertion, especially if having joint symptoms
  - Drink 2–3 Liters [Adults] of clean water daily
    - Adding a pinch of salt to each 8oz./250 mL glass

Outpatient Management of Dengue *(3 of 5)*

- HOMECARE Instructions should ALSO include:
  - Patients and their families should be instructed to watch for signs of **dehydration**:
    - I.e., decrease in urination, few or no tears, dry mouth or lips, sunken eyes, listlessness or confusion, cold or clammy extremities, sunken fontanel in an Infant

Outpatient Management of Dengue *(4 of 5)*

- Medications
  - Fever and myalgias should be managed with Acetaminophen / Paracetamol
    - Max. Adult dosage 3000 mg/24hrs (less in elderly or hepatic impairment)
  - AVOID: Aspirin or any NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) due to risk of serious bleeding
    - E.g., Ibuprofen, Naproxen, Diclofenac, etc.

Outpatient Management of Dengue *(5 of 5)*

- As fever declines (3–7 days after onset of symptoms), this is the period of maximum risk for complications
  - Essential instruction: **Seek medical attention promptly for any of these:**
    - Severe abdominal pain
    - Persistent vomiting or vomiting blood
    - Very dark feces
    - Bleeding from nose or gums
    - Drowsiness or irritability
    - Difficulty breathing

MGMT IF AT HIGH-RISK FOR SEVERE DENGUE *(1 OF 2)*

- HOSPITAL Inpatient Management
  - Warranted for patients meeting criteria for:
    - (a) "Dengue With Warning Signs"
    - (b) "Severe Dengue" or
    - (c) Dengue with "Coexisting Conditions" (as above)
  - Provides closer monitoring, access to IV fluids, and blood transfusions PRN

MGMT IF AT HIGH-RISK FOR SEVERE DENGUE *(2 OF 2)*

- HOSPITAL Inpatient Management (Cont'd)
  - As noted, plasma leakage, typically becomes evident during the 24 hours pre/post defervescence
    - Dramatic plasma leakage may develop suddenly with minimal hemorrhagic manifestations
      - Making early identification of patients at risk for shock and other complications critical

PROGNOSIS

- Severe Dengue can be life-threatening if not treated aggressively in the hospital (usually in the ICU)
  - WHO reports:
    - The Case Fatality Rate (CFR) can be <1% with proper inpatient care
    - In its absence, a CFR of >20% can occur in patients with Severe Dengue

PREVENTION – PUBLIC HEALTH *(1 OF 4)*

- Mosquito control includes:
  - Remove any standing water where mosquitoes can breed
    - Both inside and outside the residence – no matter how small a volume – even soft drink bottle caps!
  - Cover water storage containers / barrels / cisterns to prevent mosquito access
  - (**SEE:** your Handout for more information in this section)

PREVENTION – PUBLIC HEALTH *(2 OF 4)*

- Minimize mosquito bites (indoors & outdoors) as much as possible
  - Apply Repellent (e.g. DEET 30–50%) on all exposed skin – esp. ankles – 3–4 times daily
    - Safe for all patients including Pregnant Women
    - EXCEPTION: avoid for Infants <2m
    - If also using Sunscreen: apply Sunscreen first, Repellent second

PREVENTION – PUBLIC HEALTH *(3 OF 4)*

- Mosquito control *(Cont'd):*
  - Mosquito-proof the inside of the home
    - Fine mesh screens
    - Indoor residual spraying with insecticides
    - Bednets, esp. long-lasting insecticidal pre-treated
      - Including for anyone with a fever – prevents spreading to others

PREVENTION – PUBLIC HEALTH *(4 OF 4)*

- "Endosymbiotic Control" recently reported in the N*ew England Journal of Medicine*
  - A novel DENV Infection Control Strategy against *Ae. aegypti* mosquitoes
    - Releasing mosquitoes infected with *Wolbachia pipientis* – an obligate intracellular bacterium
      - With highly effective reproductive and viral transmitting impacts
    - Now being deployed in >14 countries

Prevention – Travelers & Volunteers *(1 of 2)*

- Most travelers from nonendemic countries are at low risk for Severe Dengue (in the absence of a prior Dengue illness)
- Potential exceptions include:
  - Frequent international travelers
  - Frequently deploying military personnel
  - Immigrants from endemic areas returning to their home countries

PREVENTION – TRAVELERS & VOLUNTEERS *(2 OF 2)*

- People with history of Dengue infection need not necessarily avoid subsequent travel to Dengue-endemic regions:
  - However, preventing mosquito bites (as above) is certainly advisable

Prevention – Vaccines

- A prior vaccine, **CYD-TDV (Dengvaxia®)**, is being phased out
  - Due to low global demand (with its extremely restrictive protocol)
- A newer vaccine: **TAK-003 (Qdenga, Takeda)**
  - While not yet FDA-approved, it has been approved in 40+ countries and WHO-qualified by late 2025
- Recently another arrival: **TV003 (Butantan-DV)** is ONLY licensed in Brazil

Information Resources

Please see your Handout for details

Tropical Diseases of Significance

THANK YOU!