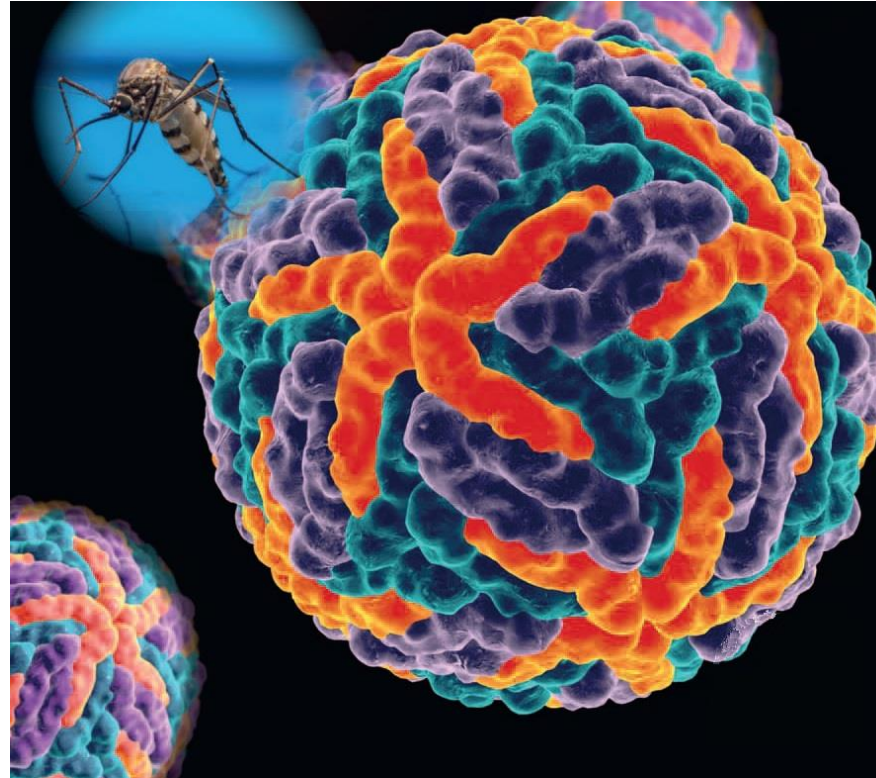


Dengue and Emergency Response

Outlook, Diagnosis, Management



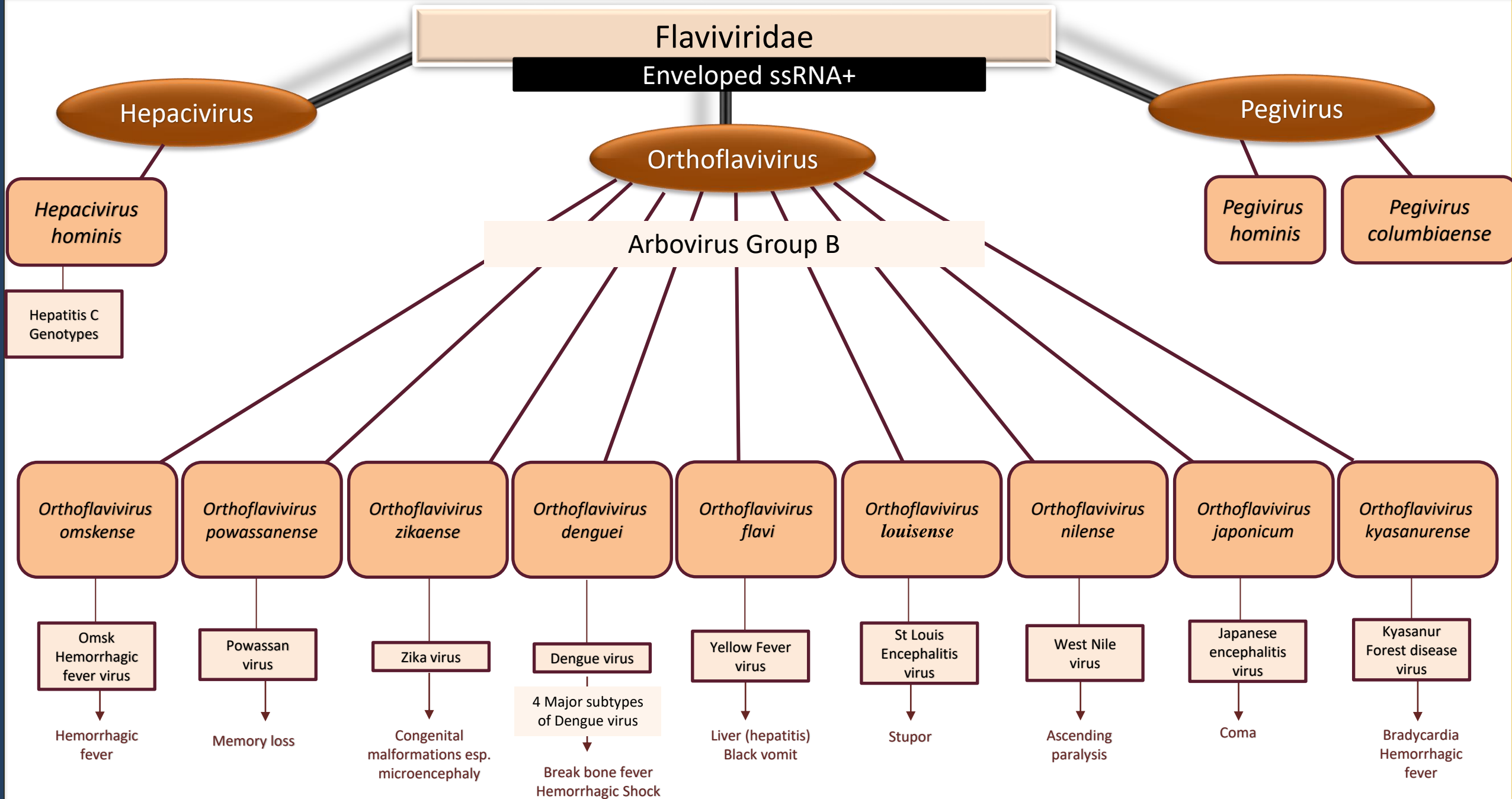
24 June 2024, The Eagles

Aileen M Marty MD, FCAP

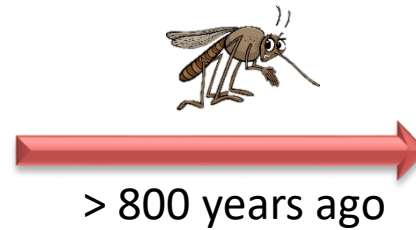
Distinguished University Professor, Infectious Diseases and Outbreak Response

HWCOR, Department of Translational Medicine

Aileen.Marty@FIU.edu



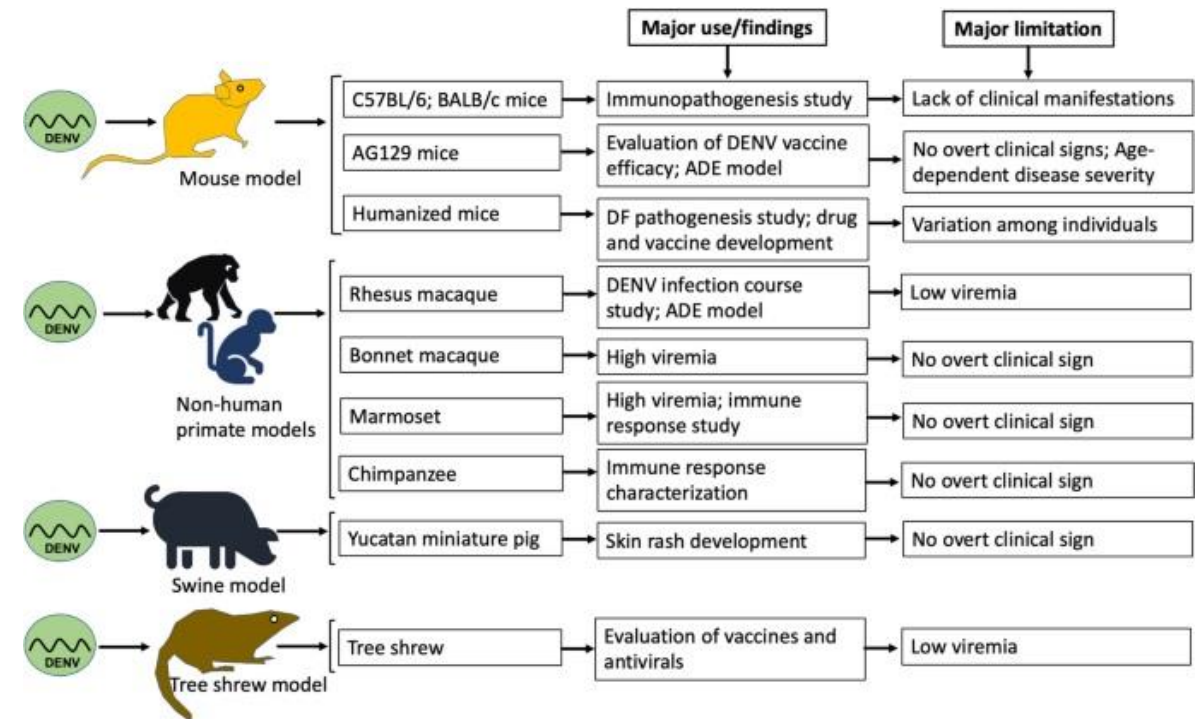
Origin of Dengue (Swahili phrase "ki denga pepo")



Dengue is a zoonotic disease

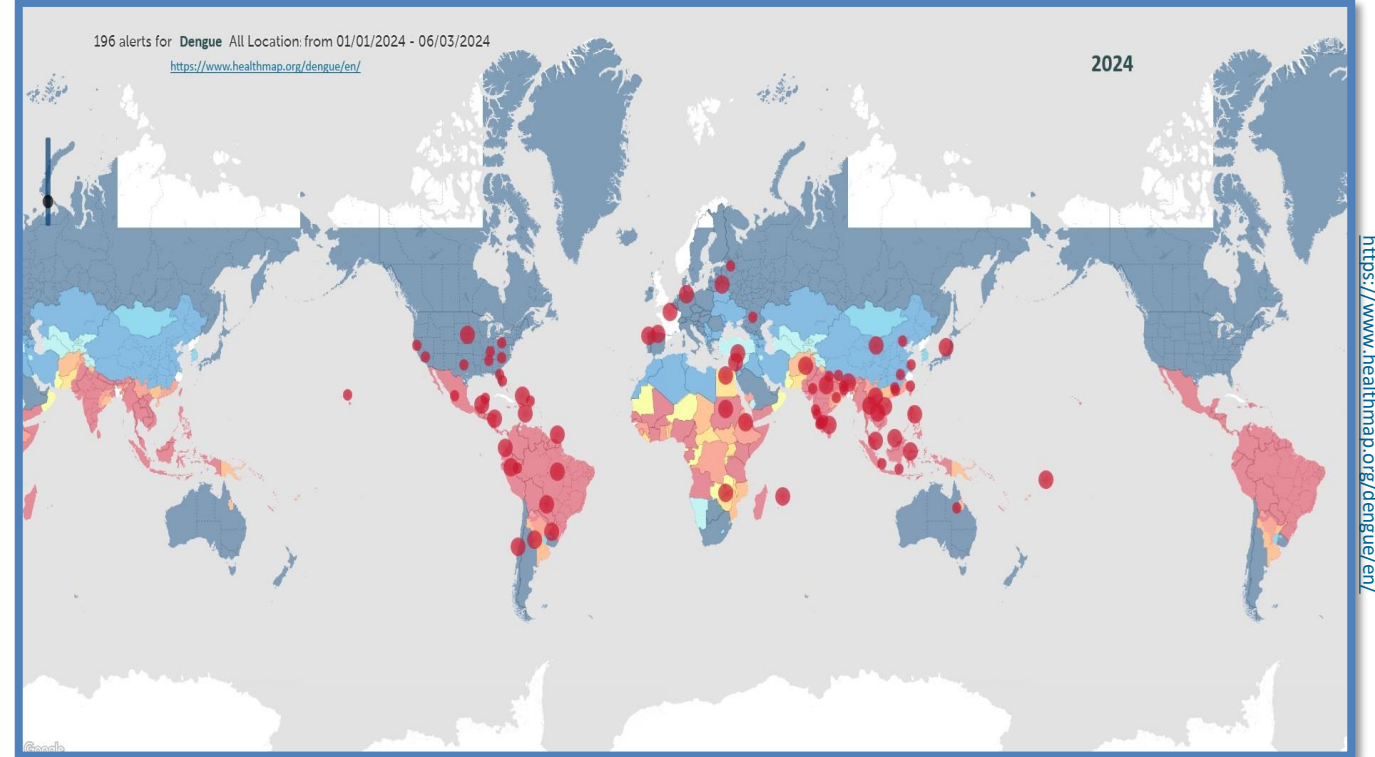
- Non-human primates
- Bats
- Pigs
- Birds
- Rodents
- Marsupials

*NHPs, Birds, Pigs, and rodents harbour all 4 serotypes



- There is an Increasing Global Burden
 - Incidence has doubled each decade since 1990 and is **now doubling yearly**
- We used to see Dengue Epidemics manifest ~ every 3 to 5 years, but over the last 3 years, cases have simply exploded
- Causes for Increasing Global Burden
 - Climate Change and El Niño phenomenon
 - Population growth
 - Uncontrolled urbanization
 - Ineffective/unsustainable approaches to vector control
 - Increased mobility and travel

206% increase compared to the same period in 202



- 01 Jan to 31 Dec 2022, **2.8 million** cases of dengue registered
- 01 Jan to 01 July 2023, nearly 2.99 million. Total for 2023: **6 million** worldwide, in the Americas: 4.6 million
- **01 Jan to 30 April 2024: > 7.6 million worldwide, with > 7.5 million of these in the Americas**

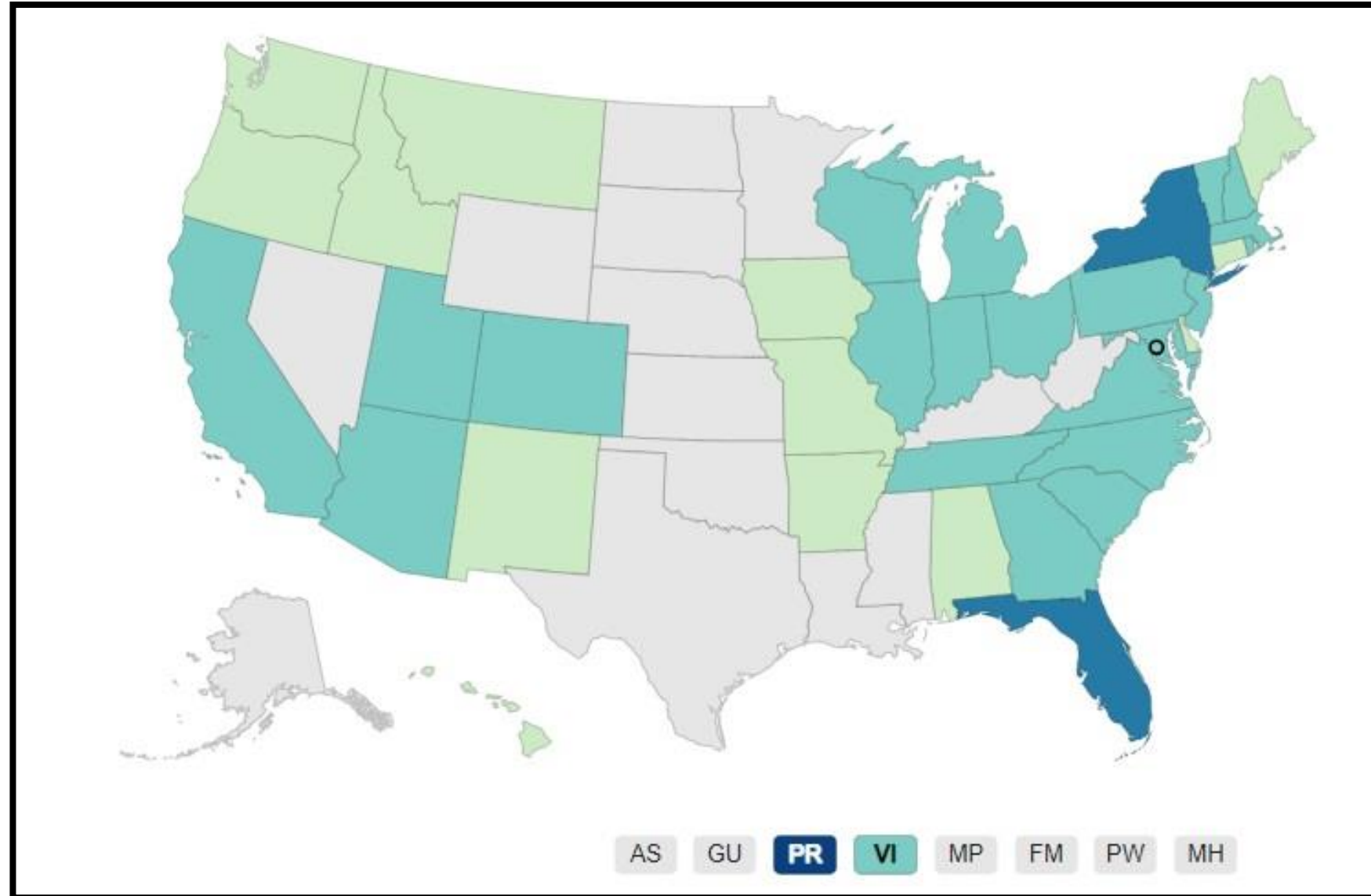
Dengue cases reported to ArboNET by state or territory of residence – United States, 2024 (as of June 03, 2024)

US States

•1,706 dengue cases reported (locally acquired 6 Florida, 1086 in PR, 6 in US Virgin Islands)

US Territories

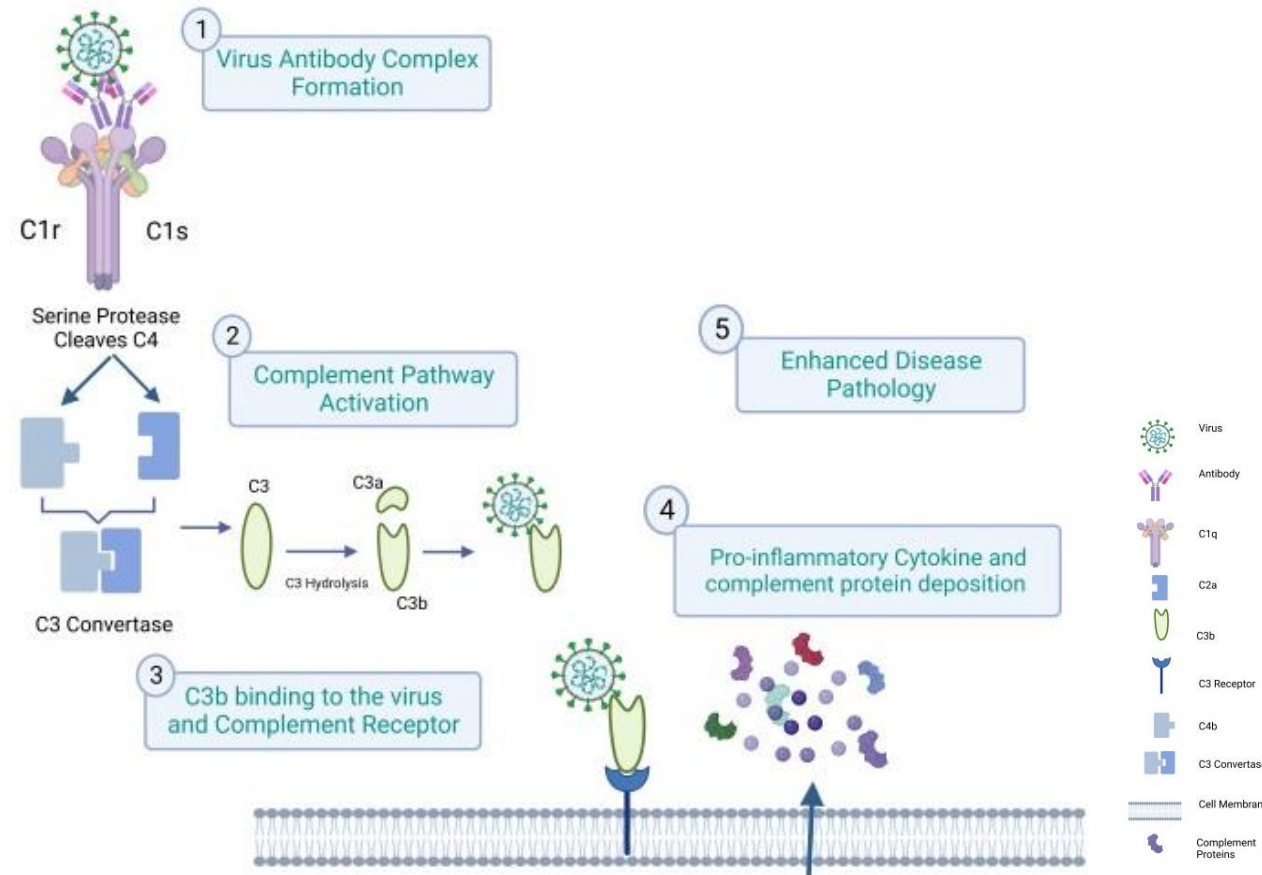
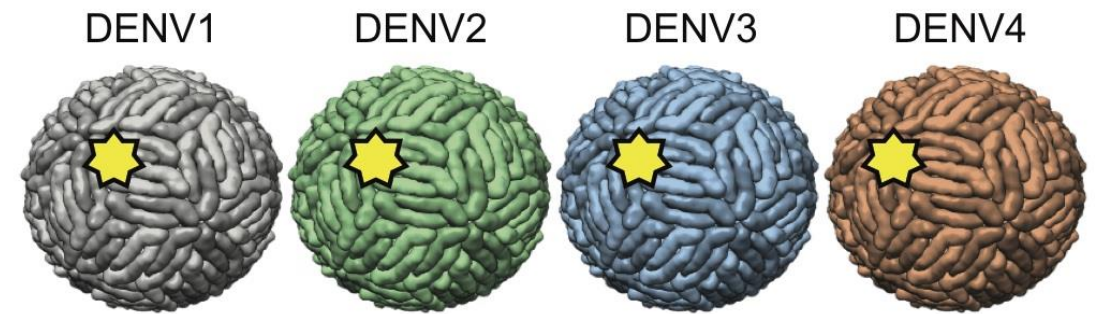
•1,100 dengue cases reported in Puerto Rico (all but 14 were locally acquired) and 6 in the US Virgin Islands



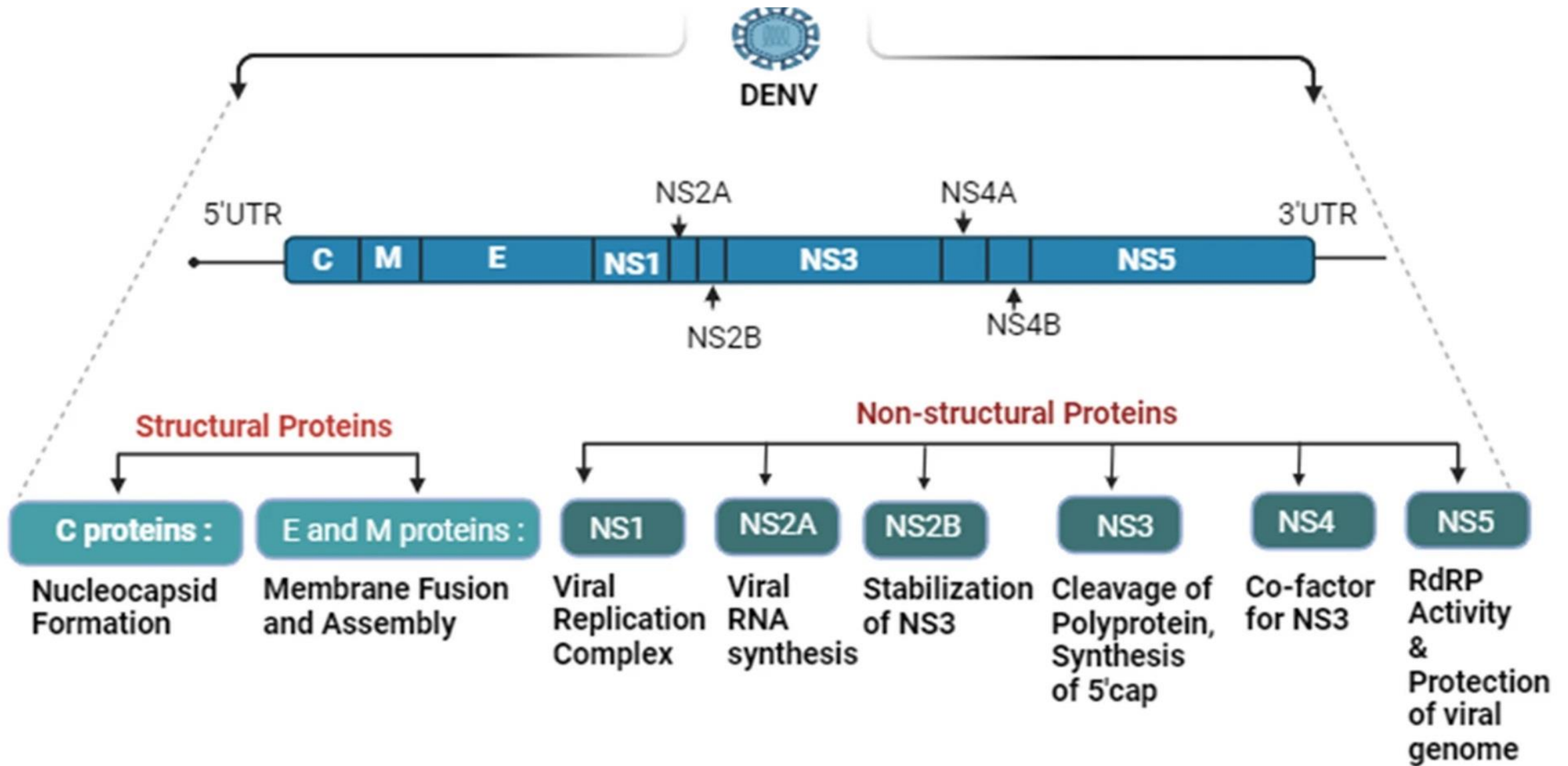
Dengue Virus: DENV-1, -2, -3, -4

- All four serotypes cause disease
- Each provides lifelong, type-specific immunity
- Each also provides Short-term, cross-immunity (1 to 3 years)

- Genetic variation with DENV types
- Host factors/Exposure factors
 - Some variants may be more virulent, but many factors determine disease severity
- **Age**
- **Strain of virus**
 - NS1 toxicity
- **Timing of previous dengue infection**
 - **Antibody Dependent Enhancement (ADE)**
 - » Timing between infections
 - » Order of infection



Structural organization of DENV



Intracellular Life Cycle of Dengue virus

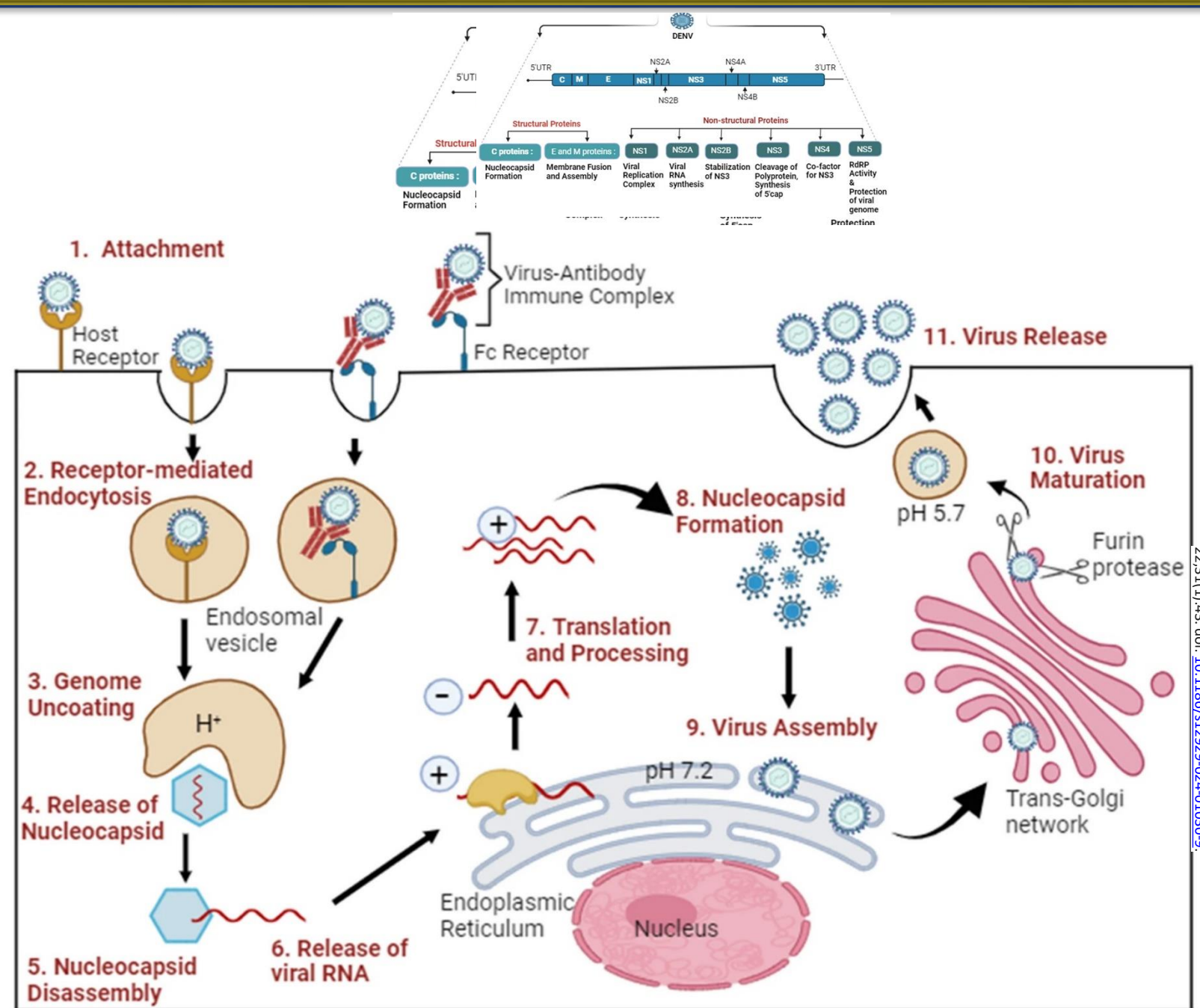
Direct:

1. E protein binds to DC-sign and other lectins → receptor-mediated endocytosis
2. Fusion with endosomal membrane release of RNP

AED:

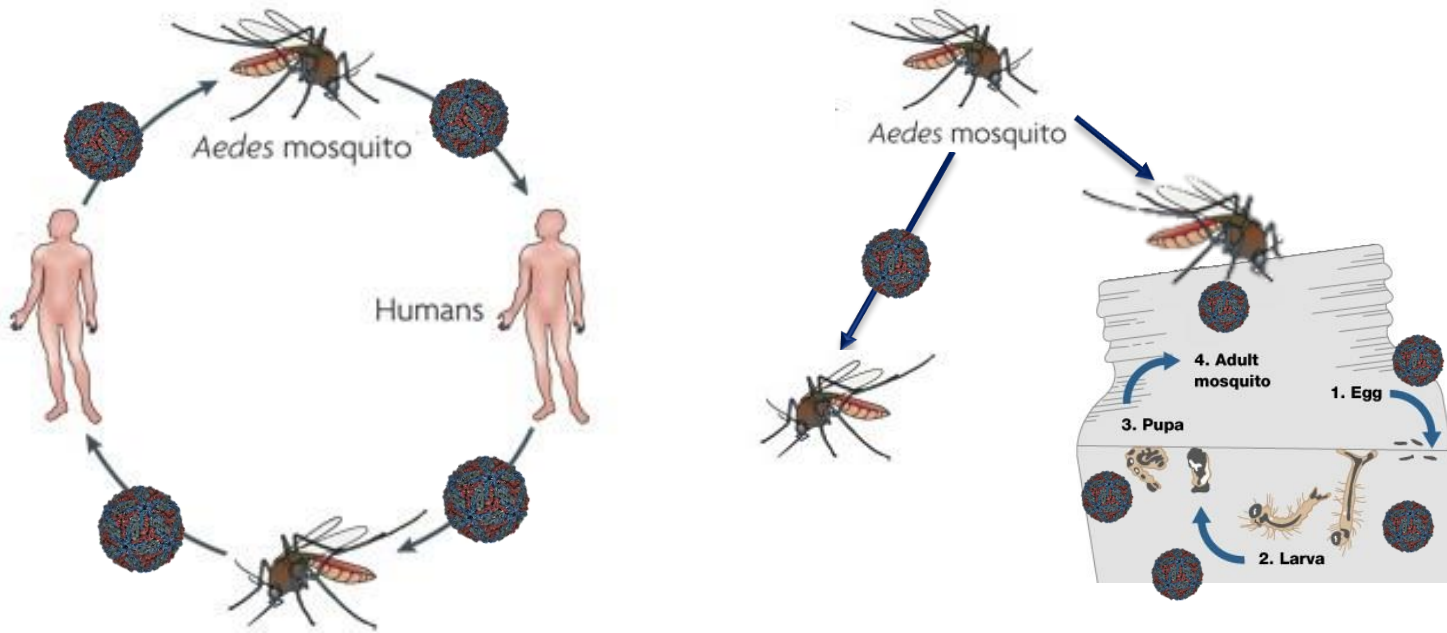
Same 2 steps, but FcR serves as the receptor

3. +ssRNA serves as mRNA, is translated into 1 long polyprotein by the host cell's ribosomes.
4. Viral and host proteases cleave the polyprotein into 3 structural proteins (C, prM/M, and E) and 7 non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 [RdRP]) in vesicles made from ER.
5. Immature to mature virus in Golgi
6. Release by exocytosis



Aedes mosquitos

- 1 infected mosquito can lead to multiple infected persons
- Once infected the mosquito remains infected its entire life (usually 3- 4 weeks) and can continue transmitting the dengue virus to healthy people.
- Asymptomatically infected persons are **INFECTIOUS** to the mosquitos

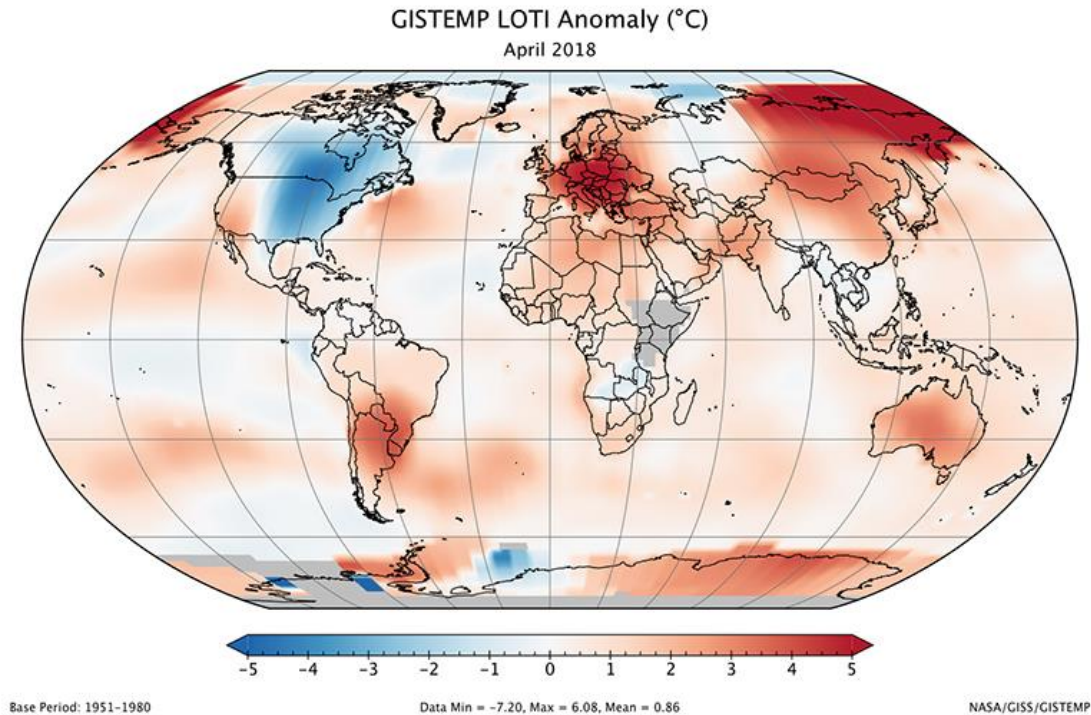


Aedes aegypti



Aedes albopictus

Climate Change



- Alters range, and nature of habitats for vectors (latitude & height)
- Alters vector behavior
- Alters life-cycle time, the warmer it is, the shorter the generation time, thus increasing population of vectors
- Alters viral particle accumulation rate
- Alters health of host / susceptibility

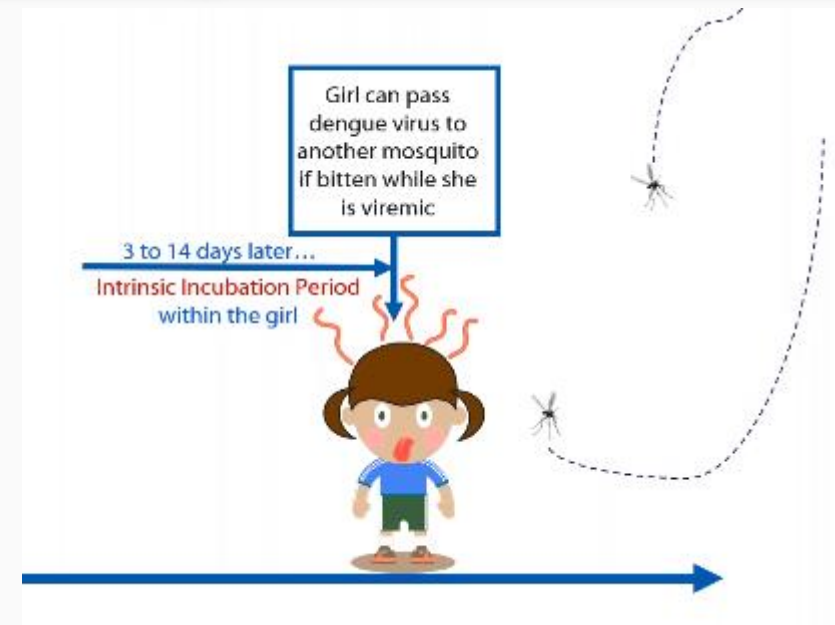
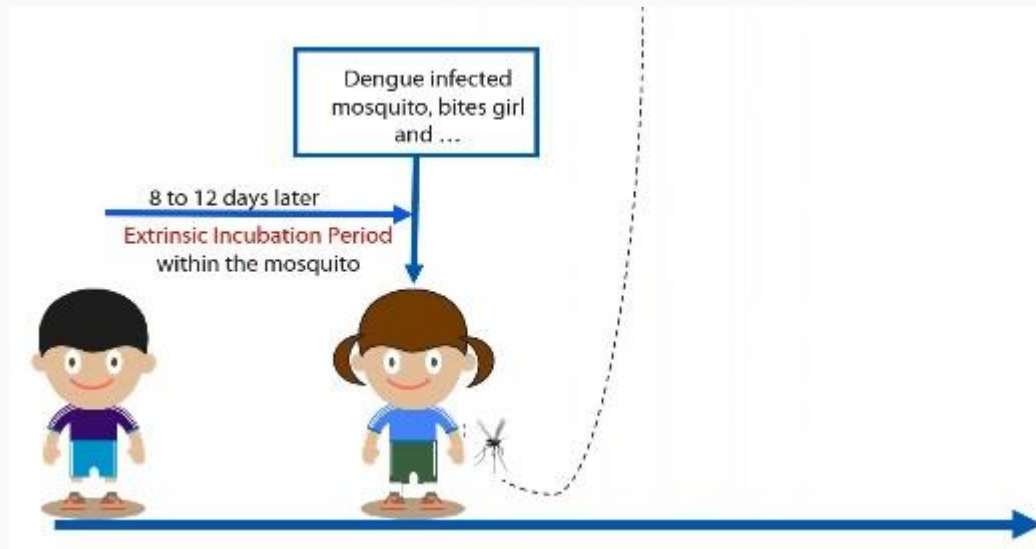


Pedersen Glacier, Alaska. Left: summer 1917. Right: summer 2005. Credit: 1917 photo captured

by Louis H. Pedersen; 2005 photo taken by Bruce F. Molnia

And Climate Change was part of the.....

Transmission of Dengue

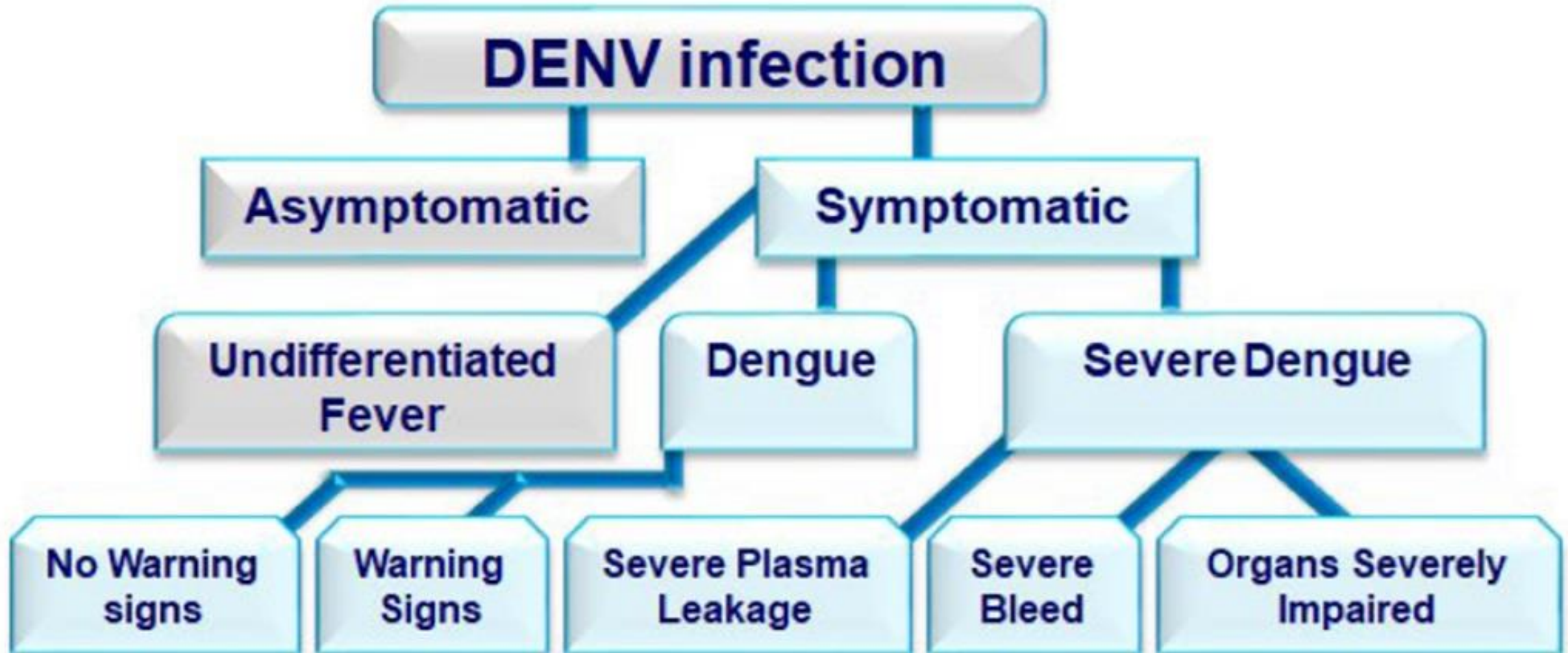


Atypical Routes of Dengue Transmission

- Vertical from mother-to-baby
 - Mother typically symptomatic at birth
- Blood products
 - Follow-up of donors to screen for new-onset fever will eliminate most contaminated units
- Breast milk
 - Possible, but quite uncommon

Dengue Clinical Syndrome Classifications

2009 WHO Case Definitions



Evaluating for Dengue and the Differential Diagnosis of Dengue

History:

- History of Fever
 - 1st day and time of fever, when was the last day & time?
- Is there exposure?
- Previous history of dengue?
- Is it currently dengue or influenza season?
- Recent travel to an area with dengue (or another infectious outbreak)?
- Exposure to mud, river waters, flood waters, animals
- Food exposure, camping, large social events?
- Behavior, e.g., New sexual partner, illicit drug/alcohol use, smoking?
- Is there a history of mosquito, tick, or other insect bite?
- Are there sick contacts in the family or household?
- Do others in the household have dengue?
- Age, underlying diseases, pregnancy, weight (e.g., obese)
- Are vaccinations up-to-date?
- Meds, supplements, home remedies?
- Hydration status (quantity & quality)
 - Urine output, vomiting, diarrhea, anorexia
- Comorbidities, pregnancy
- Changes in mental state/ seizure



Exam check: Vital signs and:

1. Mental status
2. Hemodynamic status*
3. Hydration status*
4. Signs or symptoms of plasma leakage or bleeding* or other signs of severe disease

*Capillary refill, Skin temperature, color, moisture; peripheral pulse, Urine output

Rashes in Dengue Patients



Dengue rash on days 2 to 6: Macular or maculopapular truncal rash that spreads to face and extremities

Sudden flushing or erythema of face, neck, and chest for 1 to 2 days accompanied by sudden onset of fever (may also show injected pharynx and red lips)



Before (or at) defervescence: Petechiae may be present, especially on the lower extremities.



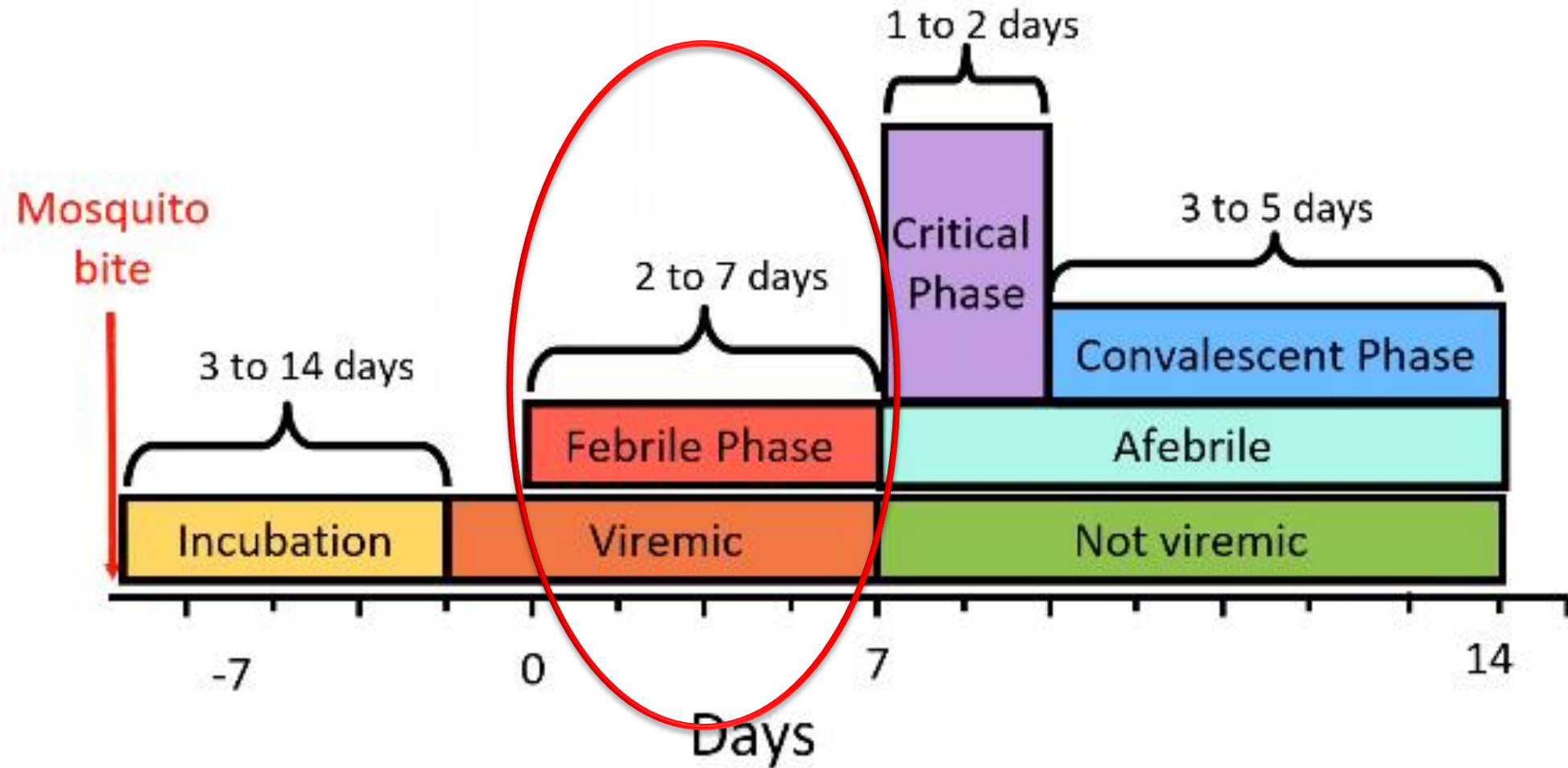
Dengue rash after defervescence: Confluent (pruritic) rash with round "islands" of normal skin on lower extremities

- **Exam check:** Vital signs and:
 1. Mental status
 2. Hemodynamic status *
 - Tachycardia
 - Narrow pulse pressure (< 20 mmHg difference, e.g., 90/72)
 3. Hydration status *
 - Fluid overload
 4. Signs or symptoms of plasma leakage or bleeding* or other signs of severe disease

*Capillary refill, Skin temperature, color, moisture; peripheral pulse, Urine output



Clinical Course of Dengue



Febrile Phase (2- 7 days)

- Abrupt onset of high fever
 - Plus, any of the following*
 - Nausea and Vomiting
 - Anorexia
 - Facial flushing or erythema
 - Injected oropharynx
 - Rash (transient macular or maculopapular)
 - Aches and pains
 - Retro-orbital pain,
 - Myalgia
 - arthralgia
 - Leukopenia
 - Minor hemorrhagic manifestations
 - Positive tourniquet test
 - Petechiae
 - Ecchymosis
 - Purpura
 - Epistaxis
 - Bleeding gums
 - Haematuria
 - Any warning sign
- *Some patients with dengue may **only** have a fever.

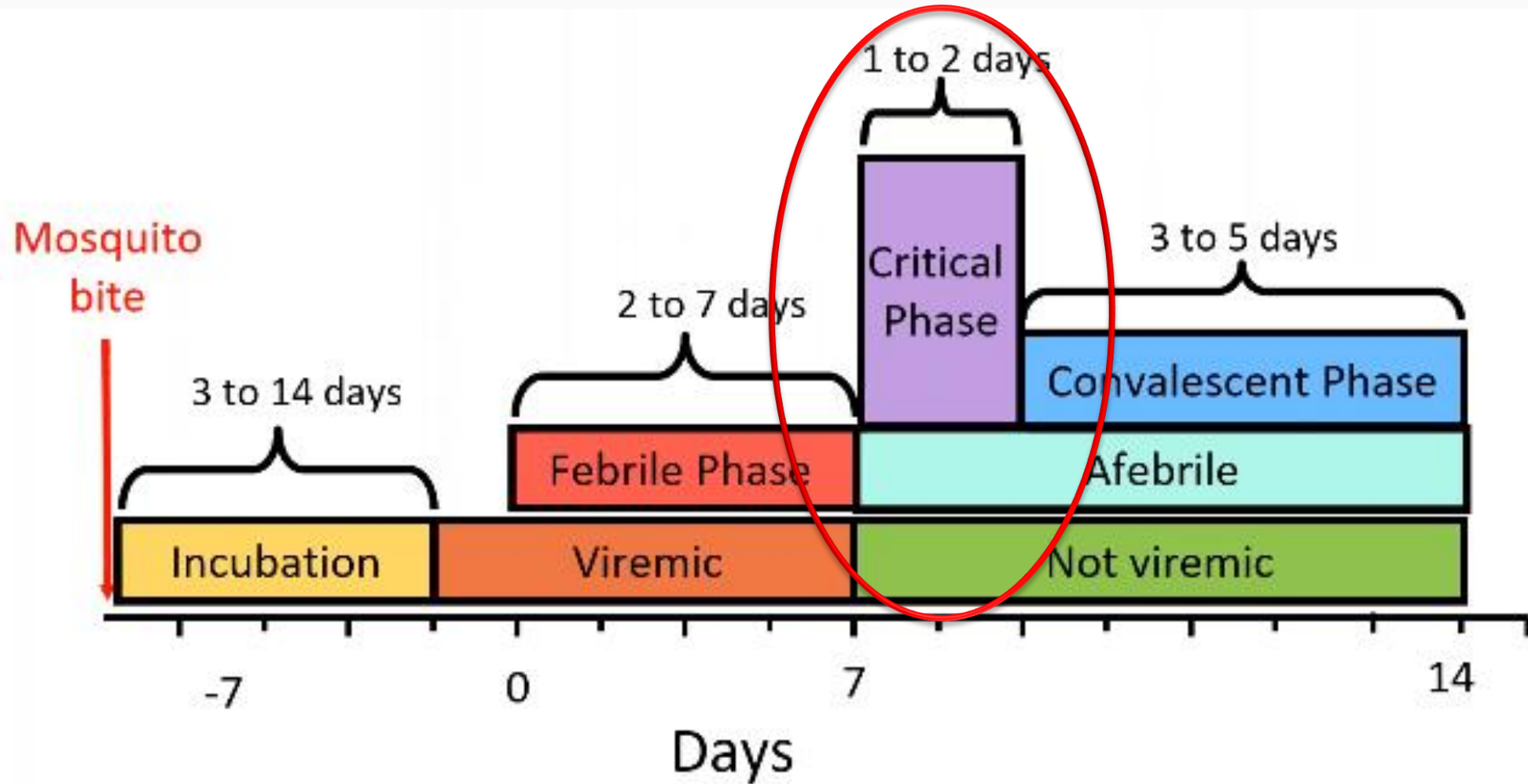
LABS

- Leukopenia
- Thrombocytopenia (Mild to moderate)
- LFT abnormalities
 - Elevated AST, ALT
- Hyponatremia

Complications

- Dehydration
- Hyponatremia
- Febrile seizures in young children
- Neurologic changes
 - Encephalitis
 - Aseptic meningitis

Clinical Course of Dengue



CRITICAL PHASE (1-2 DAYS)

- Typically starts as the fever ends (defervescence), but the patient may still be febrile
- Dangerous when patients have
 - Rise in HCT with a Rapid decline in platelet count
 - Leukopenia
 - Can manifest up to 24 hours before the platelet drop is recognized
- Watch for the development of **warning signs**
 - Abdominal pain is severe and/or continuous
 - Persistent vomiting (≥ 3 vomiting episodes within 24 hours)
 - Clinical fluid accumulation
 - e.g., ascites, pleural effusion
 - Liver enlargement > 2 cm
 - Severe abdominal pain
 - Mucosal bleed
 - Lethargy or restlessness

Labs

- Increased HCT (or haemoconcentration)
- Moderate to severe thrombocytopenia
 - Platelets (initial normal) RAPID drop shortly before or with an increase in HCT at the time of defervescence)
- Leukopenia
 - But high numbers of atypical lymphocytes
- Transient increase aPTT
- Decreased fibrinogen
- May see a drop in serum protein/albumin

Complications

- Hypovolemic shock (from plasma leakage)
- End-organ impairment (from prolonged shock)
 - Abdominal compartment syndrome
- Severe Hemorrhage
- Neurological complications
 - Encephalopathy
 - Encephalitis

Patients may rapidly deteriorate to severe dengue and may be lucid!

A clinically significant plasma leakage is one that lasts 24-48 hours from the time of defervescence

Monitor carefully for the resolution of the plasma leak and for the start of the recovery phase to avoid fluid overload.

Ascites

- Symptoms
 - Abdominal discomfort
 - Flank pain
 - Respiratory distress
- Signs
 - Fluid wave
 - Shift in dullness
- Ultrasound assessment
 - Rapid and easy
 - May be overly sensitive?



Pleural effusion



- **Hemoconcentration**
 - HCT \geq 20% higher than the person's baseline HCT
 - or –
 - HCT \geq 20% higher than normal max value
- **Hypoalbuminemia or hypoproteinemia**

Dengue

- About 30% have minor bleeding
 - Petechiae
 - Purpura
 - Epistaxis
 - Gingival bleeding
 - Mild hematuria

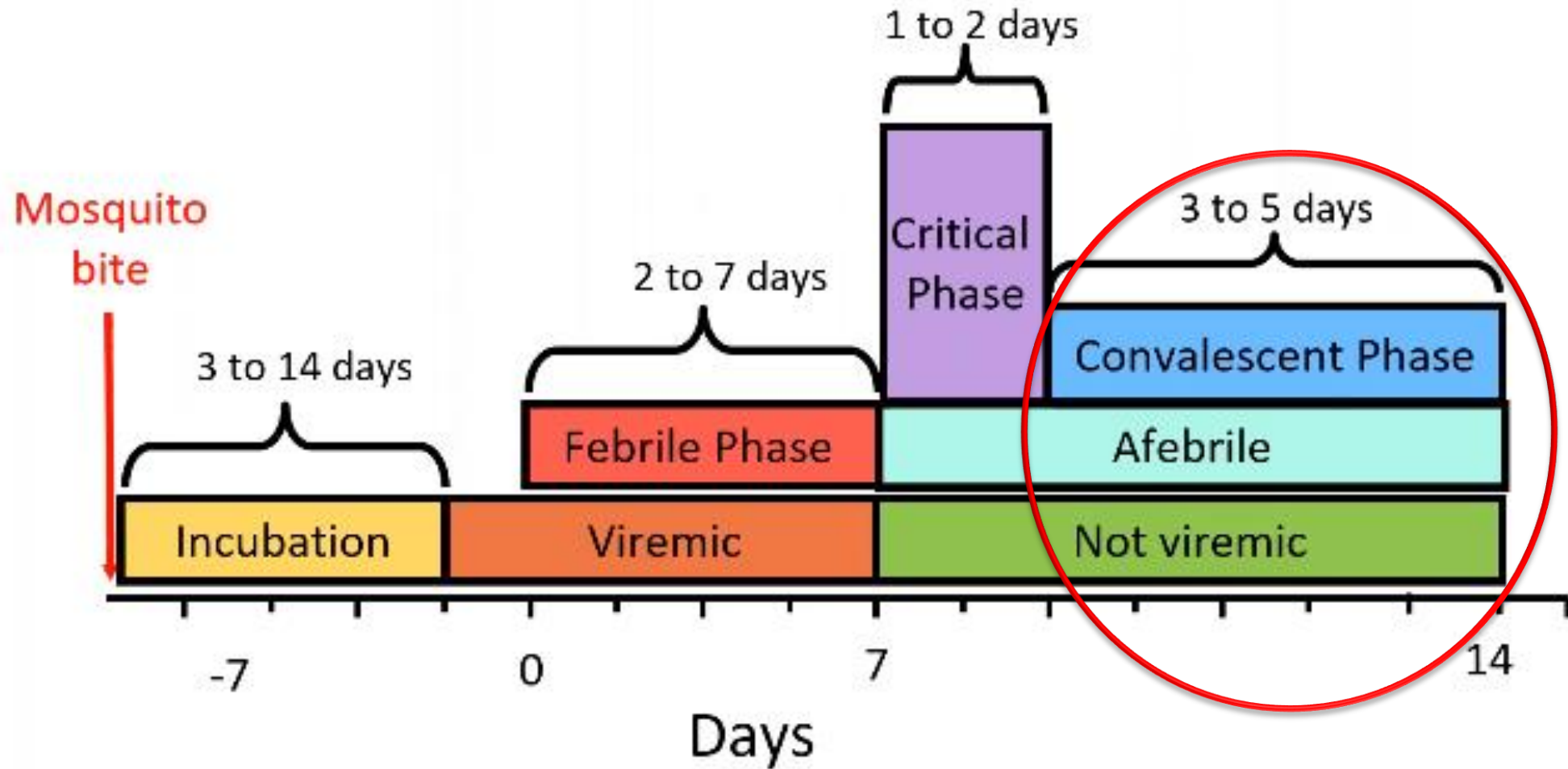


Severe Dengue

- Massive GI bleeding
 - Associated with prolonged shock and metabolic acidosis
 - May be occult
- Severely bleeding at venepuncture
- Pulmonary bleed (uncommon)

- Risk factors for bleeding
 - Prolonged or refractory shock
 - Hypotensive shock and renal failure or liver failure and or severe persistent metabolic acidosis
 - Use of NSAID or anticoagulant therapy
 - Pre-existing peptic ulcer disease
 - Any form of trauma, including intramuscular injection

Clinical Course of Dengue



Does the Patient Have Dengue?

- **Fever** is the most common presenting sign in a person with dengue. Dengue presents like many other acute febrile illnesses
- **Clinically diagnosing dengue is difficult** because early signs and symptoms are nonspecific, but early clinical diagnosis is needed for appropriate anticipatory guidance and timely treatment to prevent morbidity and mortality.
- **The clinical presentation changes throughout the course** of the illness and varies by disease severity.
- Familiarity with diseases on the differential diagnosis of dengue helps in clinical diagnosis.



Depending on the clinical presentation and patient exposure history (e.g., recent travel), vaccine history, etc., there are **many infectious illnesses on the differential diagnosis** of dengue

Enteroviral infection	Measles
Adenoviral infection	Rubella
Influenza	Scarlet fever
West Nile virus infection	Toxic shock syndrome
Bacterial sepsis	Viral hepatitis
Erythema infectiosum (fifth disease)	Rickettsial diseases
Roseola infantum (sixth disease)	Meningococcemia
Epstein-Barr virus infection	Leptospirosis
HIV seroconversion illness	Typhoid fever
Melioidosis (<i>Burkholderia pseudomallei</i>)	Malaria
Chikungunya	Chagas disease
Rocky Mountain spotted fever	Ehrlichia
Other spotted fever diseases	Anaplasmosis
Zika fever	
Other viral hemorrhagic fevers (e.g., hantavirus, CCHV, Ebola, etc.)	

**Non-Infectious
(or post-infectious)
Entities on the
Differential
Diagnosis of
Dengue**

- Idiopathic (immune) thrombocytopenic purpura (ITP)
- Acute leukemia
- Drug reaction
- Diabetic ketoacidosis
- Lactic acidosis (severe dehydration)
- Kawasaki disease

A 10-year-old boy is found non-responsive at home by his mother, who calls emergency responders. The child has had a high fever for the past 5 days, severe abdominal pain, persistent vomiting, and mucosal bleeding. On examination by the emergency responders, he is febrile (39.5°C), hypotensive (BP 80/50 mmHg), tachycardic (HR 130 bpm), and has a petechial rash on his trunk and extremities. The mother reports that the child has not urinated in the past 12 hours. The emergency responders need to decide on the appropriate tests to perform before starting treatment. There has been a dengue outbreak reported in the area. Which of these would help you establish a diagnosis of dengue?

- A. Blood glucose measurement
- B. Complete blood count (CBC)
- C. Electrocardiogram (ECG)
- D. Rapid diagnostic test for NS1 antigen**
- E. Urinalysis

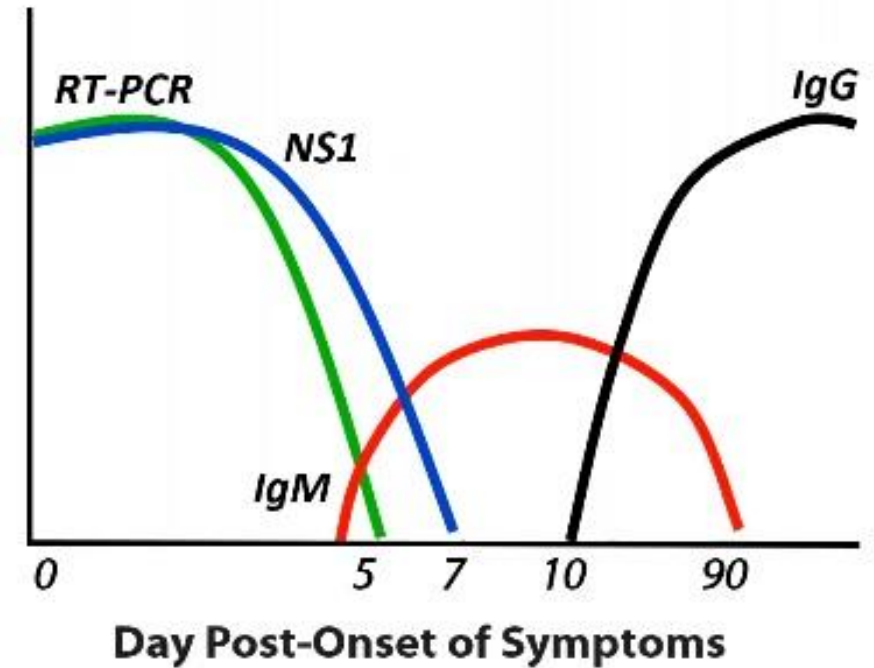


<https://www.ketto.org/fundraiser/sriwardhan>

Answer: D. Rapid diagnostic test for NS1 antigen. The child presents with signs and symptoms highly suggestive of severe dengue, including high fever, abdominal pain, vomiting, mucosal bleeding, hypotension, tachycardia, and petechial rash. A rapid diagnostic test for NS1 antigen can quickly confirm dengue infection, allowing for appropriate and timely management.

Typical Laboratory findings in Dengue

- WBC
 - Initially, WBC is normal
 - At the end of the Febrile phase:
 - neutrophils decrease,
 - atypical lymphocytes increase
 - overall drop in WBCs
- Hematocrit
 - $\geq 20\%$ above baseline
- Platelets
 - Initially, Platelets are normal
 - At the Defervescence
 - Rapid drop in Platelets (before or simultaneously to increase in HCT)
- Liver function tests
 - May have a slight elevation of AST
 - AST is usually 2 X higher than ALT
- **NS1 positive**



A 10-year-old boy is found non-responsive at home by his mother, who calls emergency responders. The child has had a high fever for the past 5 days, severe abdominal pain, persistent vomiting, and mucosal bleeding. On examination by the emergency responders, he is febrile (39.5°C), hypotensive (BP 80/50 mmHg), tachycardic (HR 130 bpm), and has a petechial rash on his trunk and extremities. Laboratory tests show a platelet count of 50,000/ μ L (reference range: 150,000-450,000/ μ L), hematocrit of 45% (reference range: 36-44%), and elevated liver enzymes. A rapid diagnostic test for NS1 antigen is positive. Intravenous normal saline is administered. Which of the following parameters should be monitored to guide further fluid management in this patient?

- A. Blood glucose levels
- B. Hematocrit levels**
- C. Serum sodium levels
- D. Serum creatinine levels
- E. White blood cell count



<https://www.ketto.org/fundraiser/sriwardhan>

Answer: B. Hematocrit levels. Monitoring hematocrit levels is crucial in dengue management to assess for hemoconcentration, which indicates plasma leakage and the need for further fluid resuscitation.

A 10-year-old boy is found non-responsive at home by his mother, who calls emergency responders. The child has had a high fever for the past 5 days, severe abdominal pain, persistent vomiting, and mucosal bleeding. On examination by the emergency responders, he is febrile (39.5°C), hypotensive (BP 80/50 mmHg), tachycardic (HR 130 bpm), and has a petechial rash on his trunk and extremities. Laboratory tests show a platelet count of $50,000/\mu\text{L}$ (reference range: $150,000\text{--}450,000/\mu\text{L}$), hematocrit of 45% (reference range: 36-44%), and elevated liver enzymes. A rapid diagnostic test for NS1 antigen is positive. The patient is started on intravenous fluids and shows some improvement. Which of the following immune responses is most likely contributing to the severity of this patient's condition?

- A. Antibody-dependent enhancement (ADE)
- B. Complement activation
- C. Cytotoxic T-cell response
- D. Interferon-gamma production
- E. Natural killer (NK) cell activity



<https://www.ketto.org/fundraiser/sriwardhan>

Answer: A. Antibody-dependent enhancement (ADE) is a feature when non-neutralizing antibodies from a previous dengue infection facilitate viral entry into immune cells, leading to increased viral replication and severe disease.

A 10-year-old boy is found non-responsive at home by his mother, who calls emergency responders. The child has had a high fever for the past 5 days, severe abdominal pain, persistent vomiting, and mucosal bleeding. On examination by the emergency responders, he is febrile (39.5°C), hypotensive (BP 80/50 mmHg), tachycardic (HR 130 bpm), and has a petechial rash on his trunk and extremities. Laboratory tests show a platelet count of 50,000/ μ L (reference range: 150,000-450,000/ μ L), hematocrit of 45% (reference range: 36-44%), and elevated liver enzymes. A rapid diagnostic test for NS1 antigen is positive. Which of the following is the most appropriate next step in the management of this patient at home?

- A. Administer intravenous normal saline
- B. Administer intravenous dopamine
- C. Administer intravenous acetaminophen
- D. Perform a lumbar puncture
- E. Start broad-spectrum antibiotics



<https://www.ketto.org/fundraiser/sriwardhan>

Answer: A. Administer intravenous normal saline. The patient presents with signs of severe dengue, including hypotension, tachycardia, petechial rash, and a positive NS1 antigen test. The initial management should focus on fluid resuscitation to address hypovolemic shock

Could you have given fresh-whole blood?

Fresh Whole Blood

- Restores blood volume, improves oxygen-carrying capacity, and provides clotting factors to address bleeding.
- Can consider using it if there is significant bleeding and the child is hemodynamically unstable despite fluid resuscitation.
- However, it also carries risks, such as
 - fluid overload,
 - transfusion reactions,
 - alloimmunization.
- The decision to use fresh whole blood should be based on a thorough assessment of the patient's clinical status and the potential benefits outweighing the risks. Continuous monitoring and appropriate communication with the patient's family are essential for optimal patient outcomes.



<https://www.jems.com/patient-care/whole-blood-in-emt-may-save-lives/>

- Fluid Resuscitation: GIVE ONLY **ISOTONIC** solutions! **Limit fluids to Febrile Phase unless dehydrated**
 - Initial Bolus: Administer 20 mL/kg of isotonic crystalloid solution (e.g., normal saline or Ringer's lactate) over 15-30 minutes.
 - Reassessment: Monitor vital signs and clinical response. If signs of shock persist, repeat the fluid bolus.
 - Colloids: Consider using colloids (e.g., albumin) if the child does not respond to crystalloids.
 - Fresh Whole Blood: Consider if there is significant bleeding and the child is hemodynamically unstable despite fluid resuscitation.
- Medications:
 - Acetaminophen (Paracetamol): Administer for fever and pain relief. Avoid NSAIDs.
 - Mechanism of Action: Inhibits prostaglandin synthesis, reducing fever and pain.
 - Ondansetron (Zofran): Administer for nausea and vomiting.
 - Mechanism of Action: Selective 5-HT₃ receptor antagonist that blocks serotonin receptors in the chemoreceptor trigger zone, reducing nausea and vomiting.
 - Dopamine: If hypotension persists despite adequate fluid resuscitation, consider administering dopamine.
 - Mechanism of Action: Dopaminergic agonist that increases blood pressure by increasing cardiac output and peripheral vascular resistance.
- Monitoring and Ongoing Assessment
 - Vital Signs: Continuously monitor blood pressure, heart rate, respiratory rate, and oxygen saturation.
 - Urine Output: Aim for at least 0.5 mL/kg/hour. Insert a urinary catheter if necessary.
 - Hematocrit and Platelet Count: Monitor for hemoconcentration and thrombocytopenia.
 - Clinical Signs: Monitor for signs of fluid overload, such as respiratory distress and edema.
 - Point-of-Care Testing (POCT): Repeat tests as needed to monitor liver function and electrolyte levels.

Dengue

- Acute febrile phase includes (2- 7 d)
 - HIGH fever
 - Generalized body ache
 - **Myalgia**
 - **Arthralgia**
 - Headache
 - Pain Behind the eyes
 - Facial flushing
 - Skin redness
 - May also have
 - Sore throat, injected pharynx
 - Nausea, vomiting, lack of appetite
 - Conjunctival injection
 - Evidence of bleeding
 - + Tourniquet test
 - Petechiae or other evidence of bleeding

Warning Signs

- Abdominal pain or tenderness
- Persistent vomiting
- Bleeding from mucosa
- Extremely tired and restless
- Liver enlargement > 2 cm
- Edema or other fluid accumulation
- Rapid loss of platelets, anemia, low white blood cells

- Severe plasma leakage leading to
 - Shock (DSS)
 - Marked fluid accumulation including pulmonary edema and respiratory distress
- Severe bleeding
- Severe organ abnormalities
 - Liver AST or ALT ≥ 1000
 - Impaired consciousness
 - Heart or kidney abnormalities

Thank you



Surveillance and Education



Florida Department of Health officials go door-to-door collecting urine specimens to test for Zika. The program was headed up by FIU medical professor Aileen Marty. (Image: Florida International University)



Dr. Aileen Marty, professor of Infectious Diseases at Florida International University, explains the use of insect repellent towelettes in Miami. There have been 238 cases of Zika reported in Florida.

Questions?

Any Day you Forget your Bug-Spray

May be a life altering day
And NOT in a good way



Aileen M Marty MD

Professor, Infectious Disease
Herbert Wertheim College of Medicine, FIU



amarty@fiu.edu

Available Dengue Vaccines

CYD-TDV (Dengvaxia)

- Developer: *Sanofi Pasteur*
- Platform: Live-attenuated tetravalent vaccine using the yellow fever 17D virus backbone.
- Availability: Licensed in several countries, including Mexico, Brazil, the Philippines, and others. Licensed for ages 9 to 45 years
- Efficacy: Approximately 60-80% efficacy in preventing symptomatic dengue.
 - DENV1: Moderate
 - DENV2: low
 - DENV3 Moderate
 - DENV4- High
- Safety: Generally safe but has a higher risk of severe dengue in seronegative individuals.
- Mechanism of Action: Induces immune response against all four dengue virus serotypes.

AK-003 (QDenga)

- Developer: *Takeda*
- Platform: Live-attenuated tetravalent vaccine based on a DENV-2 backbone with chimeric DENV-1, DENV-3, and DENV-4
- Availability: Recently prequalified by WHO, recommended for children aged 6-16 in endemic regions, (4-16 in some areas)
- Efficacy: 84% efficacy in preventing hospitalization.
 - DENV1: Moderate
 - DENV2: Highest (97%)
 - DENV3: Low
 - DENV4: Not enough data
- Safety: Safe with a good safety profile.
- Mechanism of Action: Induces immune response against all four dengue virus serotypes