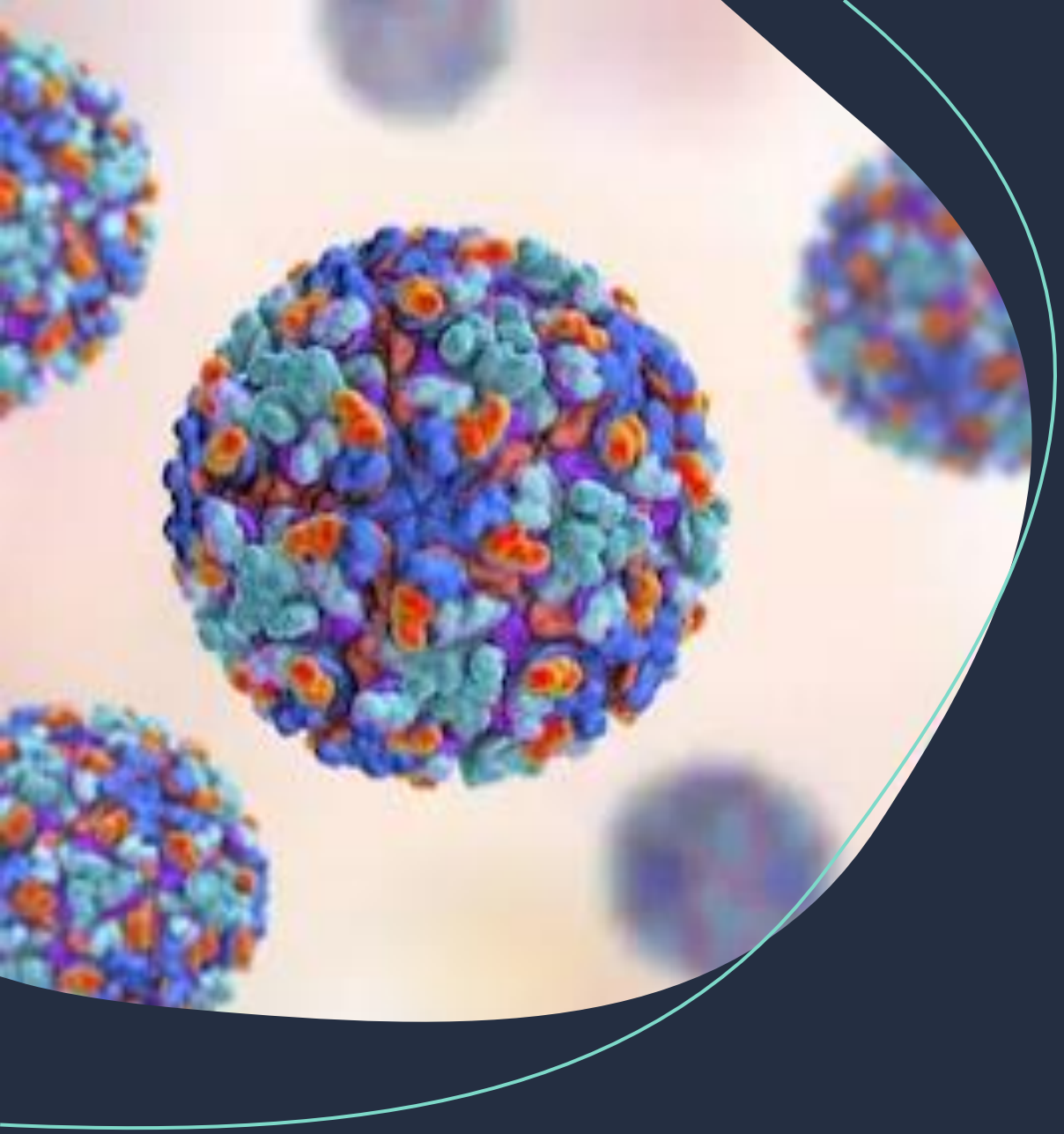

Arboviral Arthritis: Dengue and Chikungunya in 2024

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Disclosures

The following presentation as prepared by the presenter (HA) in her personal capacity. The opinions expressed in it are her own and do not reflect the view of the Food and Drug Administration, the Department of Health and Human Services, or the U.S. Government.

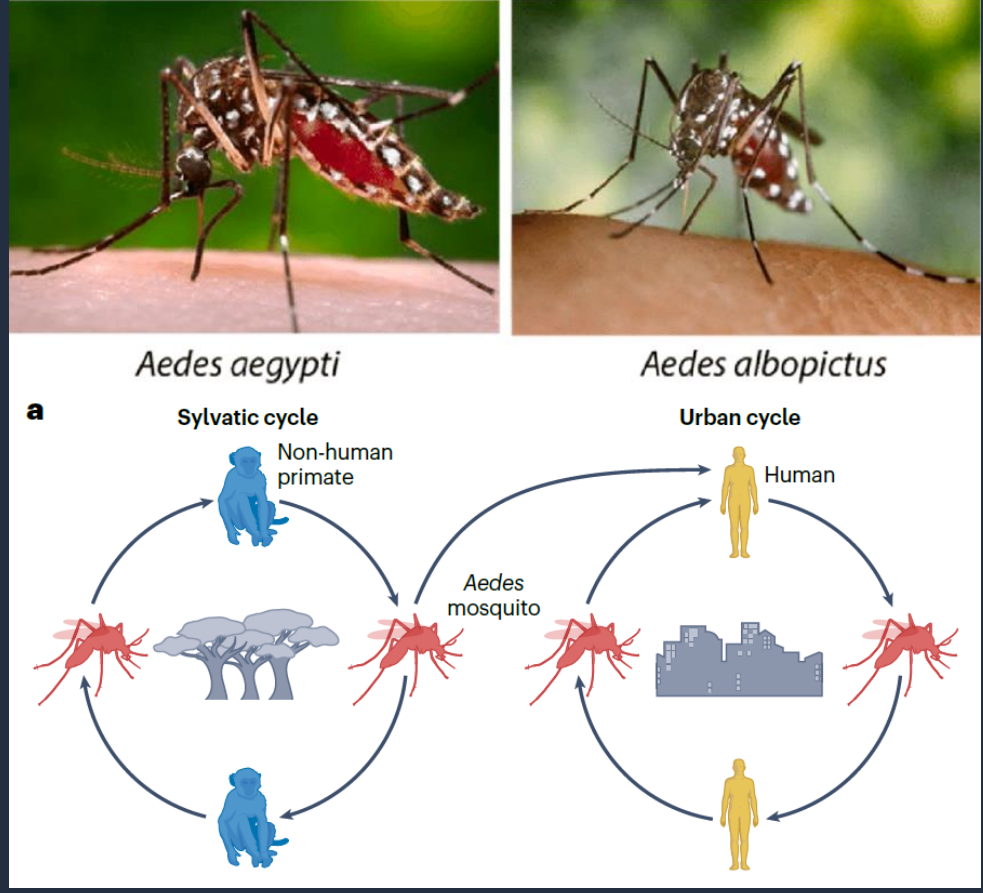
The presenter will acknowledge during this session any information that is considered investigational or exploratory.

The presenter acknowledges and gives thanks for the contributions of people with lived experience to the study of post-viral conditions.

Agenda

1. Arboviral epidemiology
2. Arboviral infection and arthritis
3. Dengue updates: what to know in 2024
4. Chikungunya updates: what to know in 2024
5. Bonus vaccine-preventable disease topic
6. Conclusions

Arboviral Epidemiology



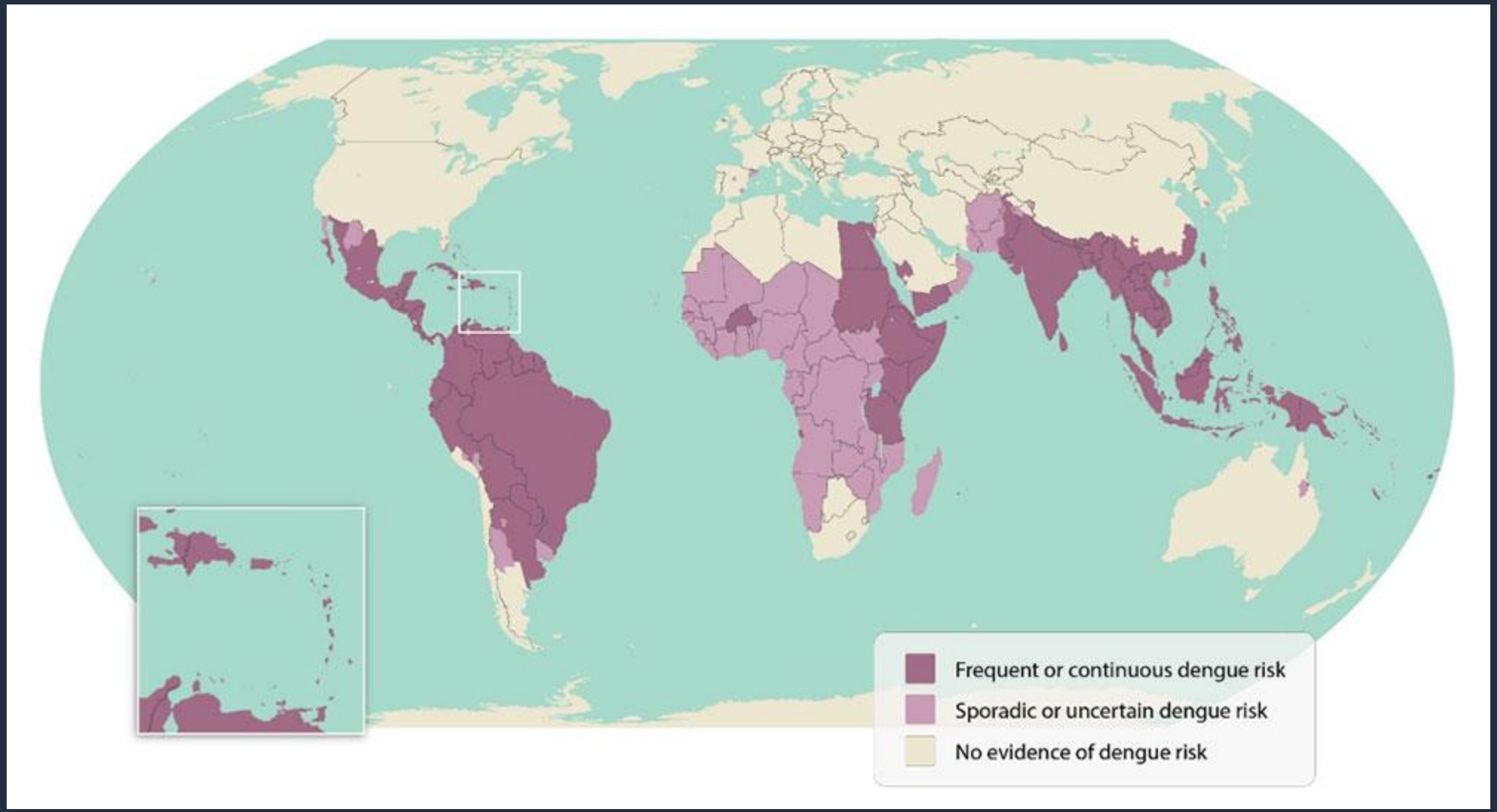
- Arbovirus = arthropod-borne virus
- Arboviruses transmitted by *Aedes spp:* DENV, CHIKV, ZIKV, YFV, more.
- DENV infects ~50 M per year in >100 countries
  - ~4 billion at risk, with range changing due to climate change, global trade, travel
  - 4 serotypes; Dengue Hemorrhagic Fever (DHF) more likely with cross-type re-infection
- CHIKV infects ~1 M per year
  - Persistent arthritis in 40-80%, significant change in function in ~25%

Dengue virus

Genus Flavivirus

From Swahili, “Ka dinga pepo”

In Spanish, “Quebranta huesos” a.k.a. “breakbone fever”



Dengue Around the World | Dengue | CDC

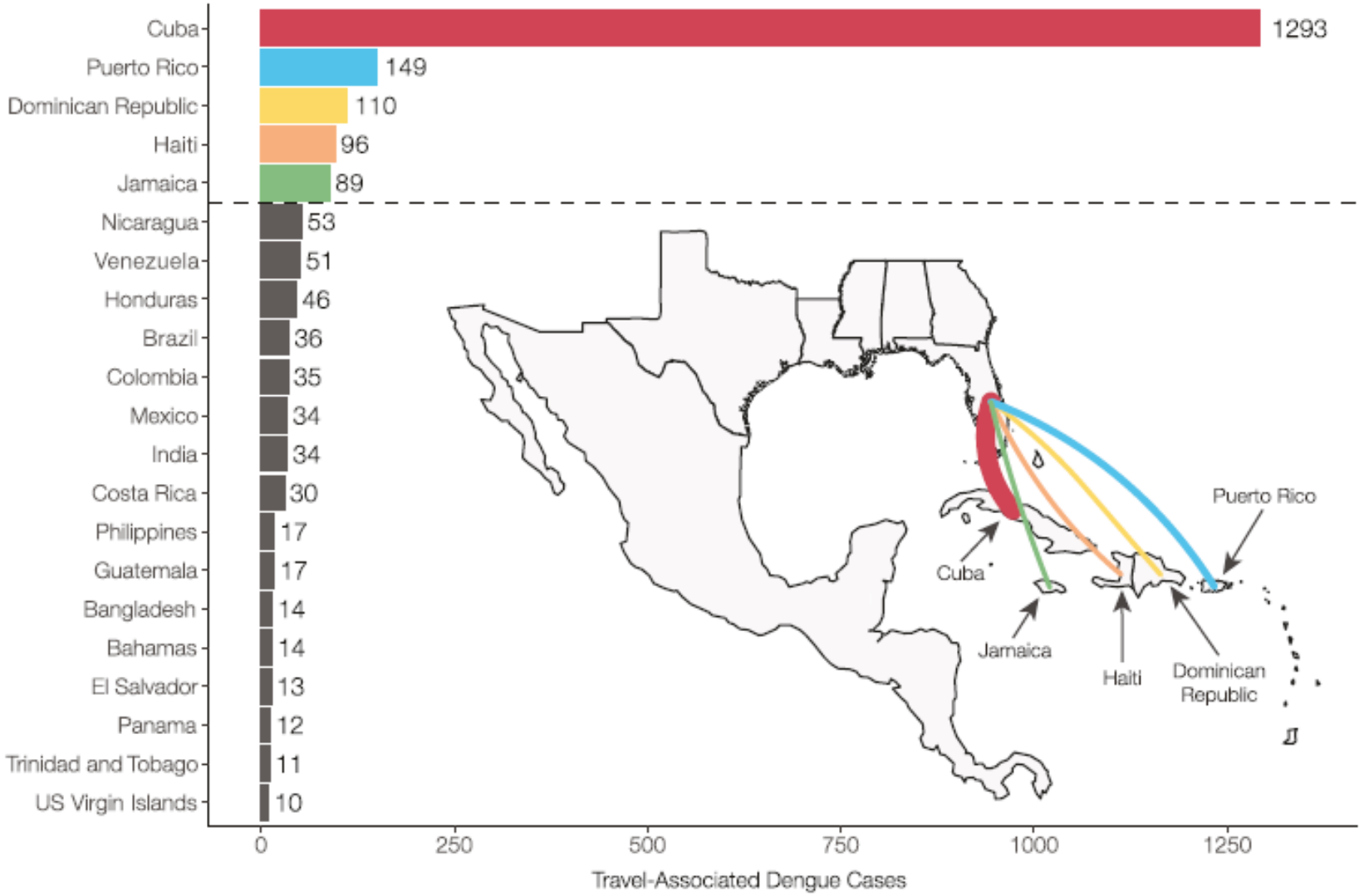
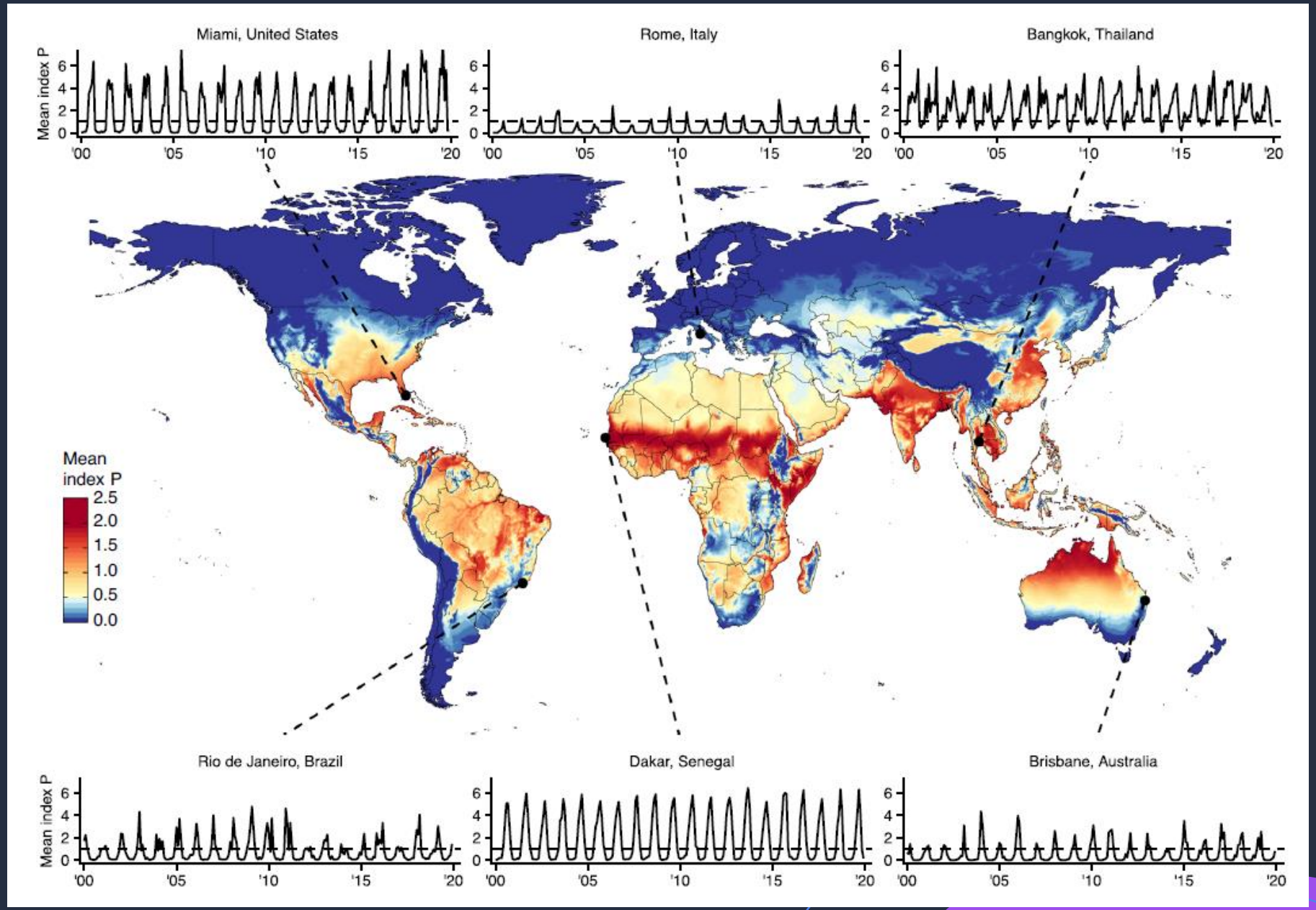


Fig. 1 | Cuba, Dominican Republic, Haiti, Jamaica, and Puerto Rico make up the majority of travel-associated dengue cases reported in Florida from 2009 to 2022. Countries and territories are listed by total number of travel cases for each inferred origin of infection based on travel history, in descending order. Only countries or territories with at least 10 associated travel infections are shown. The complete data can be found in Supplementary Table S1. The inset shows a map of the location of the top 5 associated country origins of travel cases reported in Florida, with the line width proportional to the number of travel cases.

Taylor-Salmon 2023, PMID 38664380



Nakase 2023
PMID: 37173303

RAPID COMMUNICATION

Autochthonous dengue in mainland France, 2022: geographical extension and incidence inc

Guillaume André Du

JOURNAL ARTIC

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Americas

Surging dengue cases in Americas cause alarm as potentially worst-ever season looms

By Marion Giraldo

March 28, 2024 1:54 PM EDT · Updated 2 days ago

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HEALTH

Here's what to know about dengue, as Puerto Rico declares a public health emergency

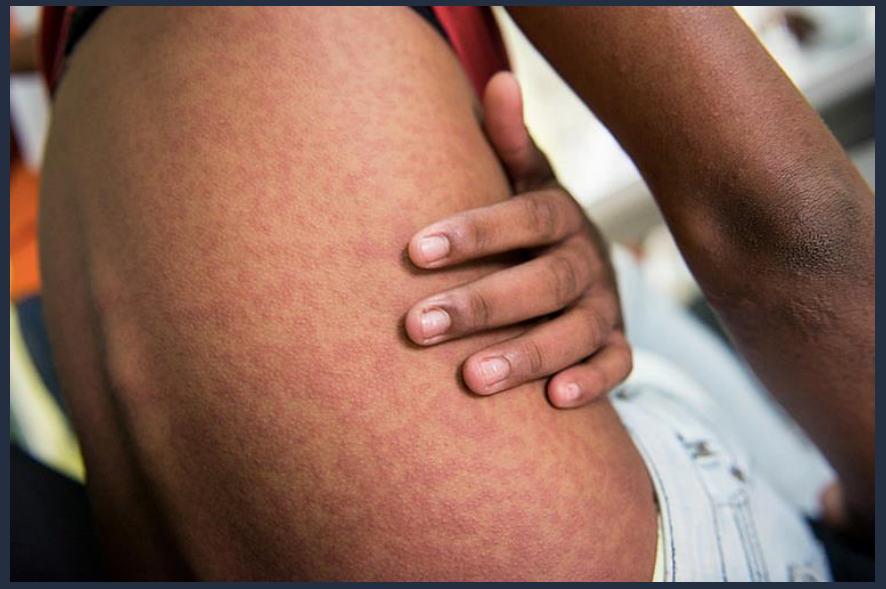
MARCH 27, 2024 · 1:59 PM ET

By Joe Hernandez

Volume 30, Number 2—February 2024

Dispatch

Introduction and Spread of Dengue Virus 3, Florida, USA, May 2022–April 2023

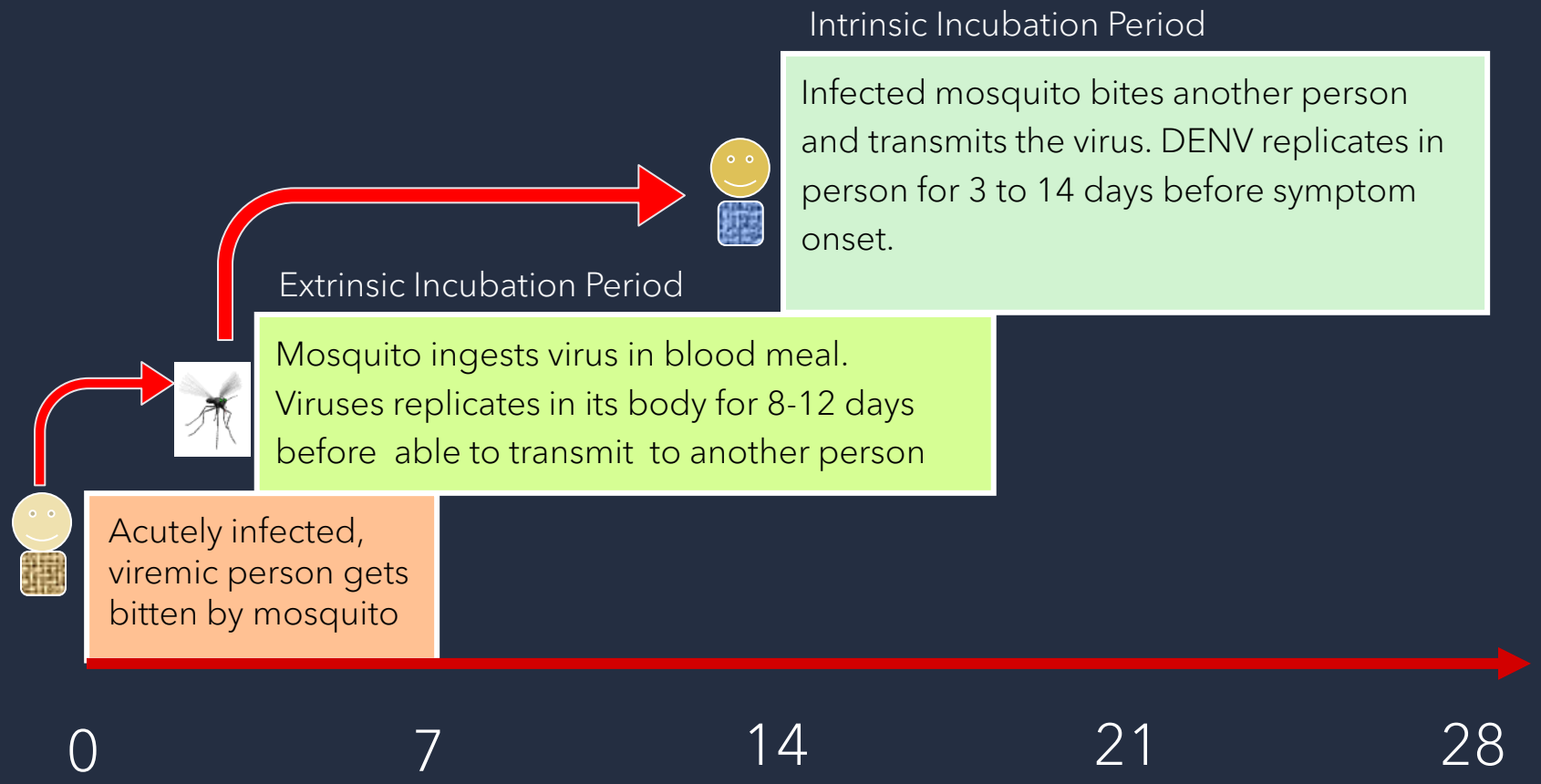


Arboviruses to Know

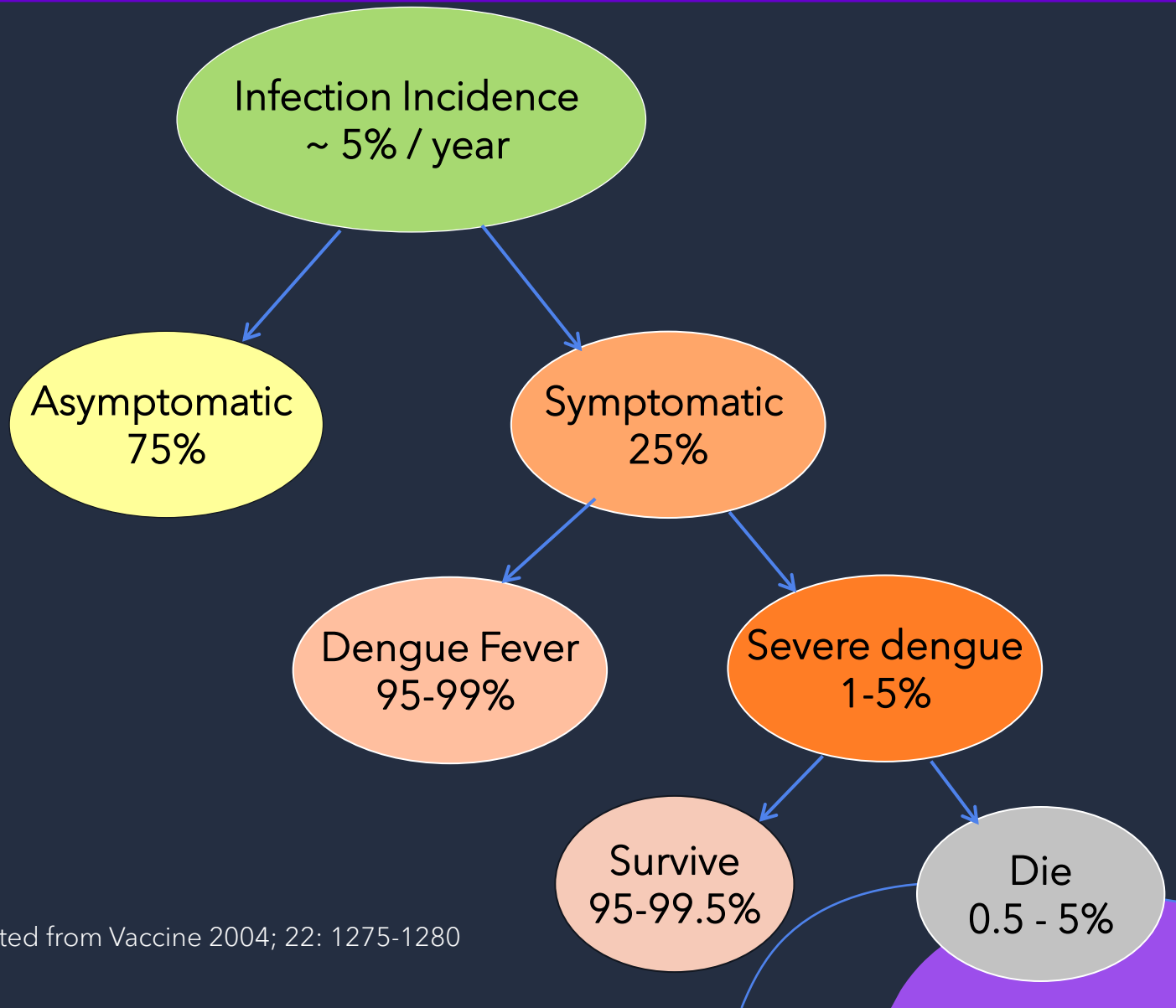
- Same vectors and geography
- Similar clinical features
- Complex immunity
- Important to suspect early and diagnose accurately
- Serologic tests may cross-react

Features	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	-	-
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Hemorrhage	-	++	-
Shock	-	+	-

Transmission of DENV

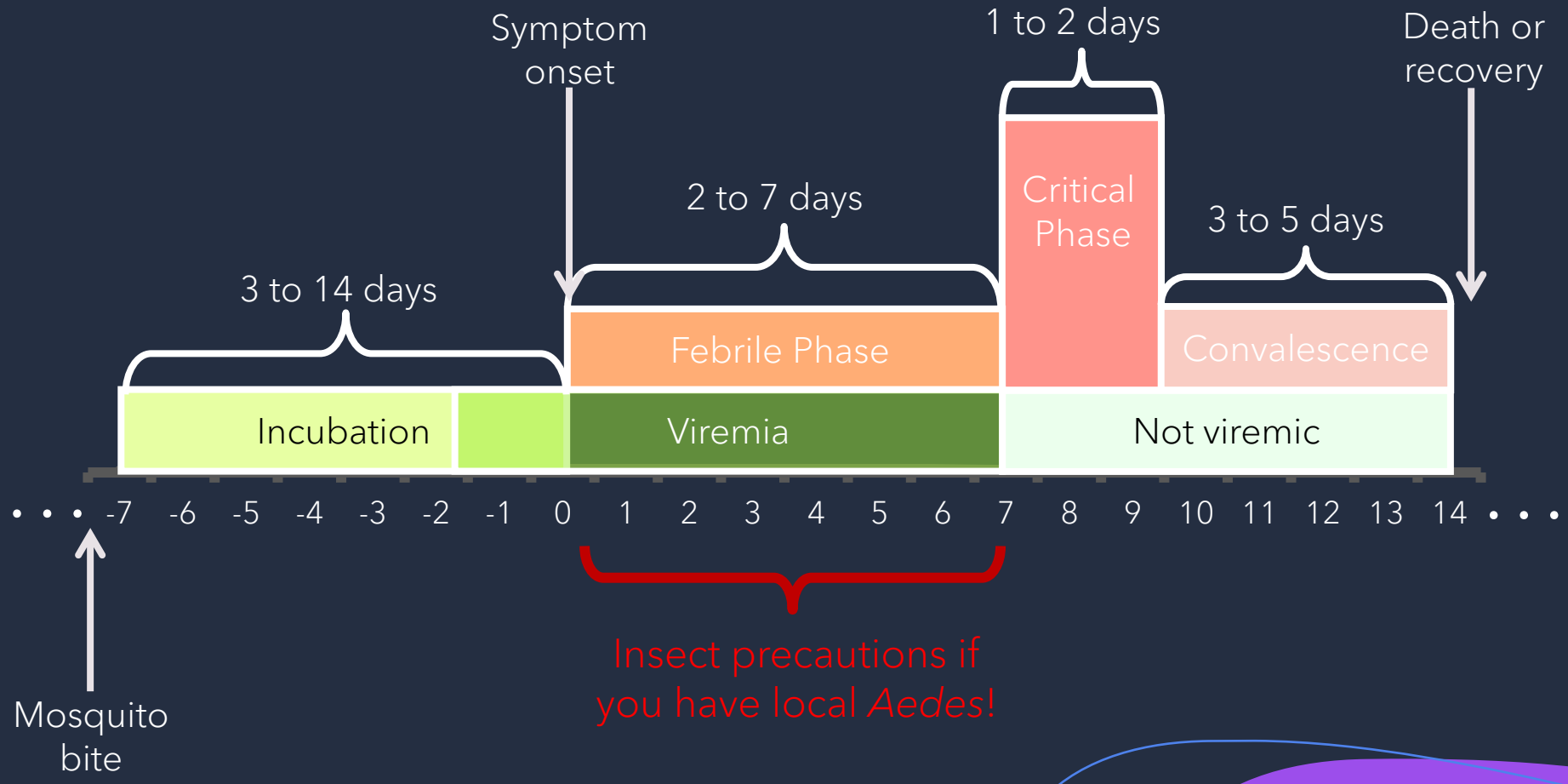


Natural History of DENV Infections

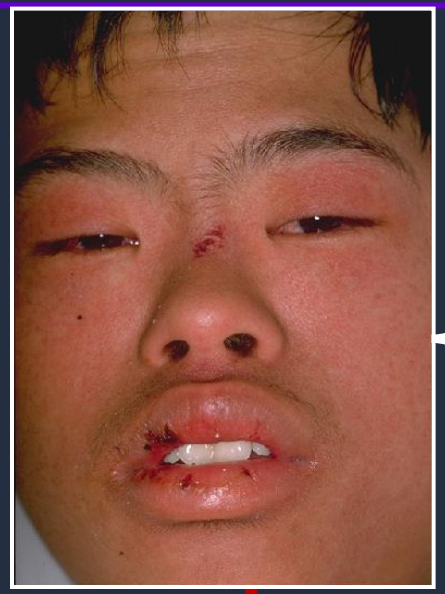


Adapted from Vaccine 2004; 22: 1275-1280

Clinical Course of Dengue

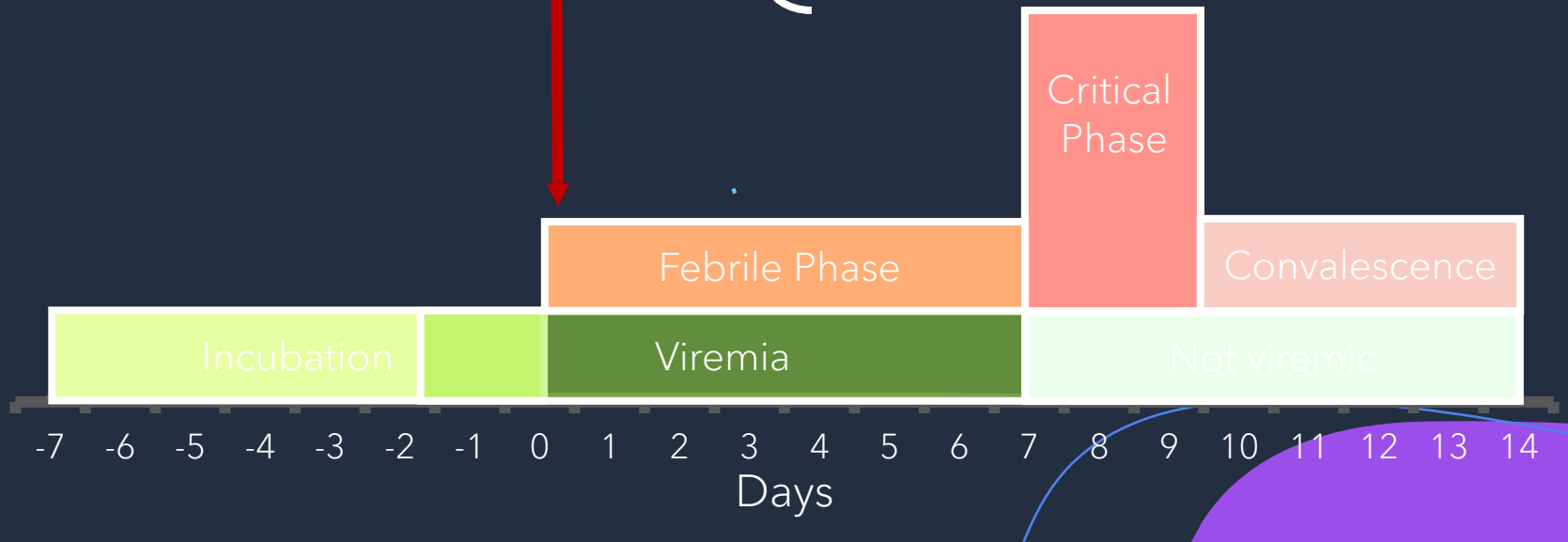


Febrile Phase

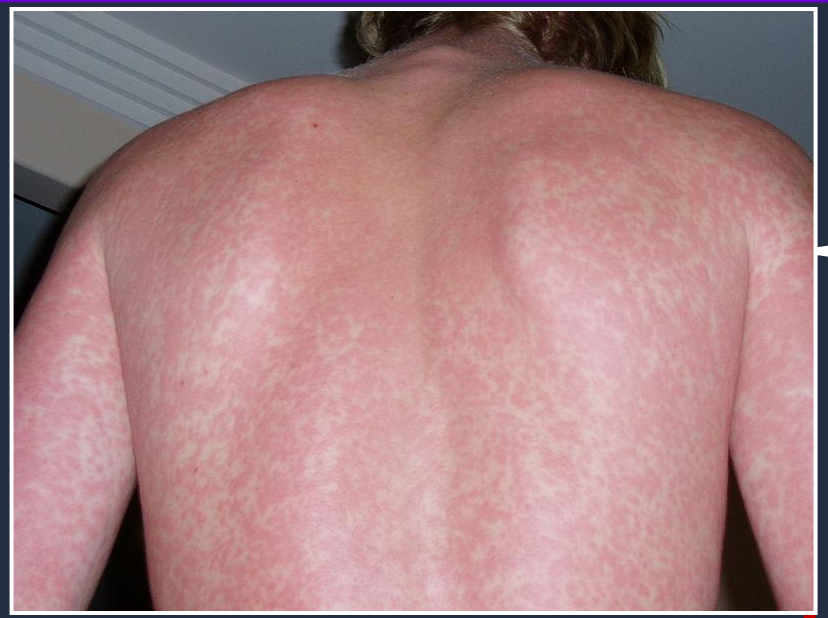


Classic signs and symptoms:

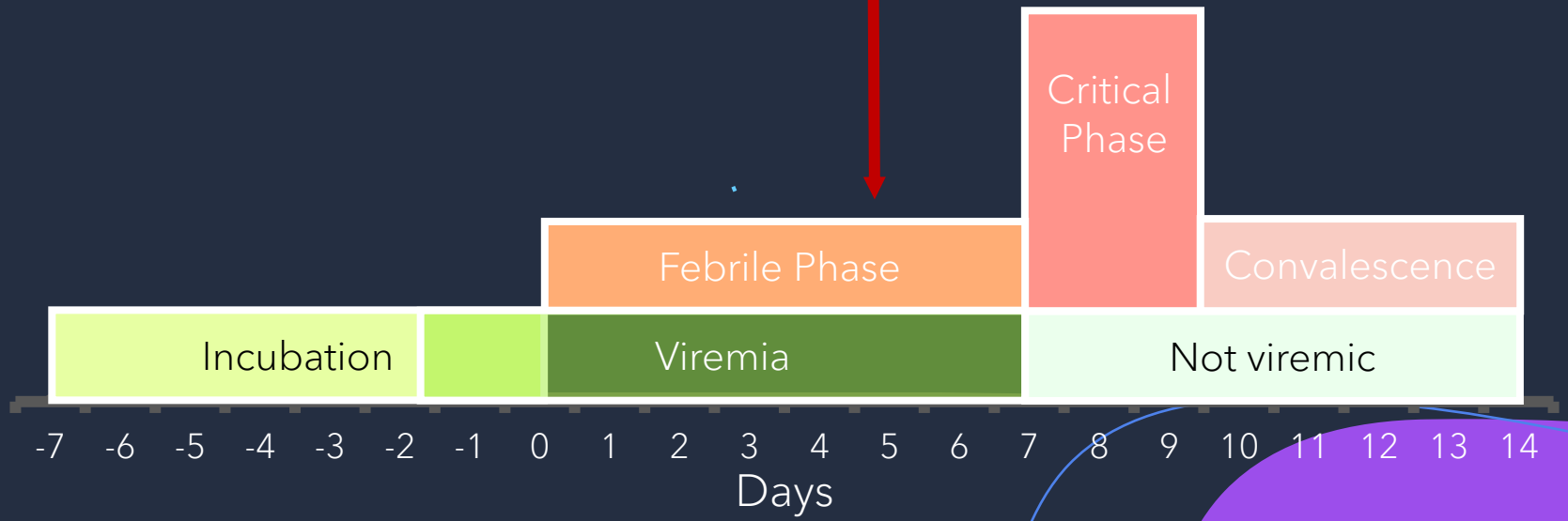
- flushing
- headache
- retro-orbital eye pain
- arthralgia, myalgia
- hemorrhagic manifestation.



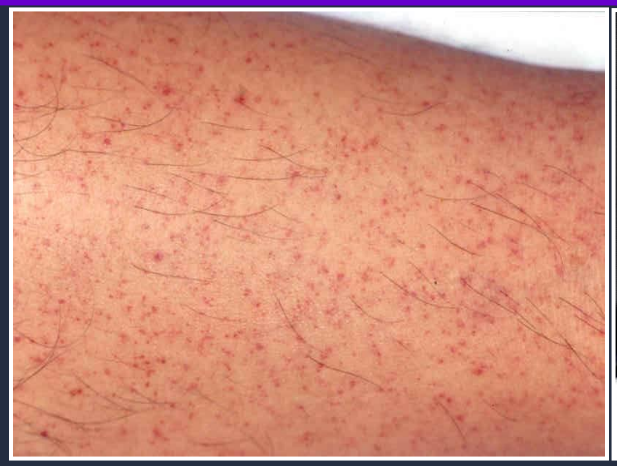
Febrile Phase

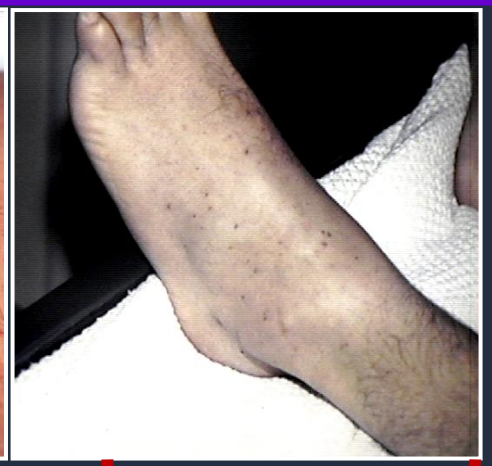


Days 2 to 6 post onset:
Macular or maculopapular truncal rash that spreads to face and extremities.



Critical Phase

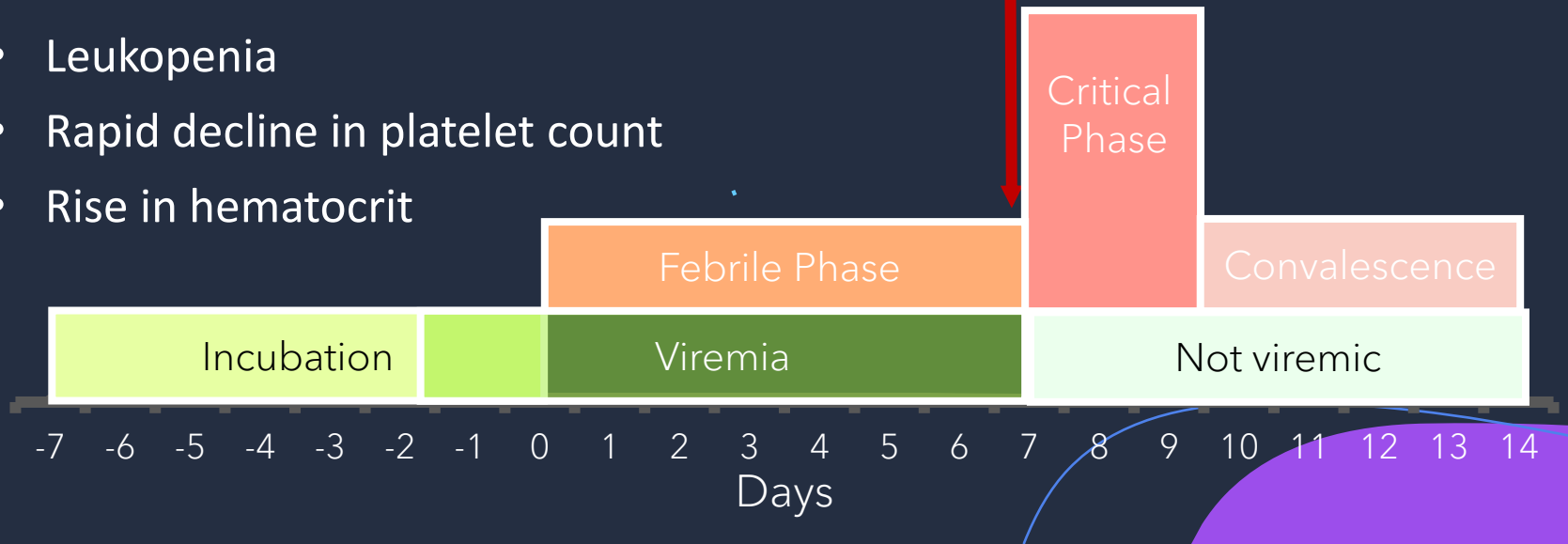




Before or at defervescence: Petechiae may appear, especially on lower extremities

The **Critical Phase** usually begins with:

- Defervescence
- Leukopenia
- Rapid decline in platelet count
- Rise in hematocrit



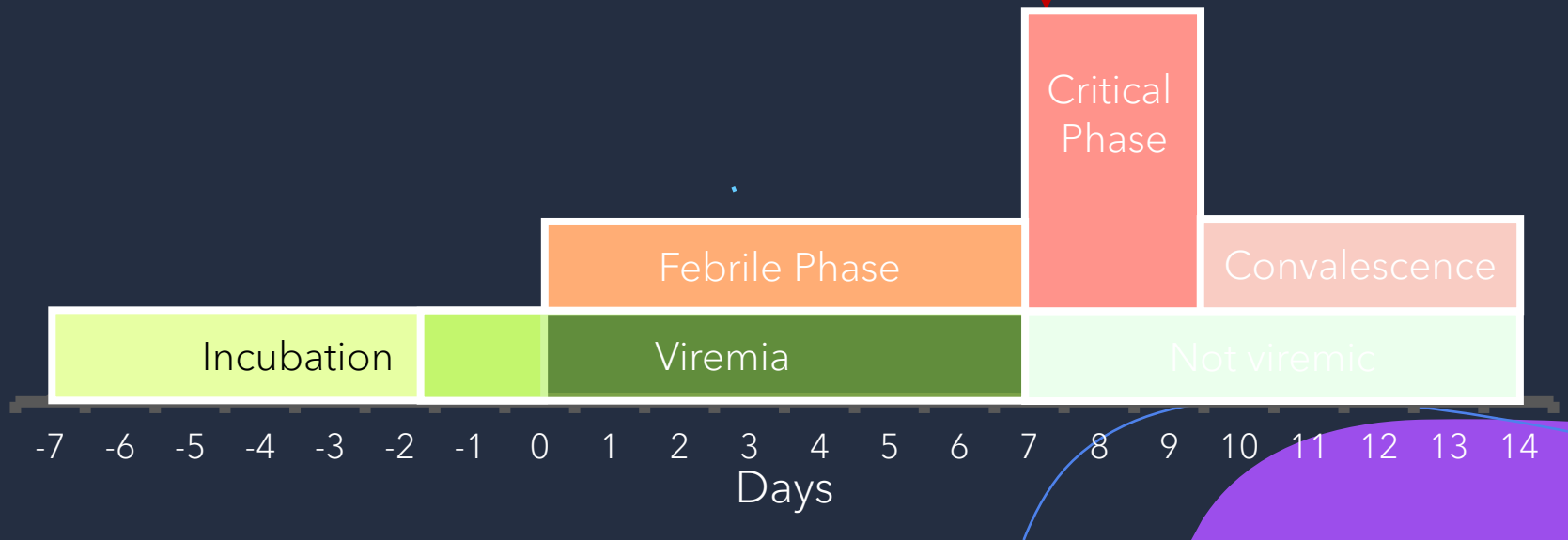
Critical Phase

Warning Signs for Severe Disease*

- Severe abdominal pain
- Persistent vomiting
- Fluid accumulation (ascites, effusions)
- Mucosal bleeding
- Lethargy; restlessness
- Liver enlargement >2cm

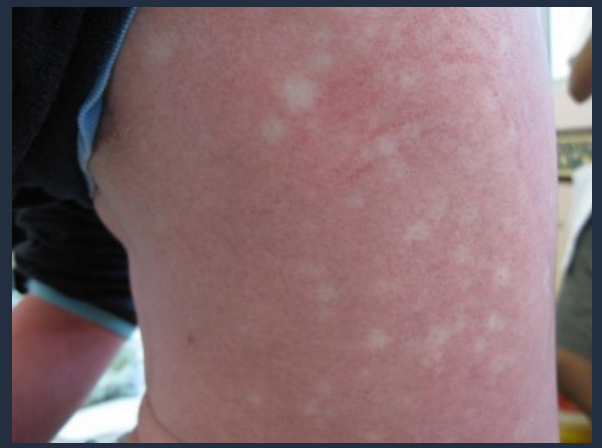
Patients with significant plasma leakage will deteriorate during this phase

* Note: not all patients will develop warning signs suggestive of significant vascular leakage

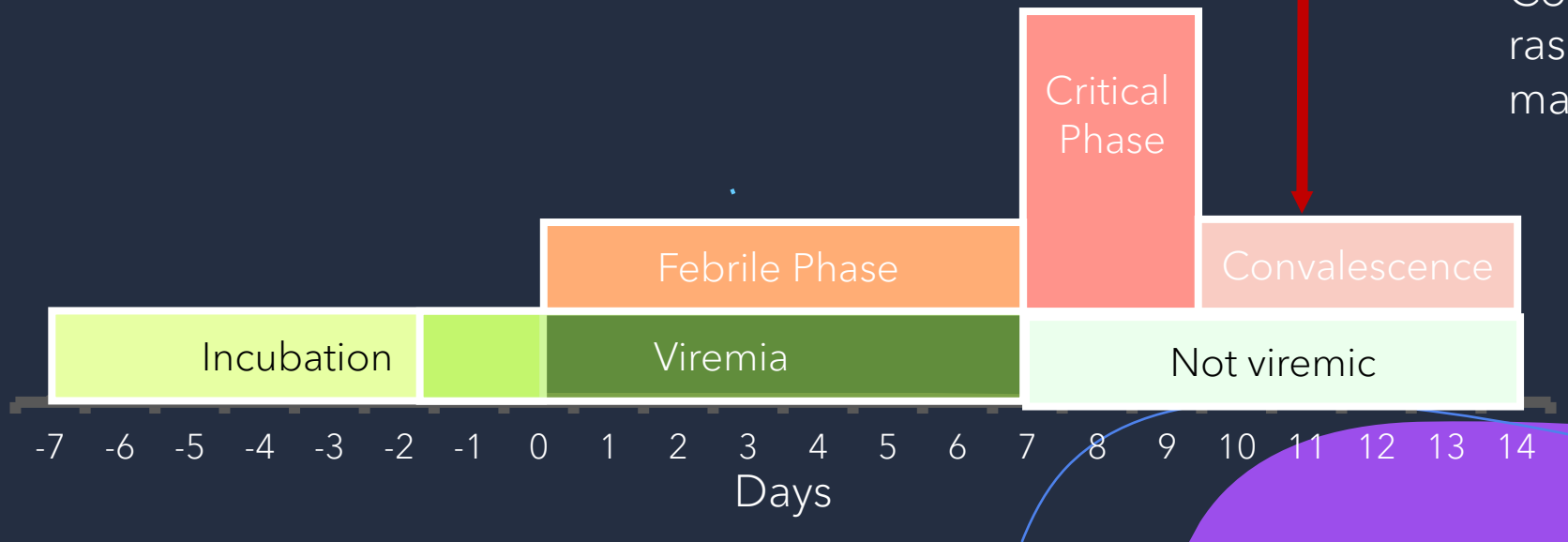


Recovery Phase

- Malaise and anorexia resolve
- Hemodynamic status stabilizes
- Re-absorption of extravascular fluid; diuresis
- Hct stabilizes; WBC and platelets recover



Confluent pruritic rash with clear spots may develop



Diagnostic Testing

- Acute phase (≤5 days post onset):
  - DENV specific polymerase chain reaction (PCR) or
  - Non-structural protein-1 assay (NS1) antigen

  and
  - IgM anti-DENV (poor sensitivity in early infection)
- Convalescent phase (5-14 days post onset):
  - IgM anti-DENV (not IgG!)
- Past infection (>2 weeks post illness):
  - IgG anti-DENV with subtypes

Management of Dengue

Group A (all of following)	Group B (any of following)	Group C (any of following)
Tolerating oral fluids Passing urine at least once every 6 hours Does not have any warning signs Has stable hematocrit Hemodynamically stable No co-existing conditions	• Has warning signs • Has co-existing conditions: diabetes mellitus, renal failure, • Is an infant, pregnant or elderly • Poor follow-up	• Severe plasma leakage with shock and/or fluid accumulation with respiratory distress • Severe bleeding • Severe organ impairment (renal or hepatic failure) • Impaired consciousness

Management of Dengue

Group A (Patient at home)	Group B (Patient at hospital)	Group C (Patient at hospital)
✓ Give anticipatory guidance before sending home (see patient handout) ✓ Follow-up daily ✓ Do serial CBCs ✓ Identify warning signs early		

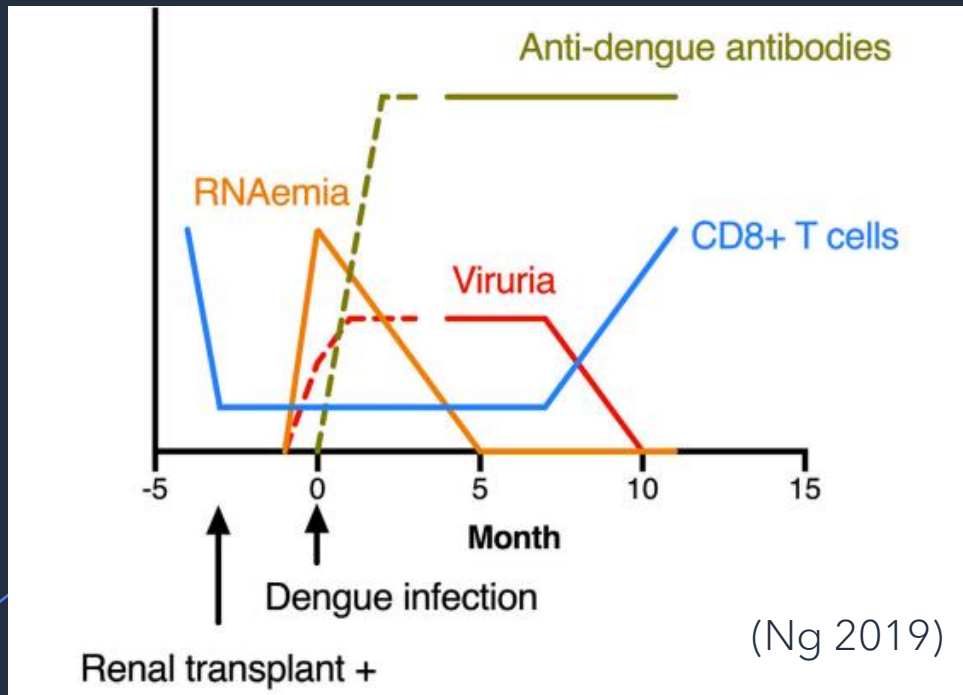
Management of Dengue

Group A (Patient at home)	Group B (Patient at hospital)	Group C (Patient at hospital)
✓ Give anticipatory guidance before sending home (see patient handout) ✓ Follow-up daily ✓ Do serial CBCs ✓ Identify warning signs early	✓ Monitor hemodynamic status frequently ✓ Use HCT to guide interventions ✓ Use isotonic IVFs judiciously ✓ Correct metabolic acidosis, electrolytes as needed	✓ Monitor for occult bleeding ✓ Prophylactic platelet transfusions not indicated ✓ Use crystalloids for shock ✓ Use colloids for refractory shock

DENV in Immunocompromised Patients

- Studies in transplant recipients and hematopoietic malignancy patients: spectrum of disease, some with 20% severe/DHF and high mortality
  - Cyclosporine possibly protective in one study
  - In RT recipients, decreasing IC not recommended
- Prolonged viremia described in RT patients
  - 23F w RT undergoing anti-rejection treatment
- Scant data on other IC types

(PMID 28475281, 29296705, 29551005, 31676304, 37365496)



(Ng 2019)

Dengue, Arthritis, and Auto-Immunity

- Variety of mechanisms proposed: cross-reacting acute antibodies, NS1-induced autophagy, complement pathway activation, parallels to SLE?
  - 2021 Taiwan health claims database study: SLE within 1-3 years of DENV: aOR 4.89 (1.54–15.58)
- 2008 Cuba study: persistent symptoms at 2 years post DENV affected >50% of patients (arthralgias ~30%); F > M; observed elevations in CRP (42%), IC (42%), ANA (23%), C4 (11%)
- 2022 Honduras study: prospectively followed patients diagnosed with DENV in 12/2019-2/2020, evaluated with WOMAC and DAS-28 questionnaires. 63% still symptomatic at 4 months, joint involvement common, significantly F>M (30-40% vs. 50%).
- 2023 Taiwan study: Largest to date, national health database, 63,814 lab-confirmed incident DENV patients between 2002-2015, 1:4 matched controls. DENV was associated with slightly higher risk of overall autoimmune diseases (aHR 1.16; P = 0.0002) but when stratified by specific diseases only autoimmune encephalomyelitis remained significant.

(PMID 21112804, 36548649, 36881559)

Dengue Vaccine

- Tetravalent, live recombinant (YFV backbone), 3-dose vaccine for DENV approved by FDA in 2019.
- For use in children 6–16 years old with lab-confirmed* previous DENV infection, living in an area where dengue is endemic (occurs frequently or continuously). VE ~76% against symptomatic disease.
- Dengue-endemic US territories: American Samoa, Puerto Rico, US Virgin Islands, associated Pacific states (Federated States of Micronesia, Marshall Islands, Palau).
- Being discontinued globally due to complexity of implementation. Doses will expire in 9/2025.
- A tetravalent, live-attenuated, 1-dose DENV vaccine (TAK-3) that can be given to previously uninfected persons is approved by WHO.
- Another tetravalent, live-attenuated, 1-dose vaccine (Butantan, Brazil) recently showed VE 80% against DENV-1,2 in phase III clinical trial (PMID 38294972).

* Laboratory Testing Requirements for Vaccination with Dengvaxia Dengue Vaccine | Dengue | CDC

Living in Puerto Rico?

What You Need to Know About the Dengue Vaccine

Accessible link: https://www.cdc.gov/dengue/vaccine/parents/eligibility/need-to-know.html

Protect Your Child from Dengue

- Ask your child's healthcare provider about the safe and effective dengue vaccine.

Chikungunya virus

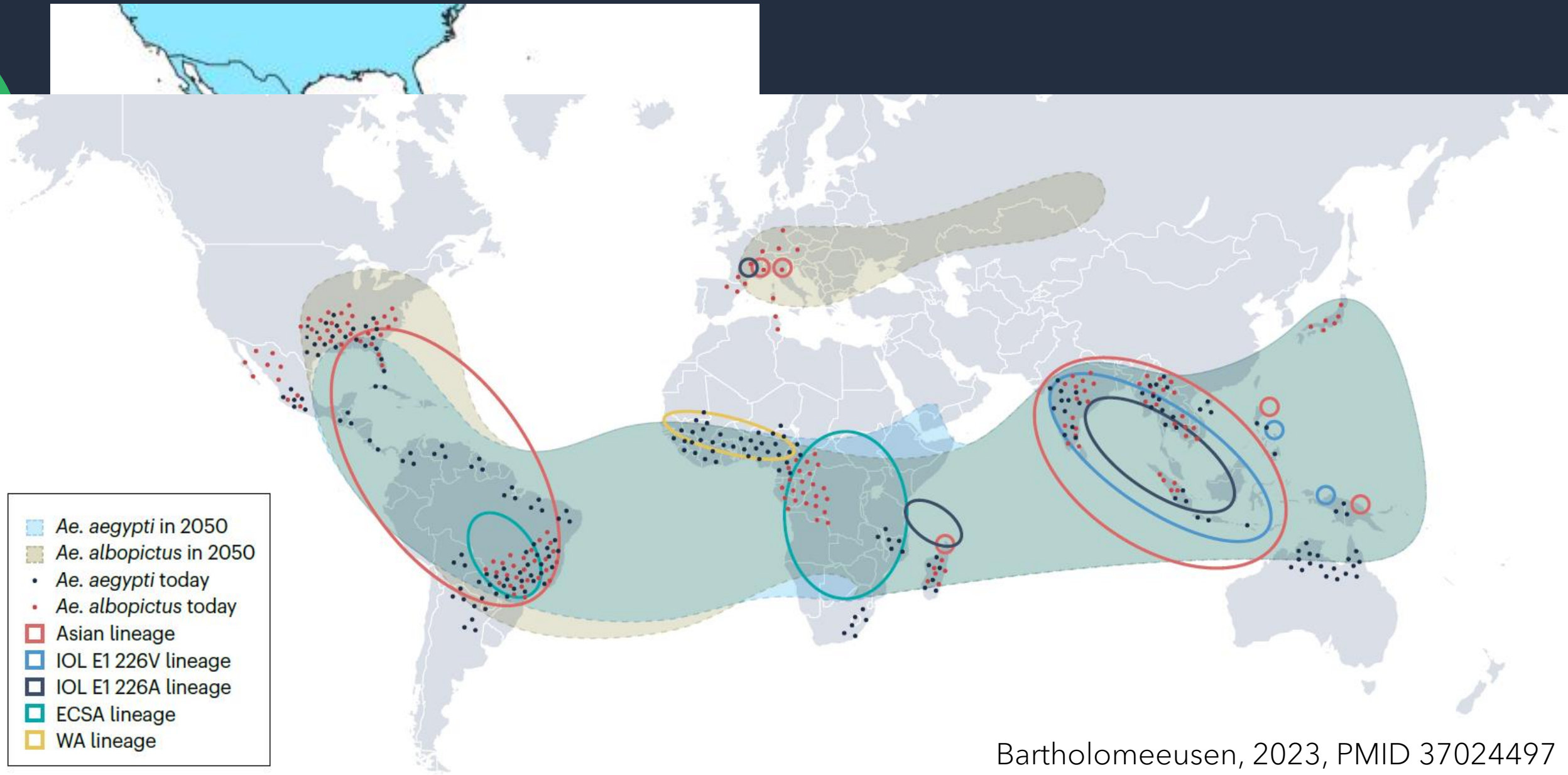
Family Togaviridae, Genus Alphavirus

From Makonde, "bent over in pain”

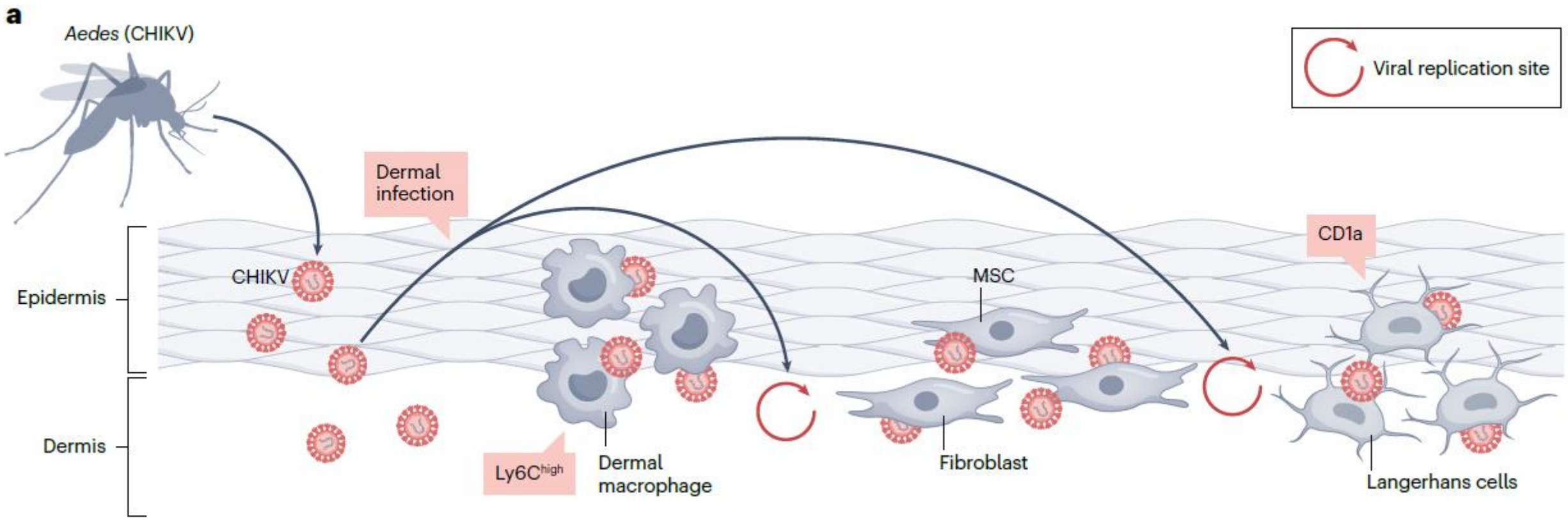
Epidemiology

- Prior to 2013, CHIKV cases and outbreaks had been identified in countries in Africa, Asia, Europe, and the Indian and Pacific Oceans.
- In late 2013, the first local transmission of CHIKV in the Americas was identified in Caribbean countries and territories.
- The virus then spread throughout most of the Americas.

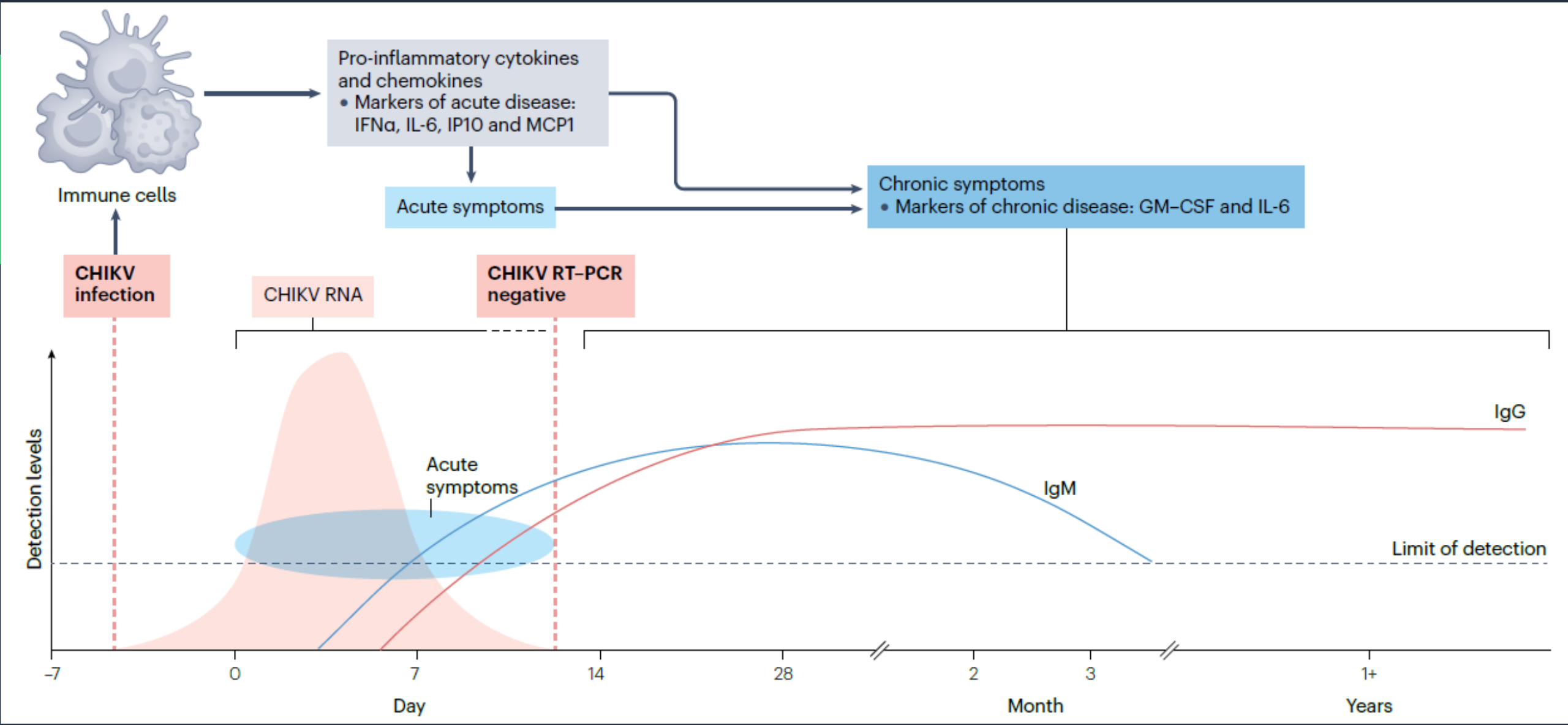
CDC, 2019



Bartholomeeusen, 2023, PMID 37024497

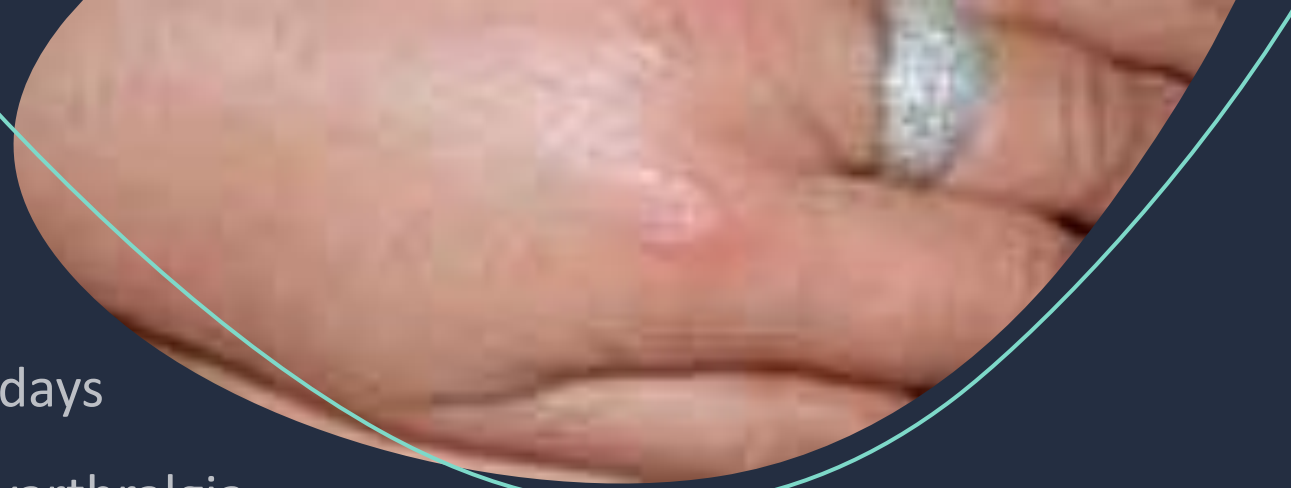


Bartholomeeusen, 2023, PMID 37024497

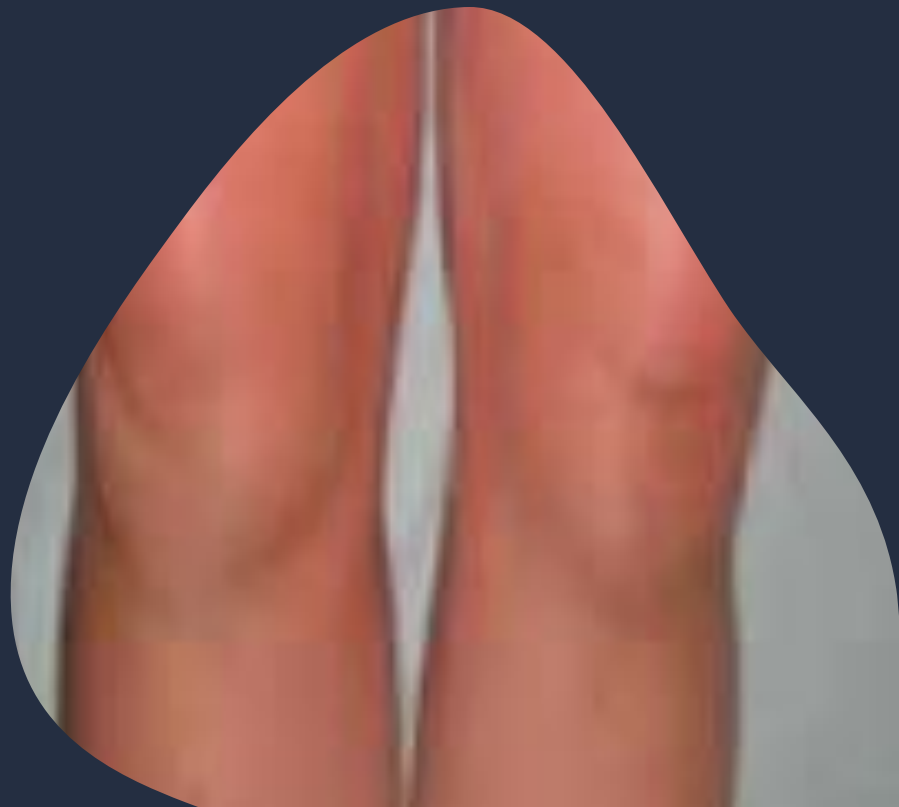


Bartholomeeusen, 2023, PMID 37024497

Clinical Presentation

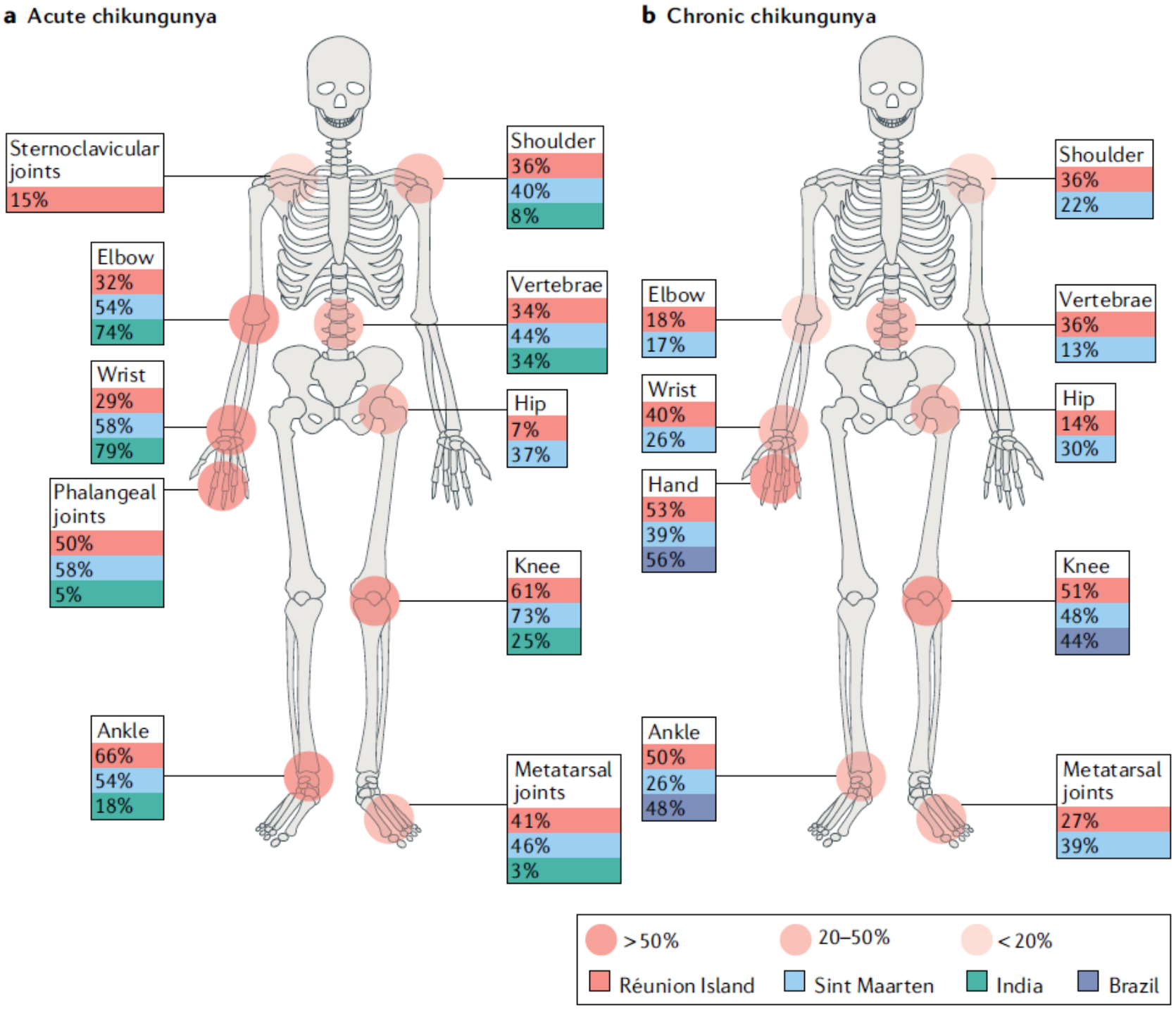


- Incubation period typically 3–7 (range, 1–12) days
- Acute onset of fever (typically >39°C) and polyarthralgia
- Joint symptoms are usually bilateral, symmetric and severe
- Other symptoms may include headache, myalgia, arthritis, conjunctivitis, nausea/vomiting, or maculopapular rash
- Laboratory findings can include lymphopenia, thrombocytopenia, elevated creatinine and LFTs
- Acute illness typically lasts 7-10 days
- Rare complications: skin bullae, uveitis, retinitis, myocarditis, hepatitis, nephritis, meningoencephalitis, GBS

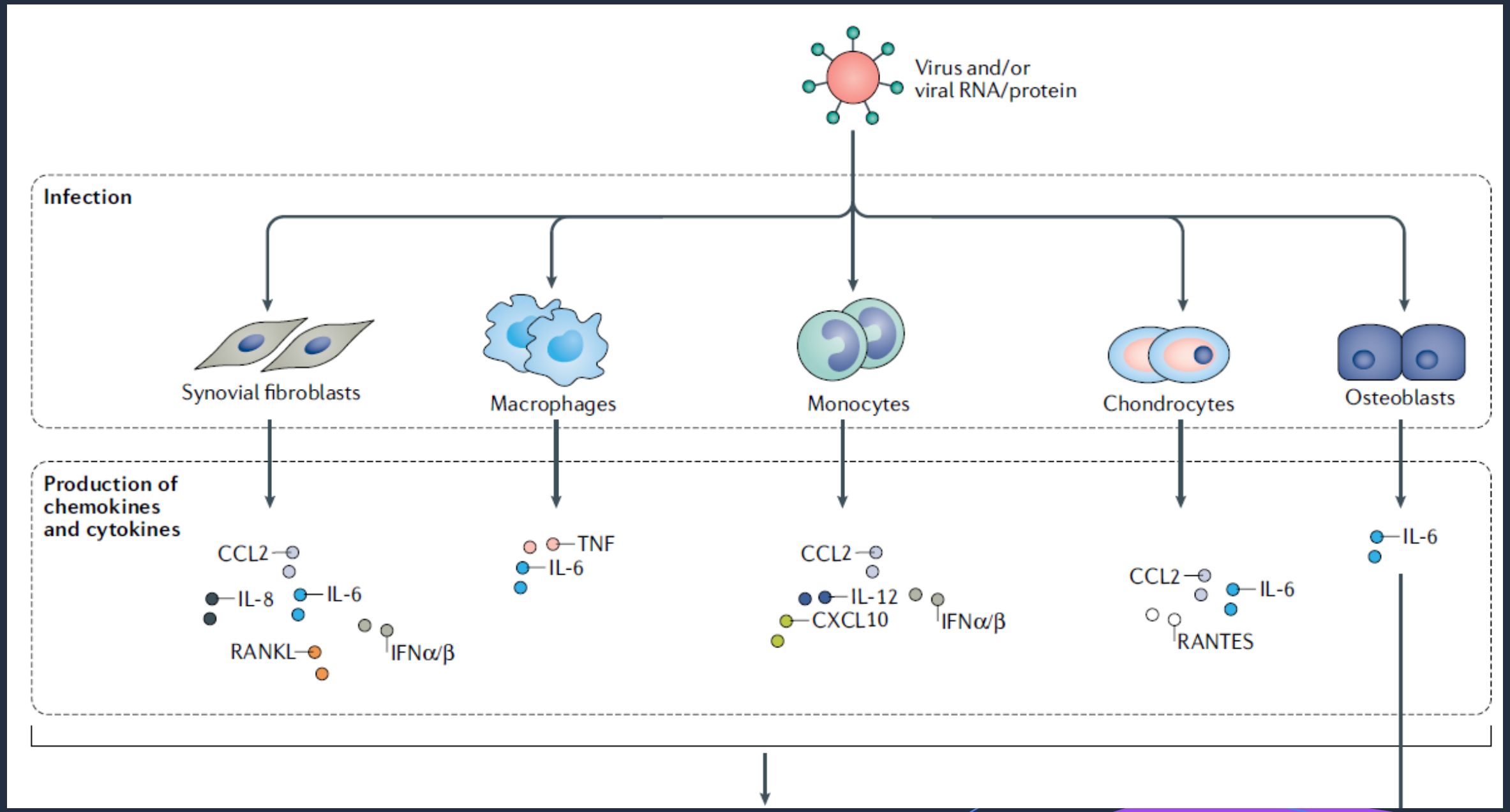


Chronic Sequelae

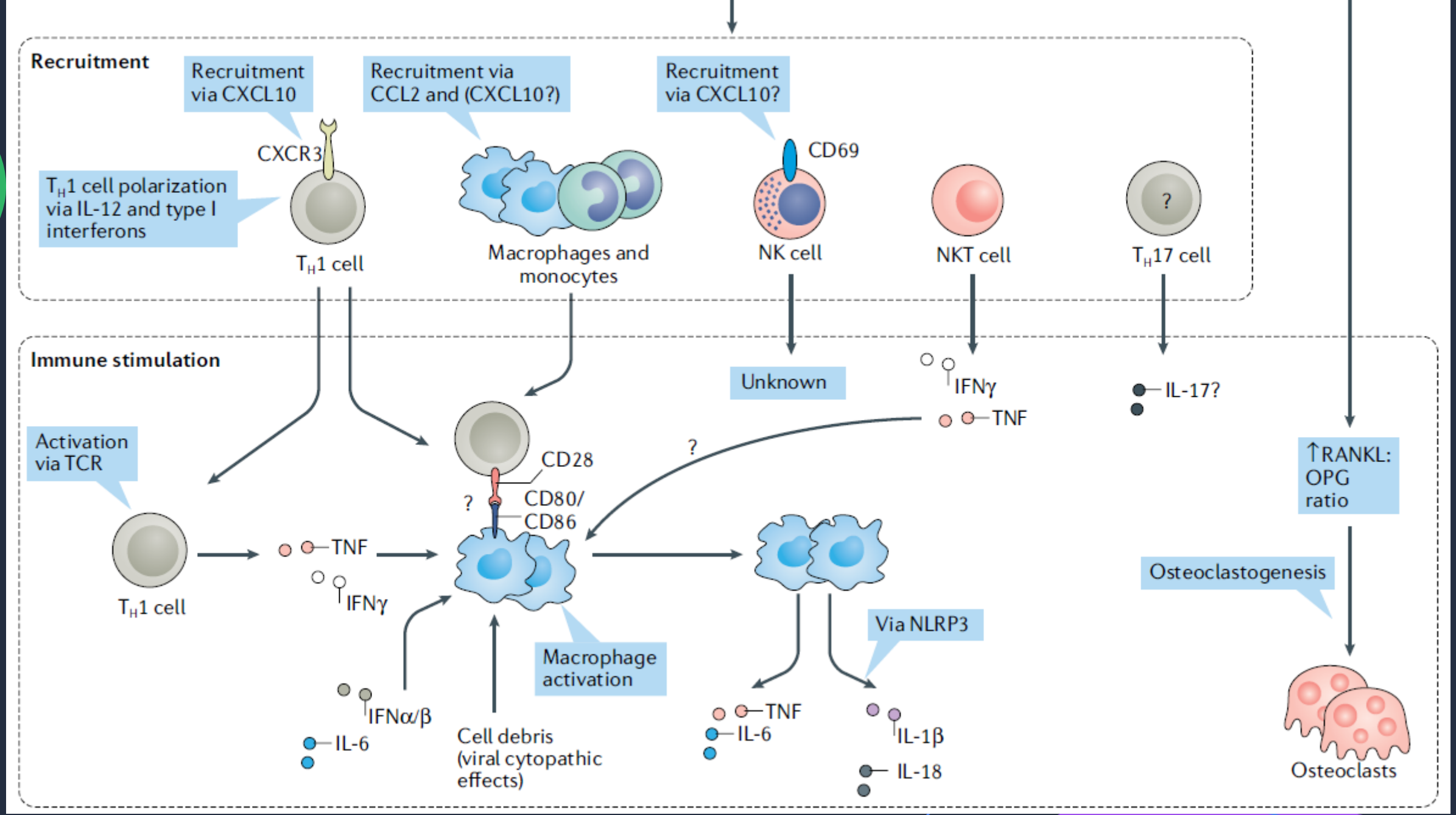
- Patients might relapse with rheumatologic symptoms (e.g., polyarthralgia, polyarthritis, tenosynovitis) in the months following acute illness
- Studies report variable proportions of patients with persistent joint pains for months to years



Suhrbier 2019,
PMID 31481759



Suhrbier 2019, PMID 31481759



Suhrbier 2019, PMID 31481759

Post-Chikungunya Arthritis

- 2019-21 Colombia study: 158 participants with CHIKV arthritis assessed with standardized questionnaires (DAS-28, Arthritis-Flare) and measured plasma cytokines, performed flow cytometry of peripheral blood T cell subsets.
- Increased arthritis disease activity was associated with increased inflammatory (IL-6, TNF, CRP) cytokines and deficient IL-2 and Treg responses. Higher IL-2 were associated with improved Treg numbers and immunosuppressive markers. (Chang 2023, PMID 38507338)
- In case series of RT recipients, CHIKV reported as uncomplicated, w/ full recovery.

Clinical Diagnosis

- Preliminary diagnosis is based on the patient’s clinical features, places and dates of travel, and activities
- CHIKV RNA detectable by PCR of serum in first week of illness
- IgM normally develop toward the end of the first week; may cross-react
- IgG can be detected later to confirm diagnosis; may cross-react

Treatment

- Acute CHIKV treatment is supportive
  - Rest, fluids, acetaminophen
  - Avoid aspirin and NSAIDS until dengue can be ruled out
- Post-acute and chronic arthritis
  - Inconsistent results with NSAIDs, injected or systemic steroids, DMARDs
  - Improvement on methotrexate reported by some groups (e.g., Amaral 2020, PMID 29361202, 30909365); ongoing clinical trials (NCT03058471, NCT03058471)
  - Physical therapy & rehabilitation, psychosocial support

Prevention

- Insect control and avoidance
- **Chikungunya vaccine (Ixchiq):** FDA approved in early 2024. Live, attenuated vaccine.
- ACIP recommends vaccination for:

1. Aged ≥18 years traveling to an area where there is a CHIKV outbreak
2. If traveling to a country or territory without an outbreak but with evidence of CHIKV transmission among humans within the last 5 years, consider vaccination for:
   - Persons aged >65 years, particularly those with underlying medical conditions, who are likely to have at least 2 weeks of exposure to mosquitoes, OR
   - Persons staying for a cumulative period of 6 months or more
3. Laboratory workers with potential for exposure to CHIKV


ERMETHRIN
PERMETHRIN
INSECT
REPELLENT
CLOTHING


Repellent

Bonus Topic: Yellow Fever

Summary

- DENV and CHIKV incidence rising in many W. Hemisphere travel destinations
- CHIKV well known for prolonged arthritis; increasingly recognized in DENV
- Risks in immunocompromised patients are poorly defined
- DENV treatment is supportive, recognition of DHF is key
- CHIKV arthritis treatment with DMARDs is being explored
- Prevention relies on vector control, personal protective measures, and risk stratification; consider CHIKV vaccine in high-risk/high-exposure travelers

Appreciation and Gratitude

Aileen Chang, MD, MSPH, Associate Professor, Department of Medicine, GWU SMHS

Adrienne Poon, MD, MPH, Associate Professor, Department of Medicine, GWU SMHS

Gary L. Simon, MD, PhD, Professor Emeritus, Division of Infectious Diseases, GWU SMHS