Diagnosis and Treatment of Dengue, Chikungunya and Zika



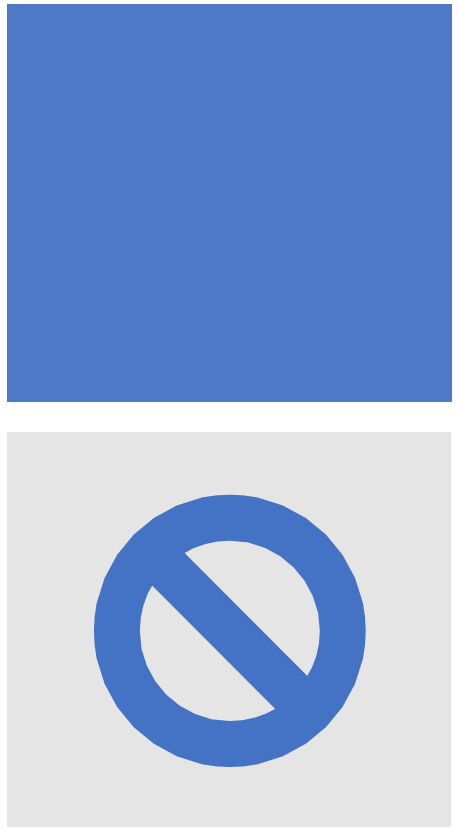
Juan C Lemos Ramirez

General and Transplant Infectious Disease Specialist

ACP Meeting

March 27, 2021

Disclosure



Nothing

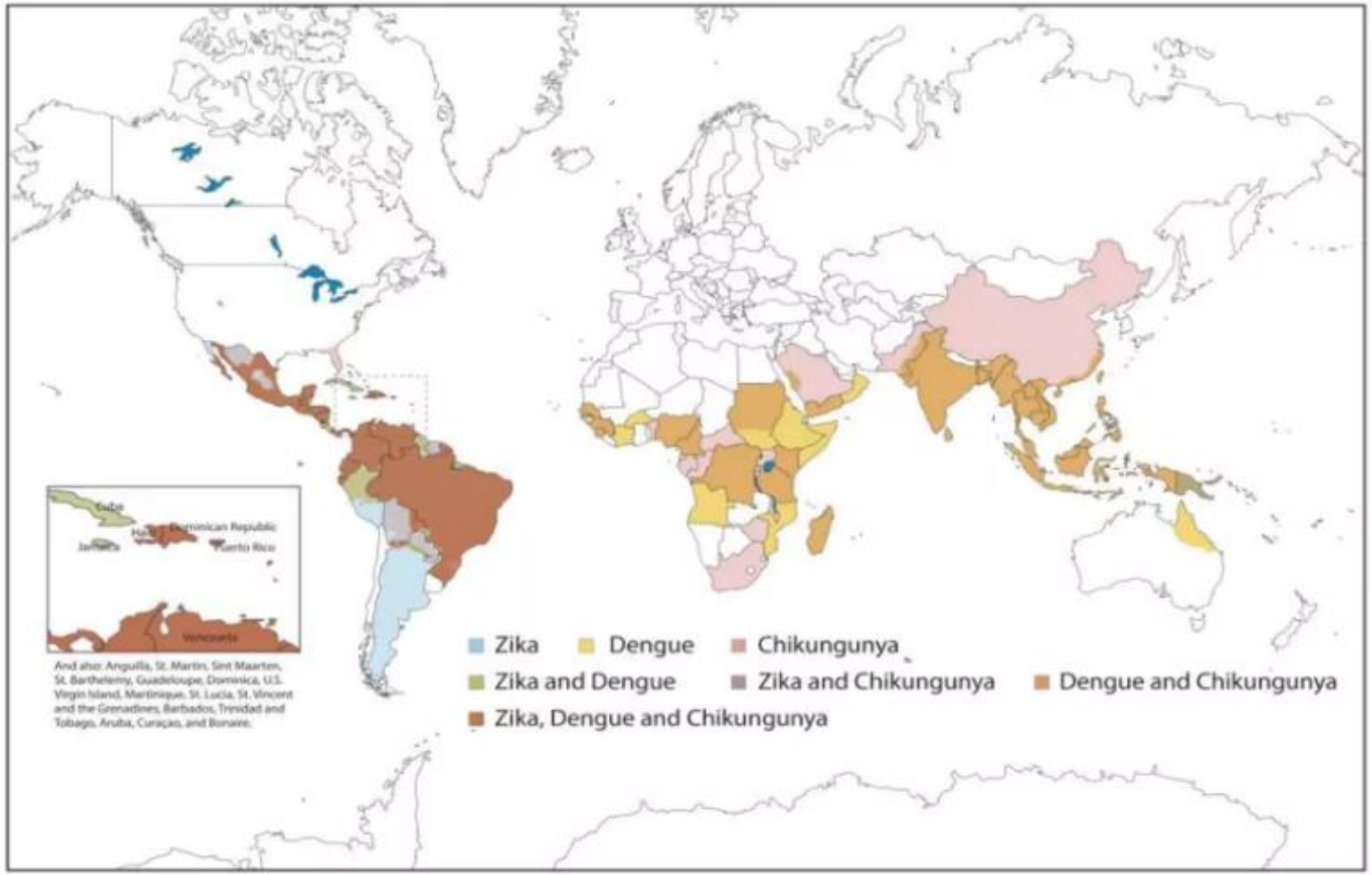
Objectives

Discuss	Discuss Dengue, Chikungunya, and Zika in the Caribbean
Compare and contrast	Compare and contrast the similarities/differences between them
Mention	Mention key points in management
Describe	Describe unique clinical manifestation of each syndrome
Recognize	Recognize possible complications or sequelae

WHAT CLINICIANS SHOULD LOOK FOR

WHAT CLINICIANS SHOULD BE AWARE OF

World Distribution of Dengue, Chikungunya and Zika

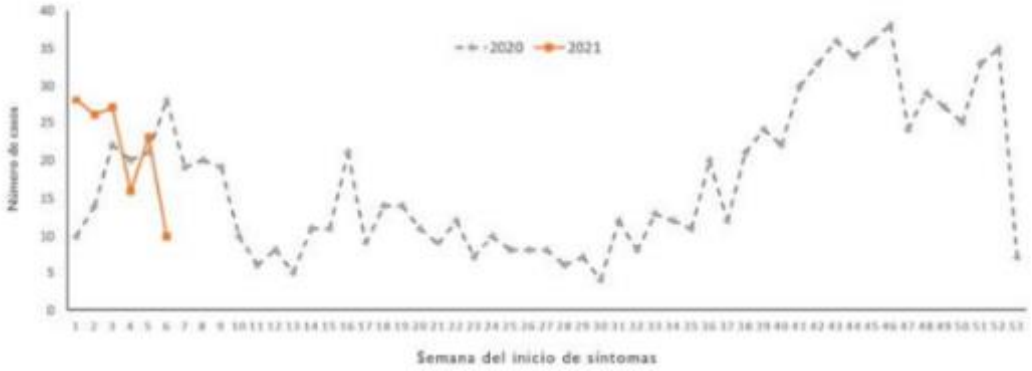




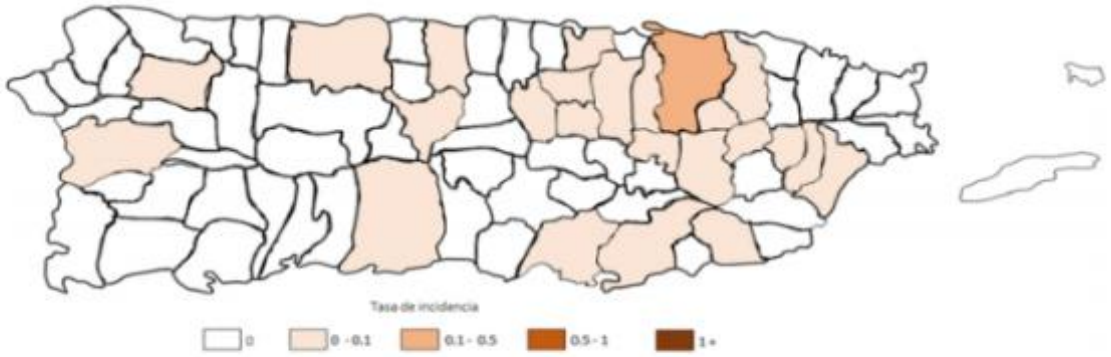
Dengue Surveillance Weekly Report

CDC Dengue Branch & Puerto Rico Department of Health

Casos acumulados de Dengue por semana, 2020 – semana 6, 2021



Incidencia acumulada de casos de Dengue, semanas 1-6, 2021



*Tasas por 1,000 habitantes

Semana 6, 2021
Casos confirmados y probables**:

DENV: 10 confirmados PCR+
0 probables IgM+

ZIKV: 0 confirmados PCR+
0 probables IgM+

CHIKV: 0 confirmados PCR+
0 probables IgM+

Casos acumulados en 2021:

DENV: 122 confirmados PCR+
8 probables IgM+

Serotipos:
11 casos DENV-1

49 casos hospitalizados

7 casos severos†

0 casos fatales

ZIKV: 0 confirmados PCR+
5 probables IgM+

CHIKV: 0 confirmados PCR+
0 probables IgM+

Resumen casos de 2020:

DENV: 859 confirmados PCR+
63 probables IgM+

Serotipos:
310 casos DENV-1
1 caso DENV-2 (asociado a viaje)

332 casos hospitalizados

32 casos severos†

0 casos fatales

ZIKV: 0 confirmados PCR+
89 probables IgM+

CHIKV: 0 confirmados PCR+
0 probables IgM+

http://www.salud.gov.pr/Estadisticas-Registros-y-Publicaciones/Informes%20Arbovirales/Reporte%20ArboV%20semana%2022-2020.pdf

Dengue cases in the US

- Dengue virus disease became a nationally notifiable condition in 2010.

US States

- 5 dengue cases reported

US Territories

- 85 dengue cases reported

States and territories reporting dengue cases – United States, 2021
(as of March 3, 2021)



*CDC reports provisional dengue case counts reported to ArboNET for the United States and its territories on the first Thursday of each month.

*CDC Disease Maps. CDC reports provisional dengue case counts reported to ArboNET for the United States and its territories.

VIRUSES & VECTORS

Aedes aegypti

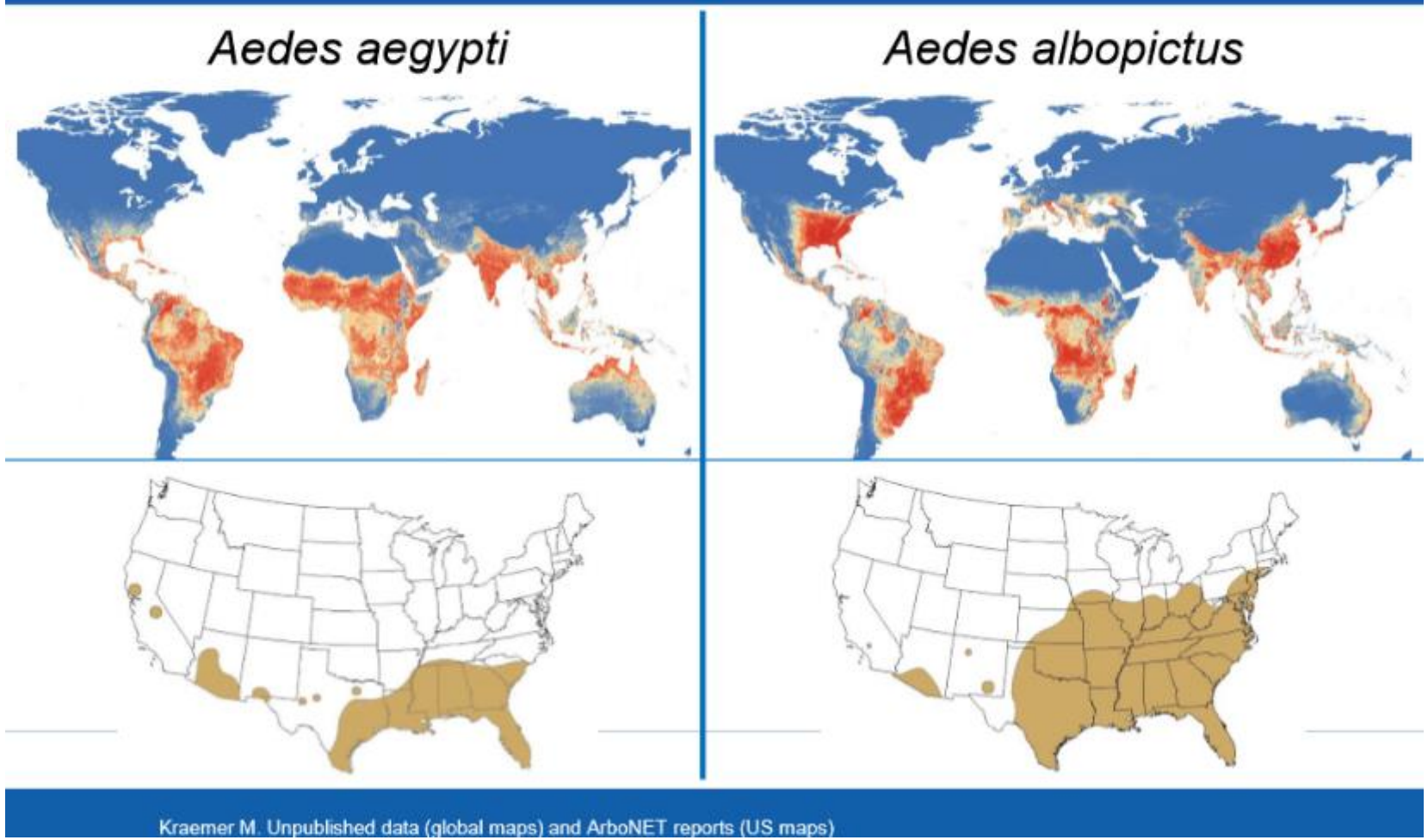
Aedes albopictus

Dengue
Chikungunya
Zika





Approximate Distribution of *Aedes aegypti* and *Aedes albopictus* Mosquitoes



Kraemer M. Unpublished data (global maps) and ArboNET reports (US maps)

Aedes aegypti and *Aedes albopictus* Mosquitoes

- *Aedes (Stegomyia)* subgenus
- Lay eggs in peridomestic water containers
- Live in and around households
- Peak feeding during daytime
- *Aedes aegypti* more efficient vector for humans



Aedes aegypti



Aedes albopictus

Schaffner F, Mathis A. Lancet Infect Dis 2014



Aedes aegypti

- Primarily a daytime feeder
  - Lives around human habitation
  - Lays eggs and produces larvae preferentially in artificial containers
  - Dengue transmitted by infected female mosquito *Aedes aegypti*

Distribution *A. aegypti* in the Americas (History)

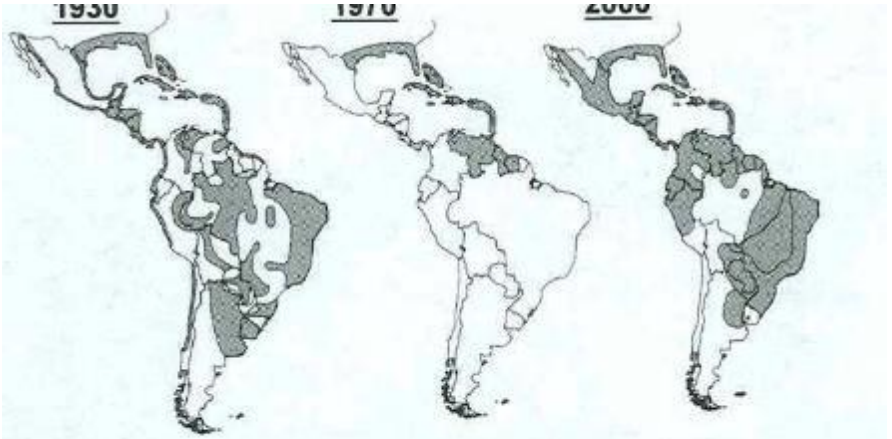


FIGURE 17 Distribution of A. *aegypti* in the Americas in 1930 before efforts to eradicate the mosquito vector, in 1970 at the end a major eradication campaign, and in 2000 showing reinfestation of much of South America by the vector. The reinfestation has led to the appearance of epidemic dengue and poses an increased risk of the return of urban yellow fever. (Courtesy of D. Gubler, Centers for Disease Control and Prevention.)



EPIDEMIOLOGY

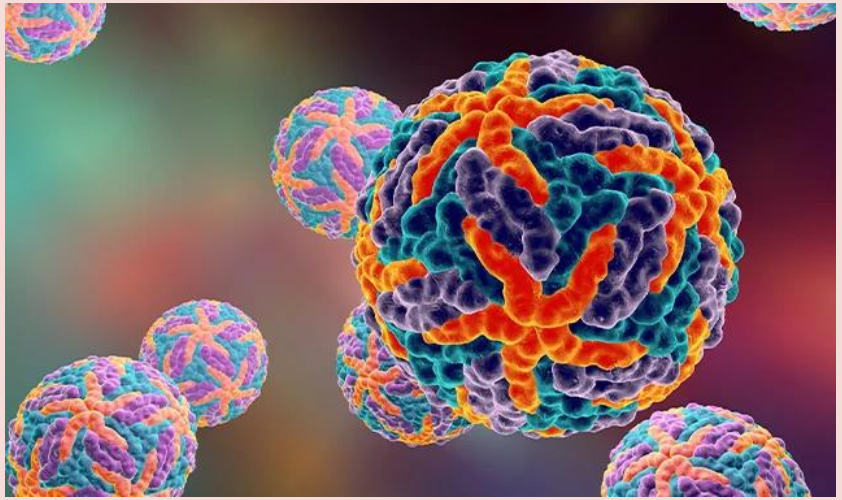
- Primarily spread through the bites of infected mosquitoes
- Mosquitoes become infected when they bite infected persons and then spread the Dengue, Chikungunya, or Zika virus to other persons they subsequently bite.
- *Aedes* species mosquitoes (females) are a principal potential vector for this viruses in the U.S.
  - *Aedes aegypti* are typically concentrated in the southern U.S. as well as parts of the Southwest.
  - *Aedes albopictus* are found in much of the southern and eastern part of the U.S.
- *Aedes* mosquitoes can also carry other arboviruses including Yellow Fever, Japanese Encephalitis, and West Nile Virus

Dengue Virus

CDC

CENTERS FOR DISEASE CONTROL AND PREVENTION

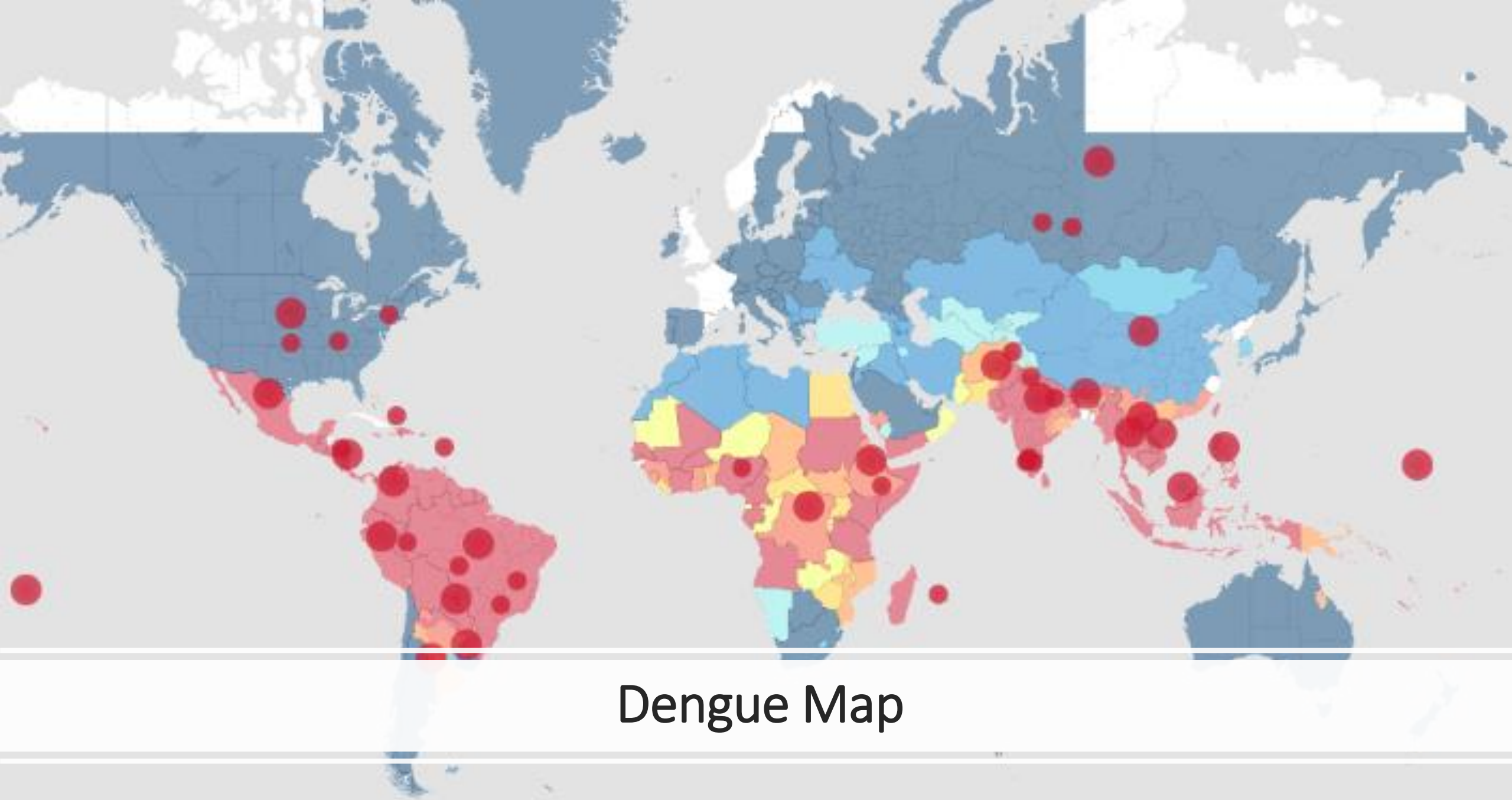
- Causes dengue and dengue hemorrhagic fever
- Is an arbovirus, genus *Flavirus*
- Transmitted by mosquitoes
- Composed of single-stranded RNA
- Has 4 serotypes (DEN-1, 2, 3, 4)



Dengue Virus Types 1–4

- **Four related viruses in genus *Flavivirus***
- ***Aedes aegypti* is primary vector**
  - *Aedes albopictus* also transmits dengue viruses
- **Humans are primary amplifying host**
  - Transmitted in epidemic (urban) cycle
  - Sylvatic cycle no longer needed to maintain virus

er SC, Reisen WK. Antiviral Res 2010



Dengue Map

States and territories reporting Dengue cases- United States, 2021
(as of March 3, 2021)



Dengue Virus Epidemiology

- **Most important mosquito-borne viral disease**
- **30-fold increase in incidence over past 50 years**
- **25% of infected people develop clinical symptoms**
  - Ranges from mild febrile illness to life threatening disease
- **Estimated 96 million disease cases in 2010**
  - 67 million cases in Asia
  - 16 million cases in Africa
  - 13 million cases in the Americas

Bhatt S, et al. Nature 2013

Dengue Virus Disease and Outcomes

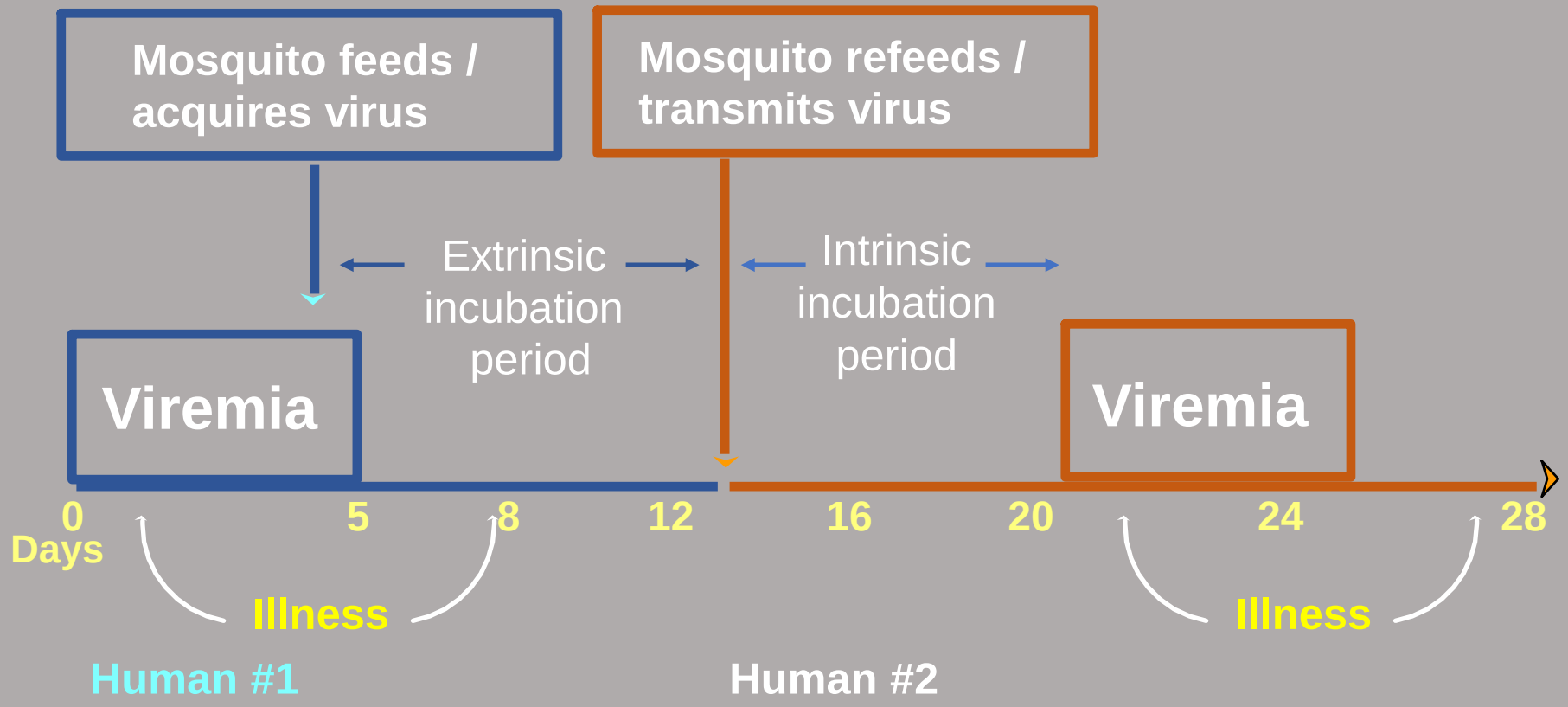
- **Acute febrile illness often with**
  - Headache, retro-orbital pain, myalgia, and arthralgia
  - Maculopapular rash
  - Minor bleeding
- **5–10% symptomatic patients develop severe disease**
  - Plasma leakage with shock or respiratory distress
  - Severe hemorrhage
  - Organ impairment
- **Subsequent infection with different type of dengue virus increases risk for severe disease**
- **Case fatality for severe dengue as high as 10%**
  - Proper case management reduces mortality to <1%

WHO 2009. http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf

Dengue Viruses

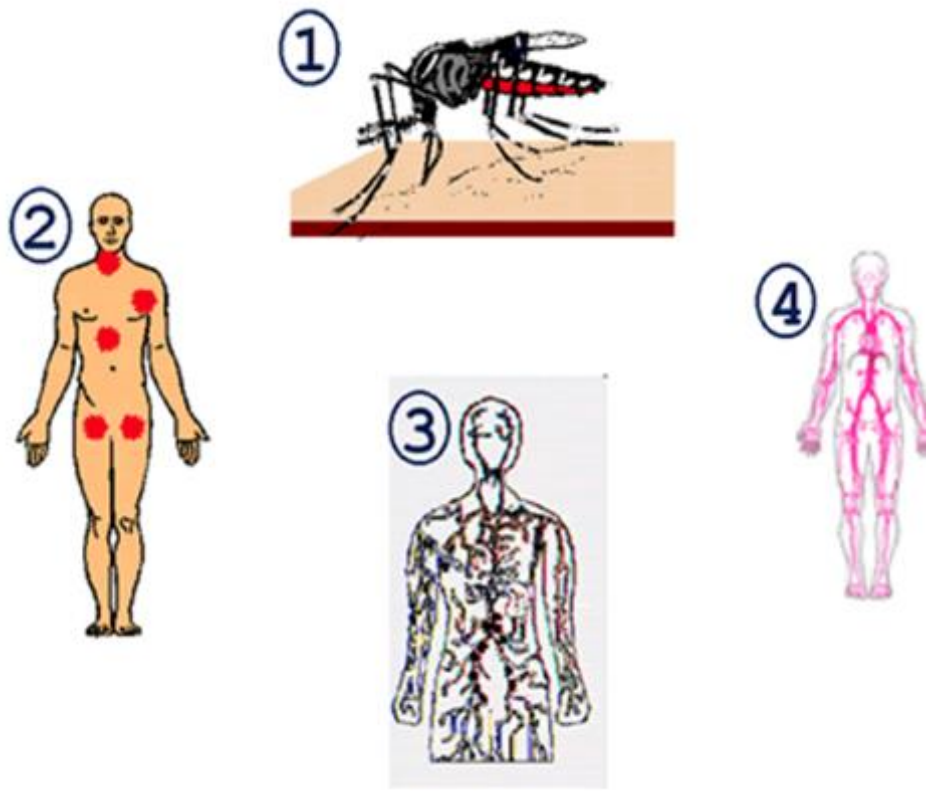
- Each serotype provides specific lifetime immunity, and short-term cross-immunity
- All serotypes can cause severe and fatal disease
- Genetic variation within serotypes
- Some genetic variants within each serotype appear to be more virulent or have greater epidemic potential

Transmission of Dengue Virus by *Aedes aegypti*

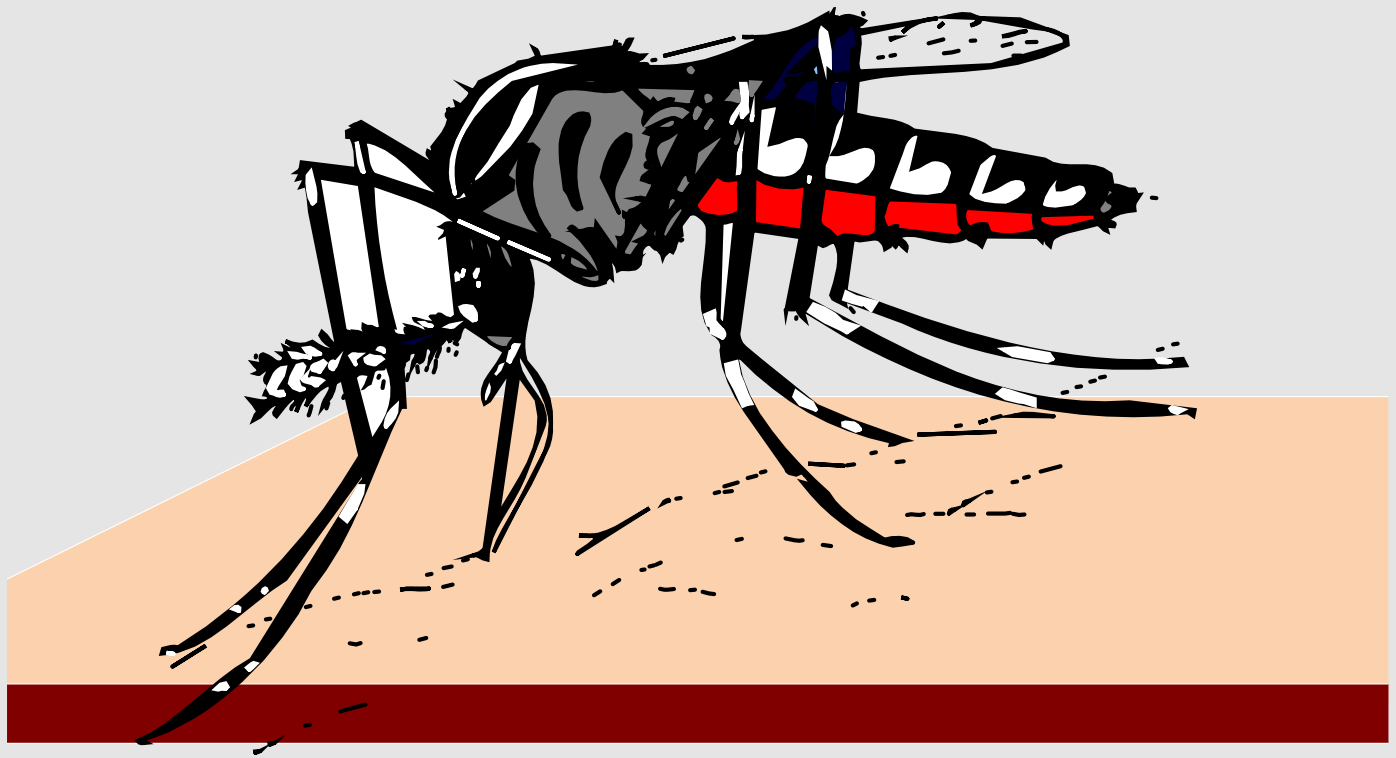


Replication and Transmission of Dengue Virus

- Virus transmitted to human in mosquito saliva
- Virus replicates in target organs
- Virus infects white blood cells and lymphatic tissues
- Virus released and circulates in blood



Replication and Transmission of Dengue Virus

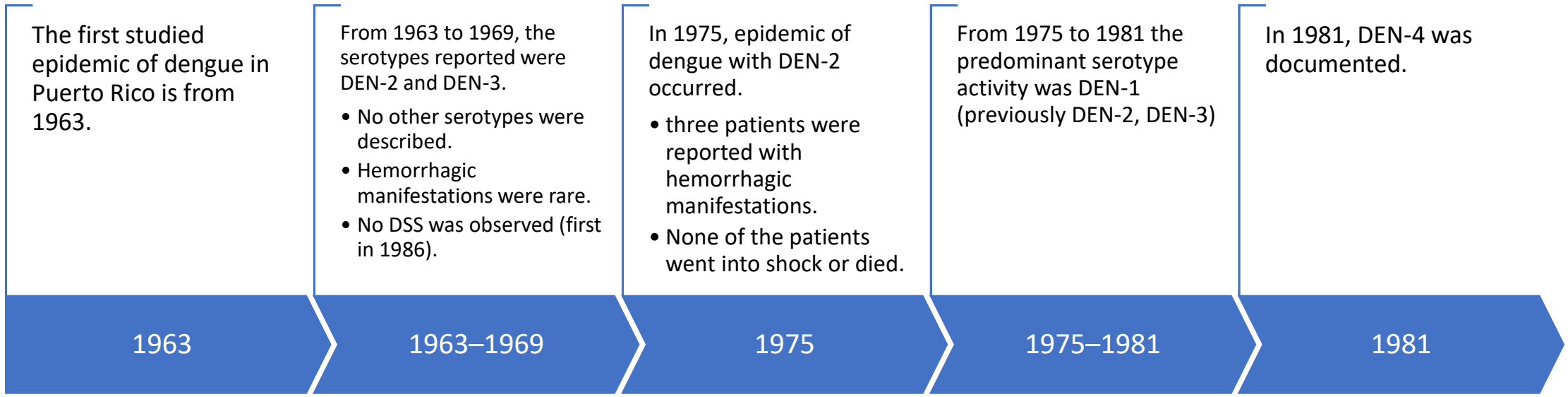


- Second mosquito ingests virus with blood
- Virus replicates in mosquito midgut and other organs, infects salivary glands.
- Virus replicates in salivary glands

Dengue Fever: Puerto Rico

- Since **1915** Dengue in Puerto Rico has been described.
- Dengue in Puerto Rico has evolved from:
  - 1960s: mild illness
  - 1980s: More serious illness with hemorrhagic manifestations (DHF)
  - 1986: dengue shock syndrome (DSS).

Dengue Fever: Serotypes in Puerto Rico



Dengue Fever: Serotypes in Puerto Rico

1975

- In 1975, epidemic of dengue with DEN-2 occurred.
  - three patients were reported with hemorrhagic manifestations.
  - None of the patients went into shock or died.

1975–1981

- From 1975 to 1981 the predominant serotype activity was DEN-1 (previously DEN-2, DEN-3)

1981

- In 1981, DEN-4 was documented.

1986

- Dengue activity in Puerto Rico increased, and cases of dengue fever associated with **DEN-1, DEN-2, and DEN-4** were documented.
- **No DEN-3 reported.**
- Cases with DHF were documented.
- DSS was documented for the first time.
- 12/21 cases of DHF developed DSS and three patients died of their illness.
- 2/3 cases that died, virologic confirmation showed **DEN-2** and **DEN-4.**

Dengue Fever: Serotypes in Puerto Rico

1994

- **DEN-3** reappeared in the Americas after more than 15 years of absence.
- Molecular studies showed that it was a new strain of DEN-3 probably introduced from Asia since was identical to the one causing epidemics in Sri Lanka and India in the 1980's.
- Since DEN-3 was absent for more than 20 years, the population had a low level of immunity and the virus spread rapidly

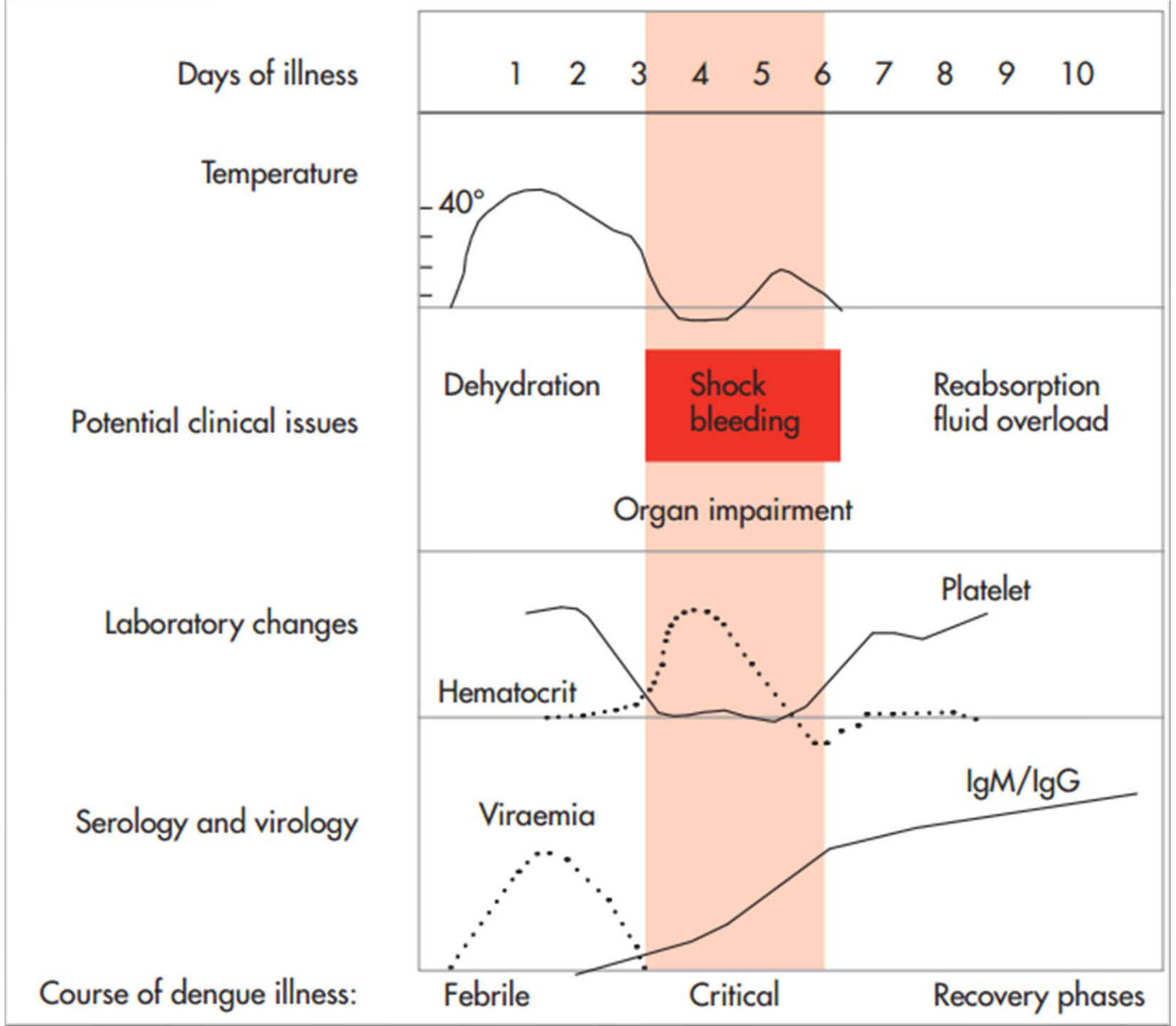
2007: All 4 serotypes had been confirmed

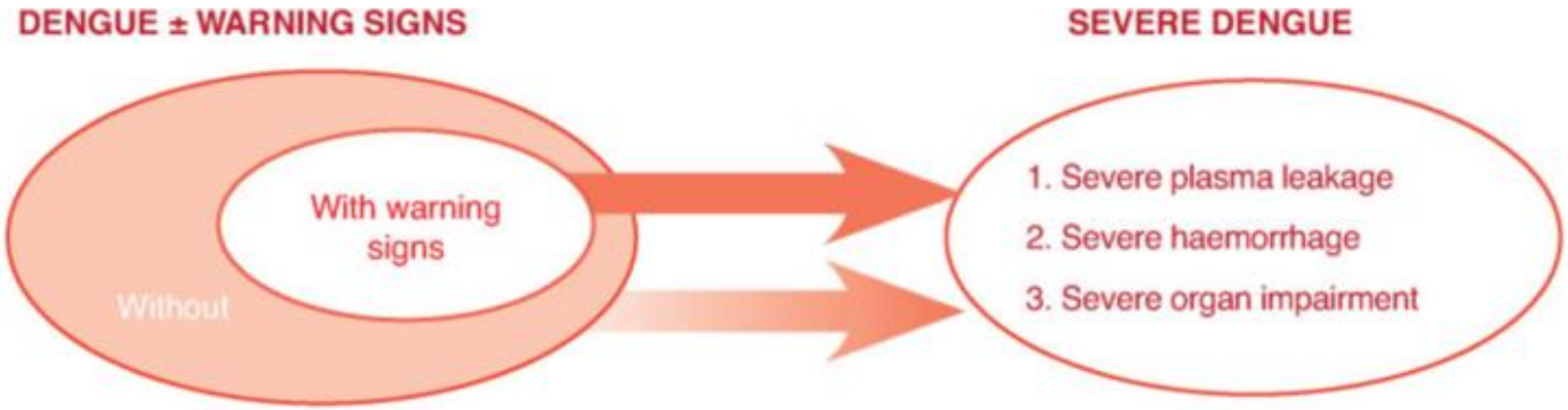
- predominant serotypes were DEN-2 and DEN-3

Dengue Time Frame

Phase	Incubation	Febrile Phase							Critical Phase		Recovery phase
Time frame	3-14 days	3-7 days							1-2 days		3-5 days
Symptoms	None	Fever is present							Fever resolves		
		>Myalgias >Rash >Petechiae >Tourniquet test >Leukopenia >Mild bleeding						Warning signs may occur	>Capillary leak >Shock >Severe hemorrhage >Severe organ involvement		> Fluid Reabsorption >Diuresis
Testing						DENV IGM					
		DENV NS1 DENV PCR									
Day of	0	1	2	3	4	5	6+	7	8	9	10+

The Course of Dengue Fever





CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue
Live in / travel to dengue-endemic area.
Fever and two of the following criteria:
- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leucopenia
- 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 enlargement >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

Warning Signs of Dengue Fever



GENERAL APPEARANCE

- Lethargy / Confusion
- Persistent Vomiting



HEAD & NECK

- Mucosal Bleeding



CHEST / LUNGS

- Dullness to percussion
- Decreased breath sounds



ABDOMEN

- Ascites (positive fluid wave)
- Abdominal Pain or Tenderness
- Liver Enlargement > 2 cm



PLATELET COUNT

HEMATOCRIT LEVEL

Hemorrhagic Manifestations of Dengue Fever

FEBRILE PHASE		CRITICAL PHASE	RECOVERY PHASE
			
PETECHIAL RASH	MINOR BLEEDING AROUND INJECTION SITE	HEMATOMA IN A PATIENT WITH SEVERE DENGUE	DIFFUSE MACULAR RASH WITH "ISLANDS OF WHITE"

The NEW ENGLAND JOURNAL of MEDICINE

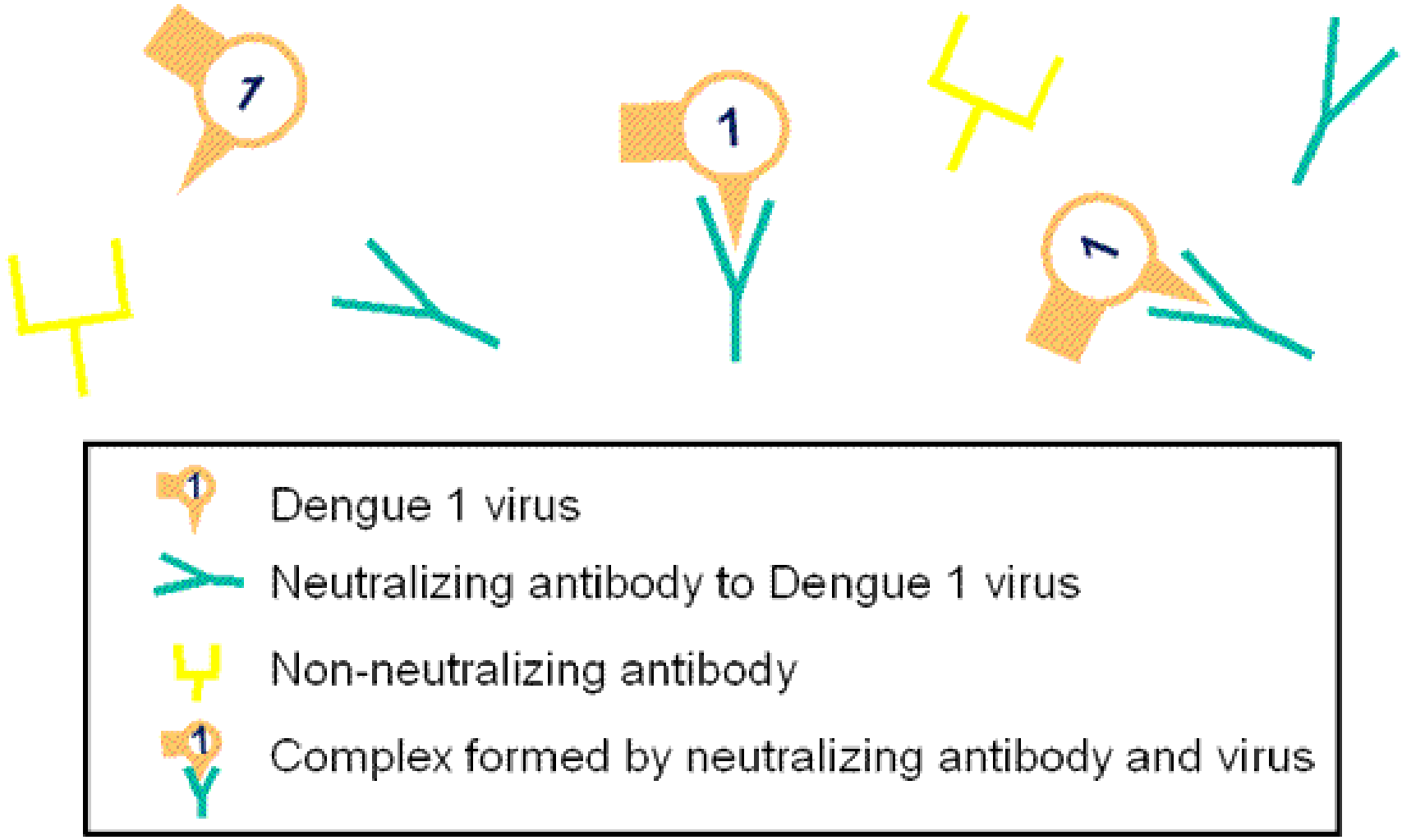
Pathogenesis of Severe Dengue

- Severe dengue most commonly occurs among patients with secondary DENV infections and infants with primary infections.
- The most widely-cited hypothesis for the pathogenesis of severe dengue is antibody-dependent enhancement (ADE)
  - Although the exact mechanisms are not clear, ADE is the process in which DENV, complexed with nonneutralizing antibodies, can enter a greater proportion of cells of the mononuclear lineage, this increasing virus production.
  - Antibodies typically protect humans from viruses in 3 ways
    - Neutralization: antibody blocks from virus interaction with host cell
    - Opsonization: antibody coats virus and typically targets it for uptake by macrophages and neutrophils.
    - Antibody-dependent cellular cytotoxicity (ADCC)
- In dengue, non-neutralizing heterotopic IgG anti-DENV antibodies produced during a person's first DENV infection (or sub-neutralizing level of antibodies in the case of infants who acquired IgG passively in utero) can form antibody-DENV complexes in the second infection that ca allow uptake of DENV by macrophages.
- DENV then replicates in these macrophages thereby increasing viral replication.

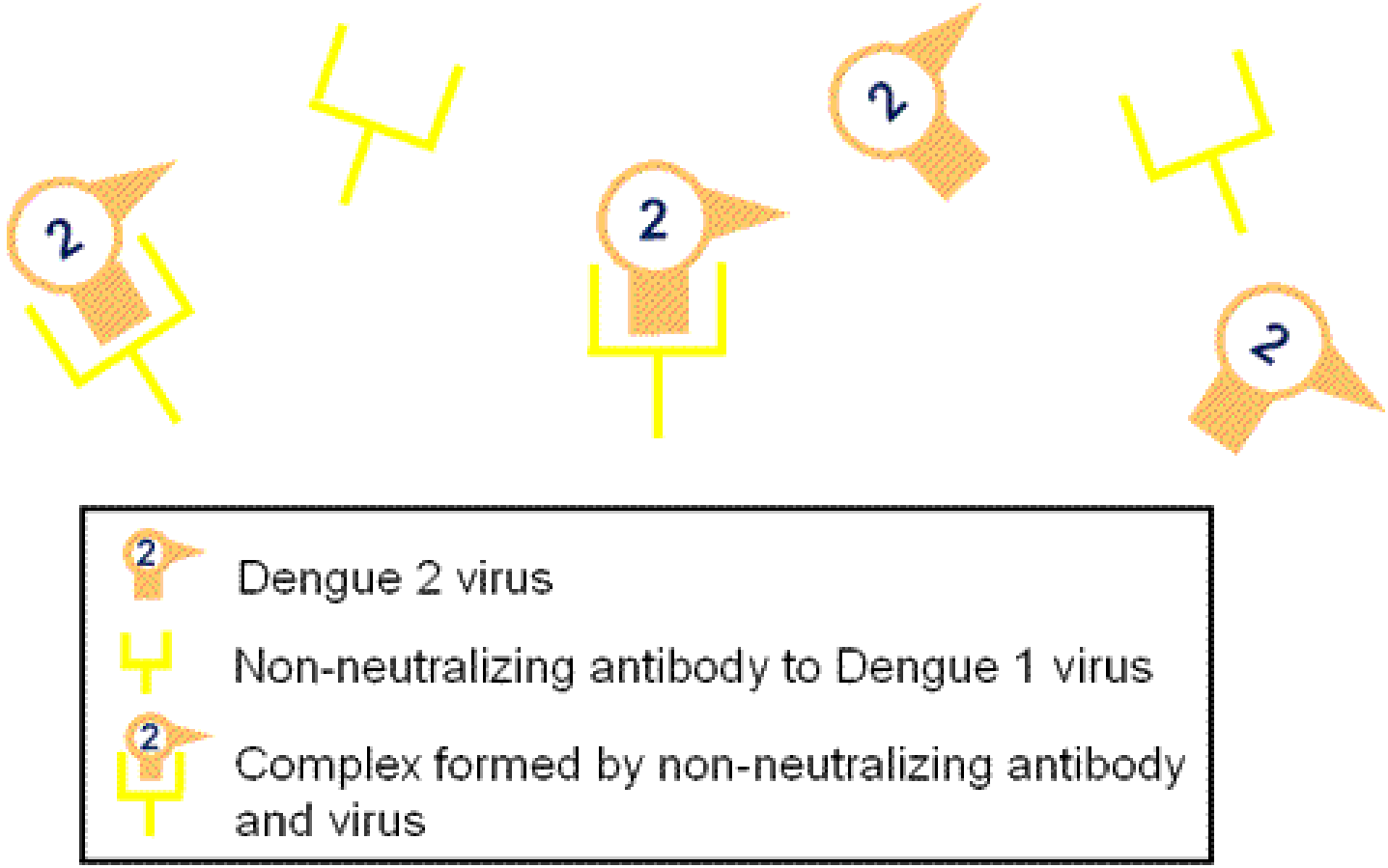


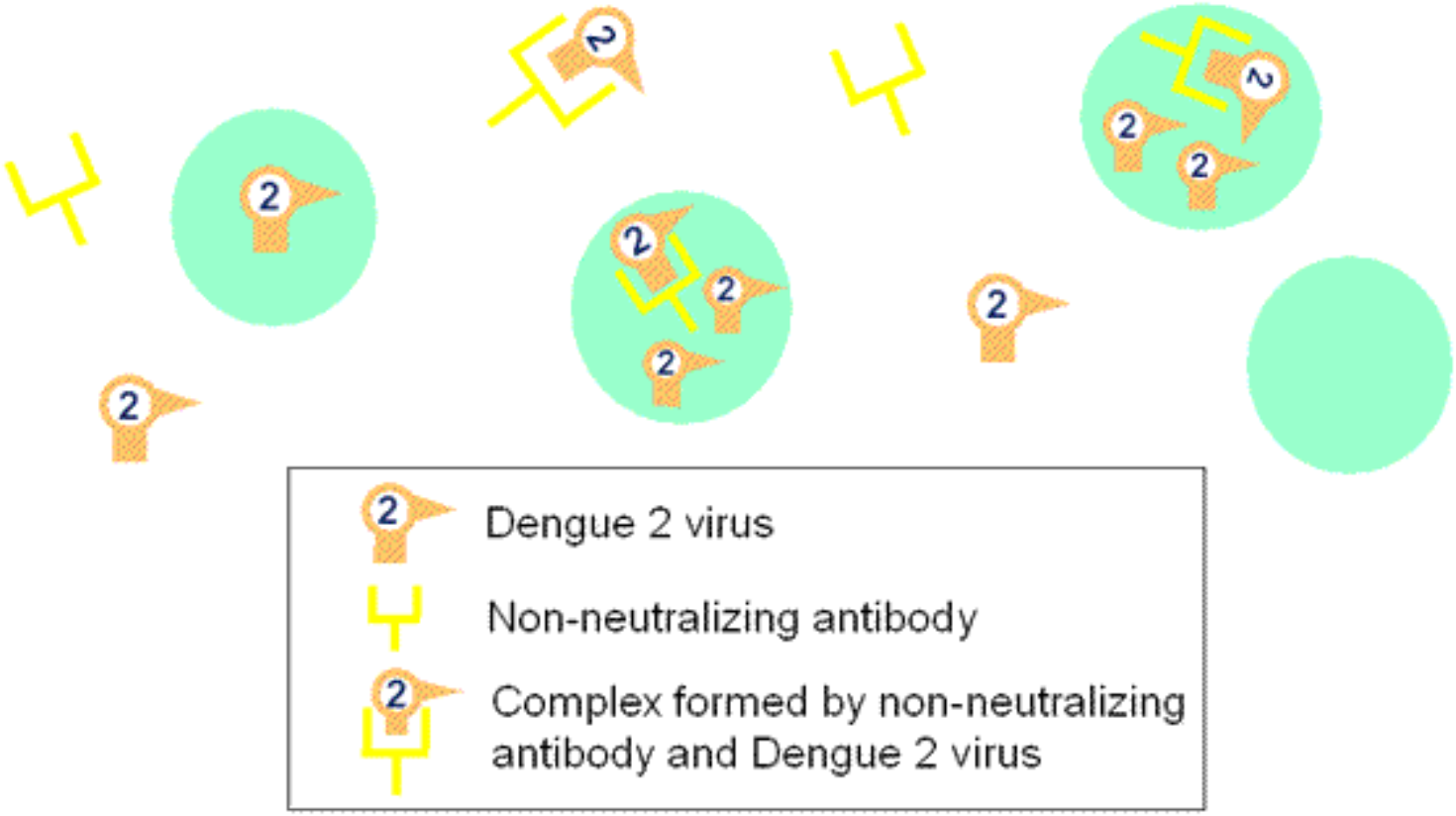


Homologous Antibodies form non-infectious complexes



Heterologous Antibodies form infectious complexes





Heterologous Complexes enter more monocytes, where virus replicates

Infected monocytes release vasoactive mediators, resulting in increased vascular permeability and hemorrhagic manifestations that characterize DHF and DSS.

PATHOPHYSIOLOGY OF ENDOTHELIAL DYSFUNCTION

NS1 Antigen

↓

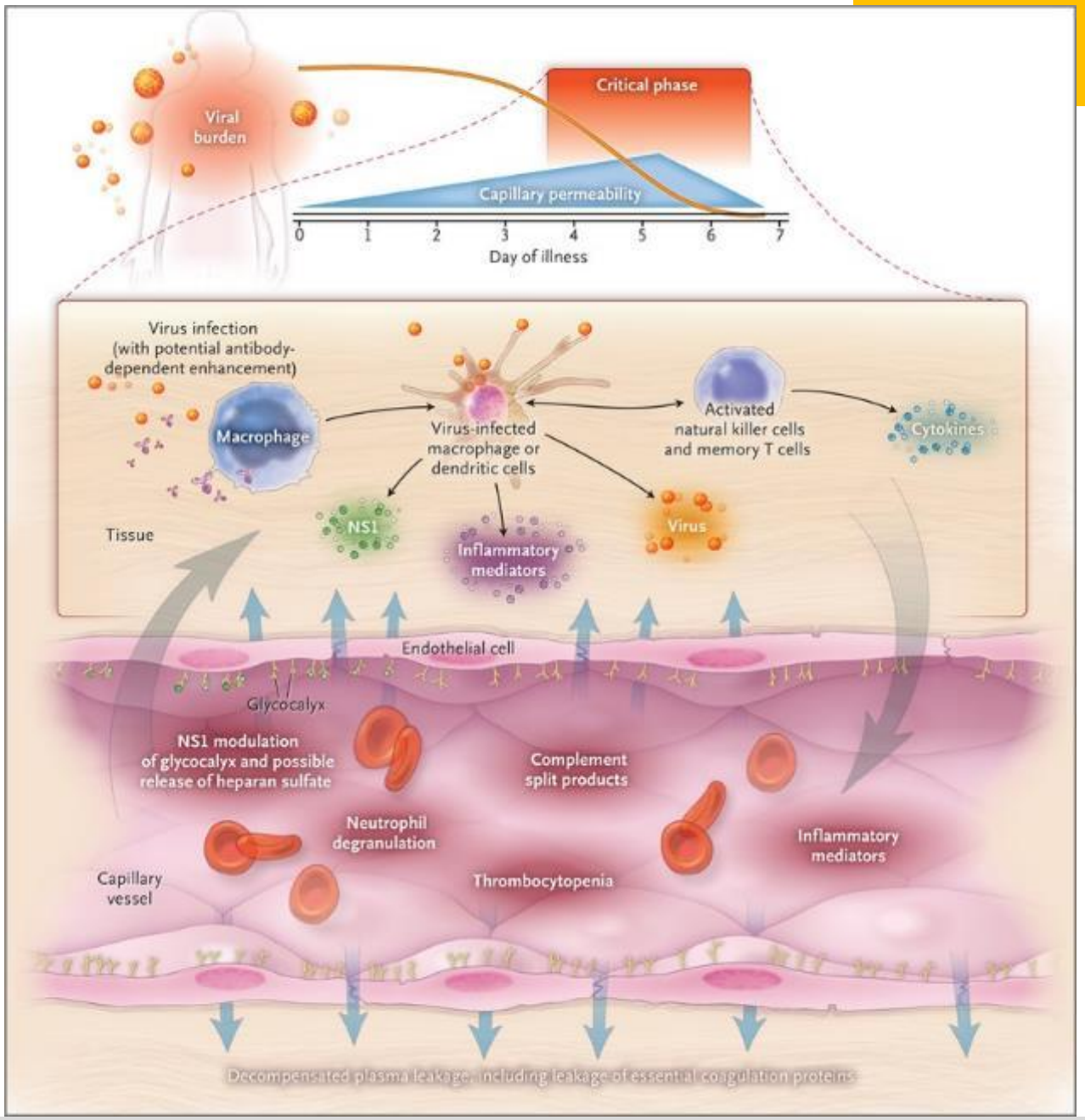
Heparan Sulfate

↓

Leakage of Proteins

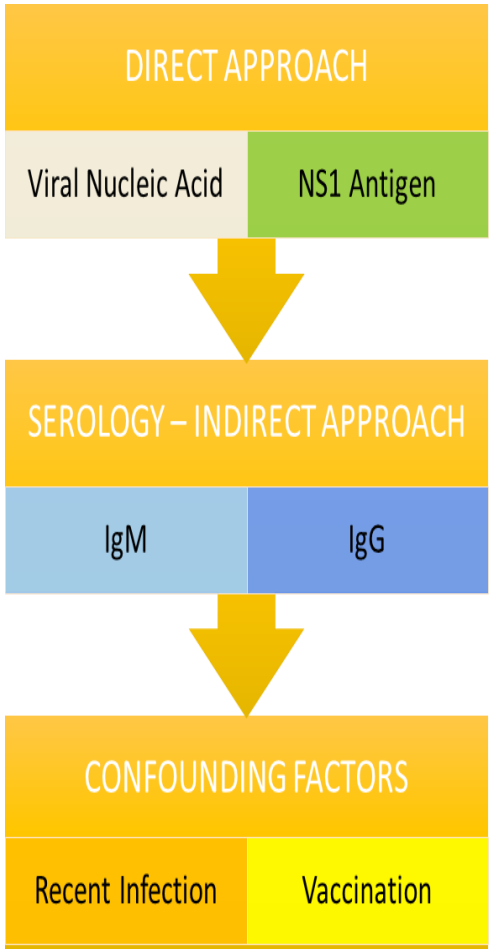
↓

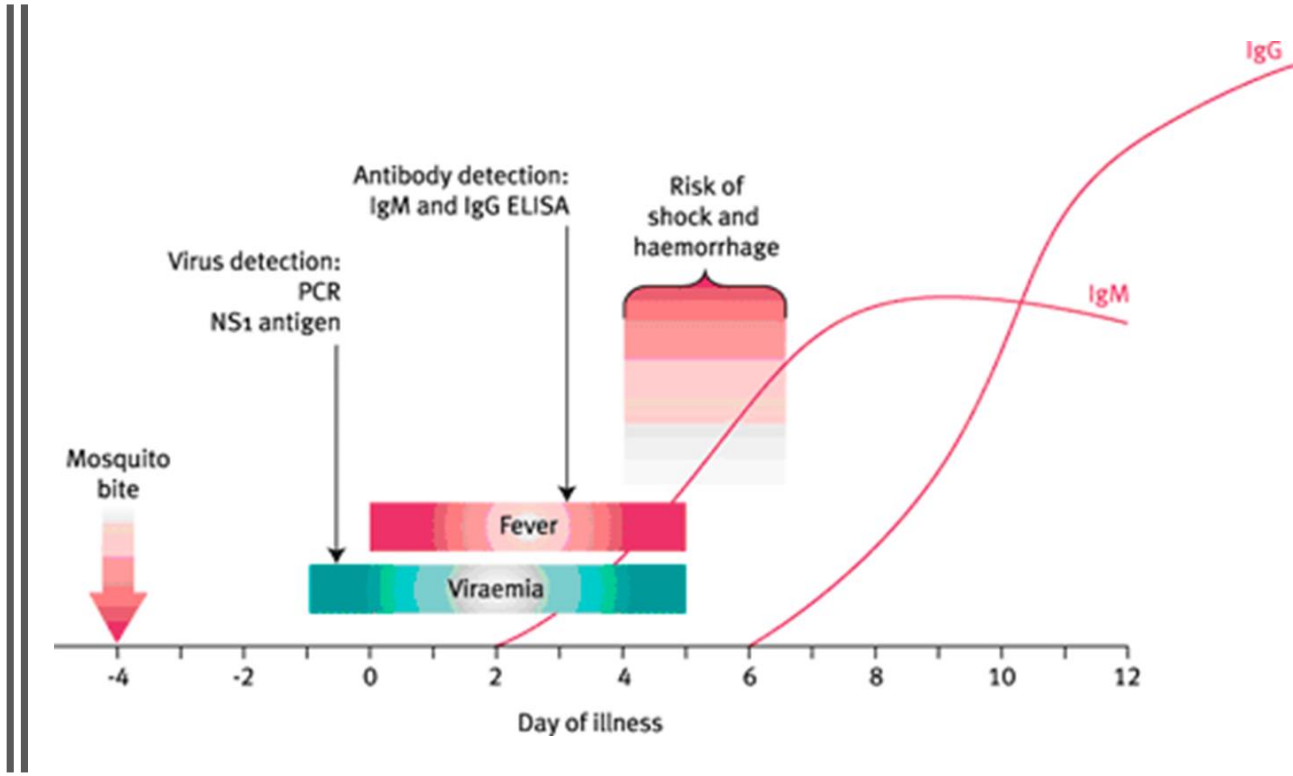
Coagulopathy



Simmons CP et al. N Engl J Med 2012;366:1423-1432

Diagnosis and Testing





Disease	Grade	Clinical Features	Hemorrhage	Hematocrit	Platelet count	Pulse pressure
Dengue fever		Fever, arthralgia, rash	None or minor	Normal	Normal or >100,000	Normal
DHF	I	Fever, gastrointestinal and respiratory symptoms	None or minor	Increased by 20%[c]	<100,000	Normal
	II	Fever, gastrointestinal and respiratory symptoms	Spontaneous hemorrhage	Increased by 20%[c]	<100,000	Normal
DSS	III	As above but with signs of hypotension[d]	None or spontaneous hemorrhage	Increased by 20%[c]	<100,000	≤20mm Hg
	IV	Profound shock	None or spontaneous hemorrhage	Increased by 20%[c]	<100,000	≤20 mm Hg

Management

Control High Fever

- Acetaminophen
- Avoid Aspirin / NSAIDs

Avoid Dehydration

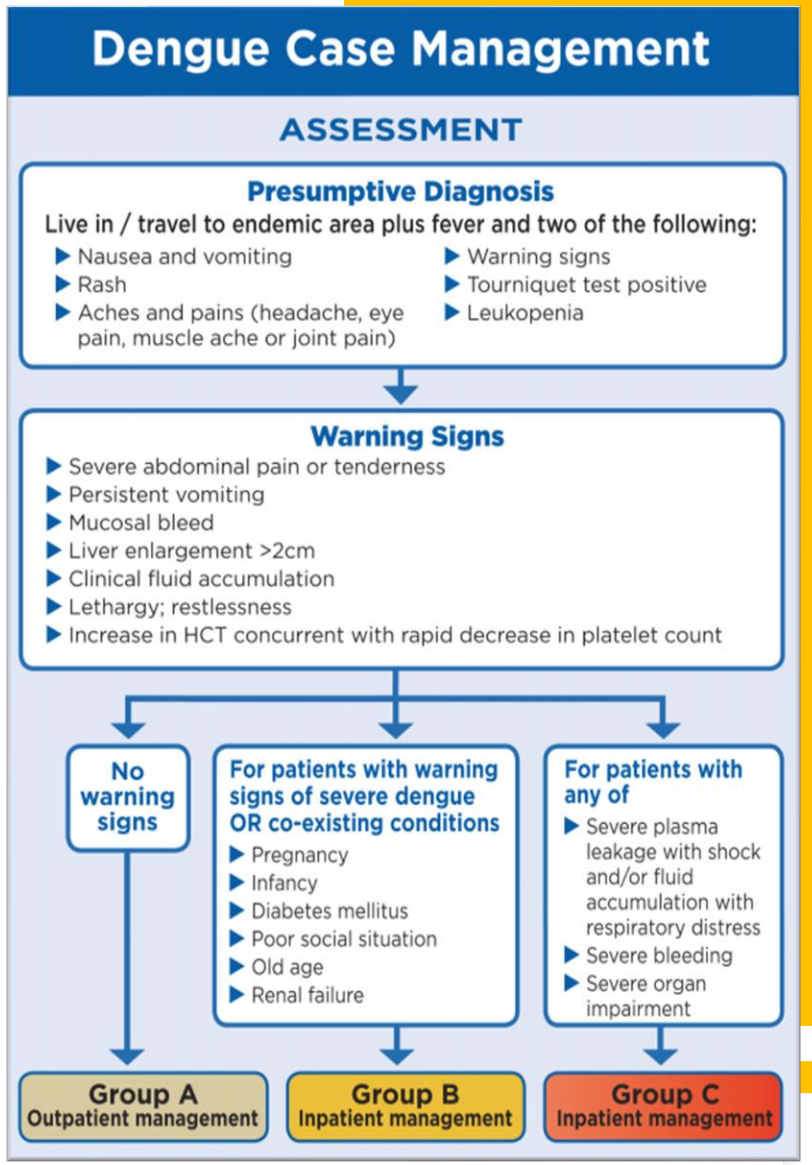
- Replace fluids via oral route

Prevent Dengue Spread

- Mosquito netting
- Insect repellant use
- Screen doors & windows
- Empty out stagnant water

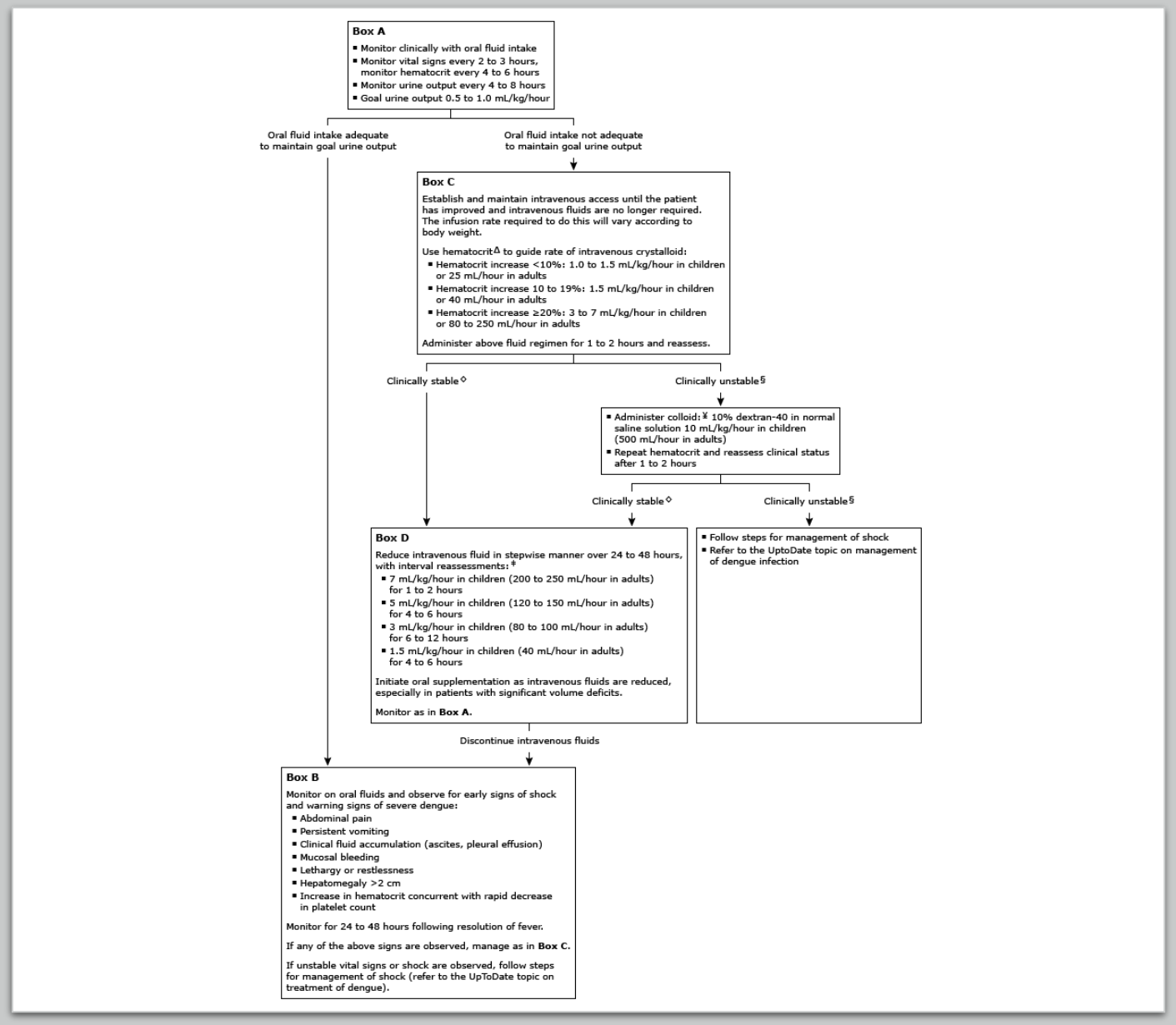
Watch for Warning Signs

- Return to emergency room

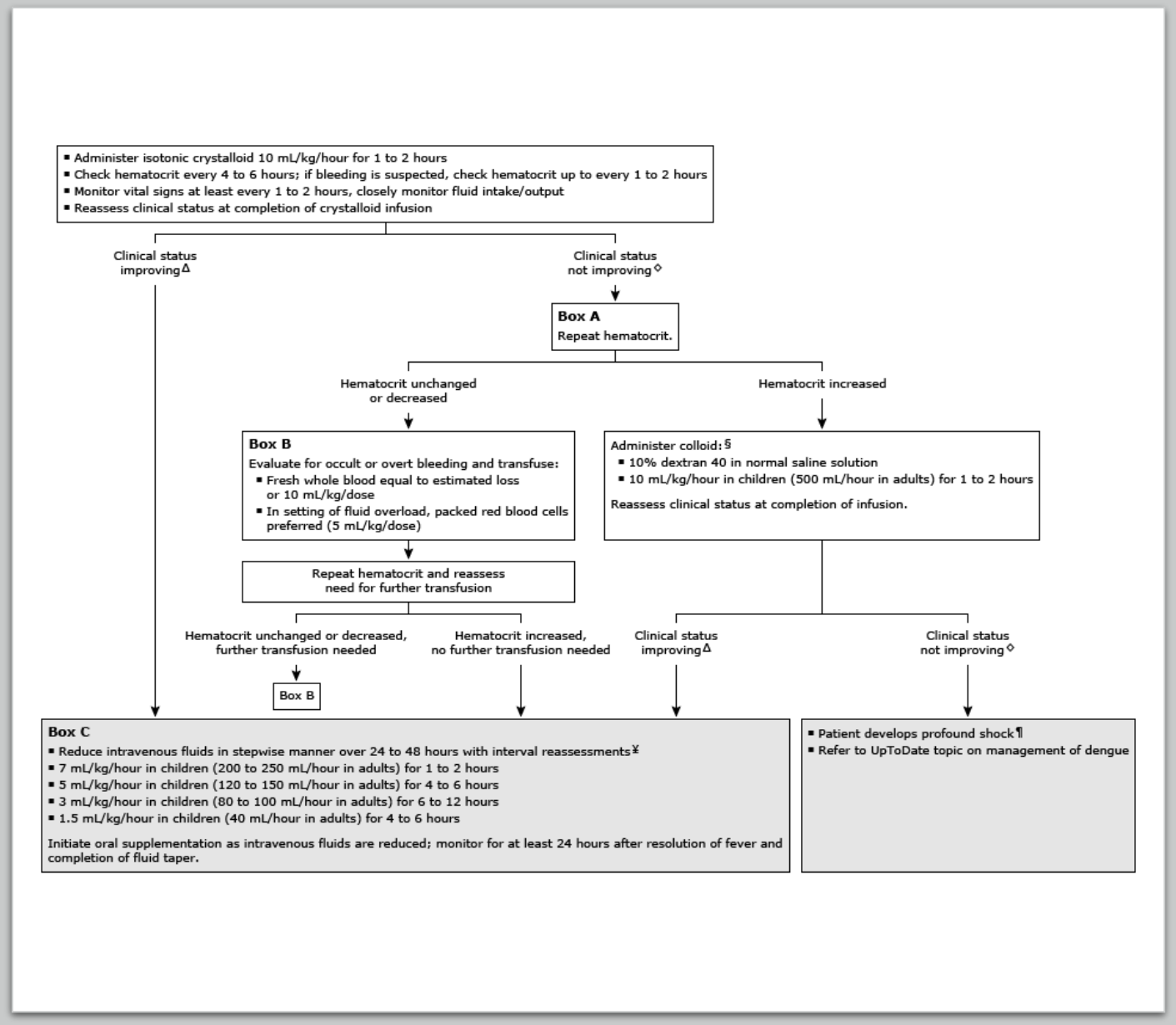


DO's	DON'Ts
✓ Recognize critical phase	× Steroids
✓ Monitor hematocrit, vital signs and output	× Platelet transfusion
	× Volume overload
✓ Treat early shock	× Half normal saline (0.45%)
✓ Colloids for refractory shock	× ASA/NSAIDs for pain control

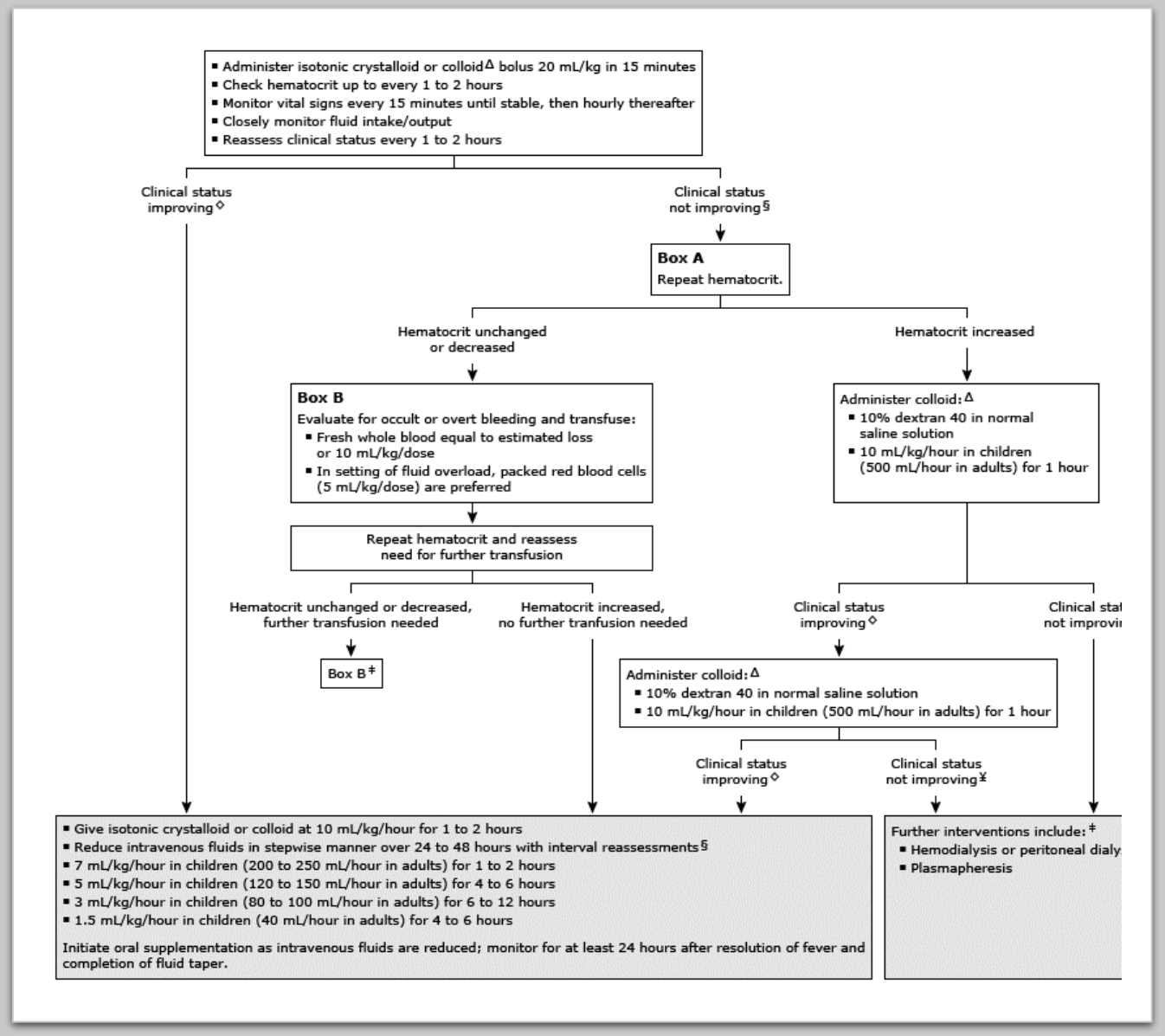
An approach to inpatient management of dengue infection with plasma leakage in the absence of shock (WHO DHF Grades I and II



An approach to management of dengue infection in the setting of shock, narrowed pulse pressure, or hypotension (WHO DHF Grade III)



An approach to management of dengue infection in the setting of profound or prolonged shock (WHO DHF Grade IV)







Dengue Vaccine Globally

- A vaccine to prevent dengue (Dengvaxia®) is licensed and available in some countries for people ages 9-45 years old.
- The World Health Organization recommends that the vaccine only be given to persons with confirmed prior dengue virus infection.
- Three doses of vaccine are required. Each shot is spaced 6 months apart.

Dengue Vaccine in the United States

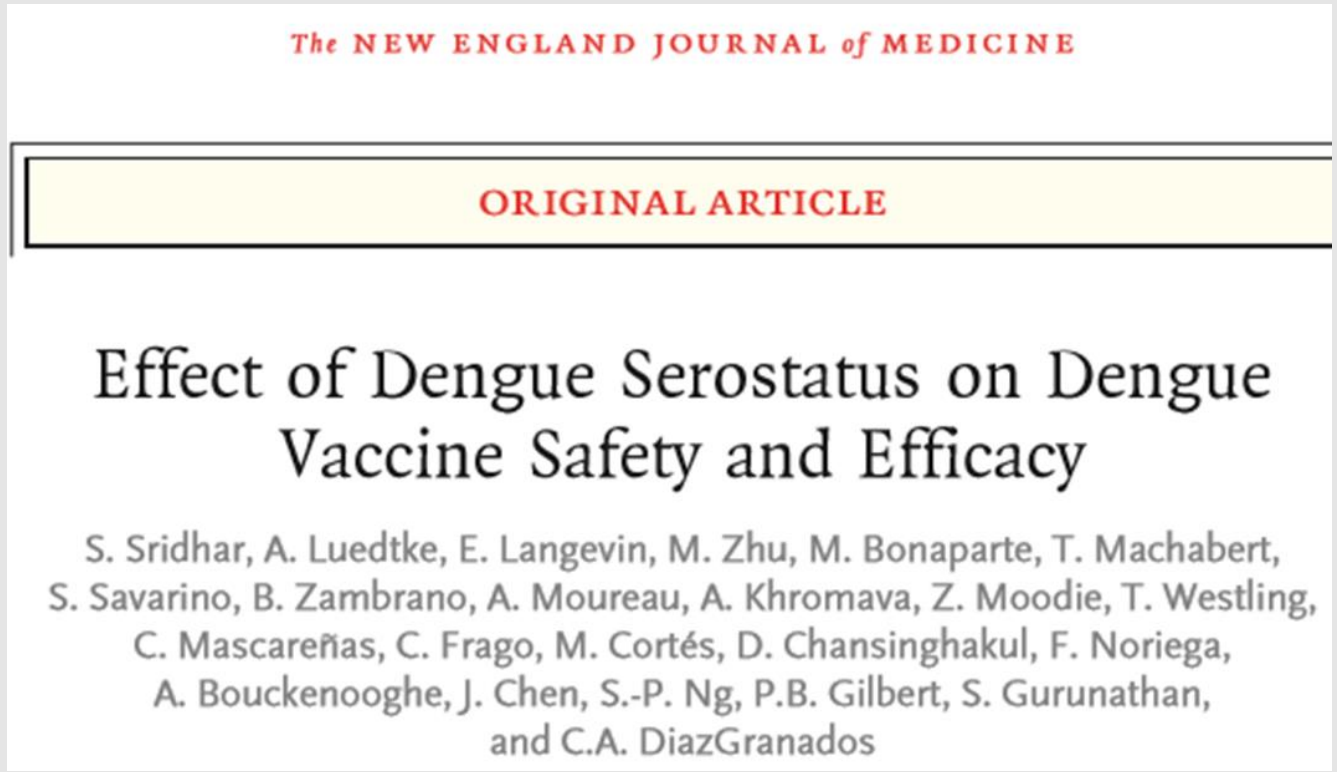
- In May 2019, Dengvaxia® was approved by the U.S. Food and Drug Administration (FDA) in the United States for use in children 9-16 years old living in an area where dengue is common (the US territories of American Samoa, Puerto Rico and the US Virgin Islands), **with laboratory confirmed prior dengue virus infection.**

Controversy

- The vaccine manufacturer, Sanofi Pasteur, announced in 2017 that people who receive the vaccine and have not been previously infected with a dengue virus may be at risk of developing severe dengue if they get dengue after being vaccinated.

What about the Dengue Vaccine

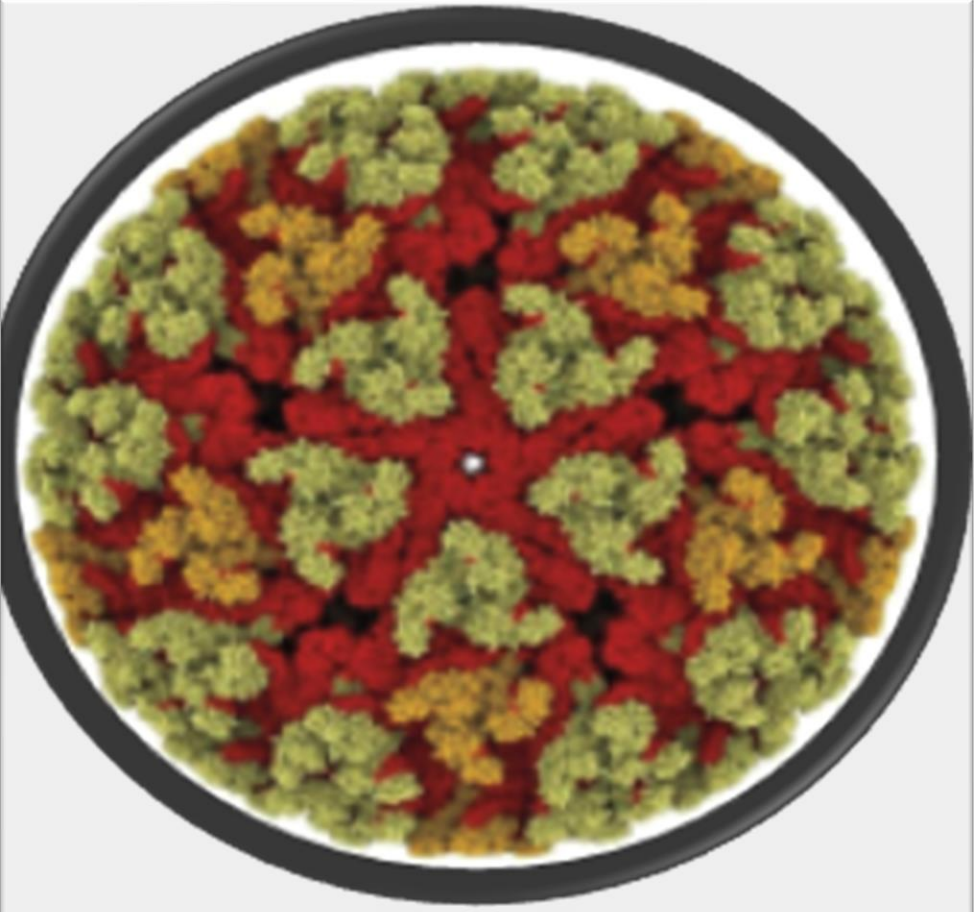
- 1st Dengue vaccine – recombinant, live attenuated, tetravalent vaccine (CYD-TDV) was licensed on the basis of three efficacy trials in the Asia-Pacific region and Latin America.
- An excess of hospitalizations for dengue among children who had been vaccinated at 2 to 5 years of age was observed in the third year of the phase 3 trial in Asia (the CYD14 trial), the potential effects of baseline dengue serostatus and age on vaccine safety and efficacy required reconsideration.
- One hypothesis for these excess cases was that CYD-TDV in recipients without previous dengue infection (i.e., dengue-unexposed vaccine recipients) mimics primary infection and, like natural secondary infection, places these people at an increased risk for severe disease on subsequent infection.



- **CYD-TDV protected against severe virologically confirmed dengue (VCD)**
- **Hospitalization for VCD for 5 years in persons who had exposure to dengue before vaccination.**
- **Evidence of a higher risk of these outcomes in vaccinated persons who had not been exposed to dengue.**

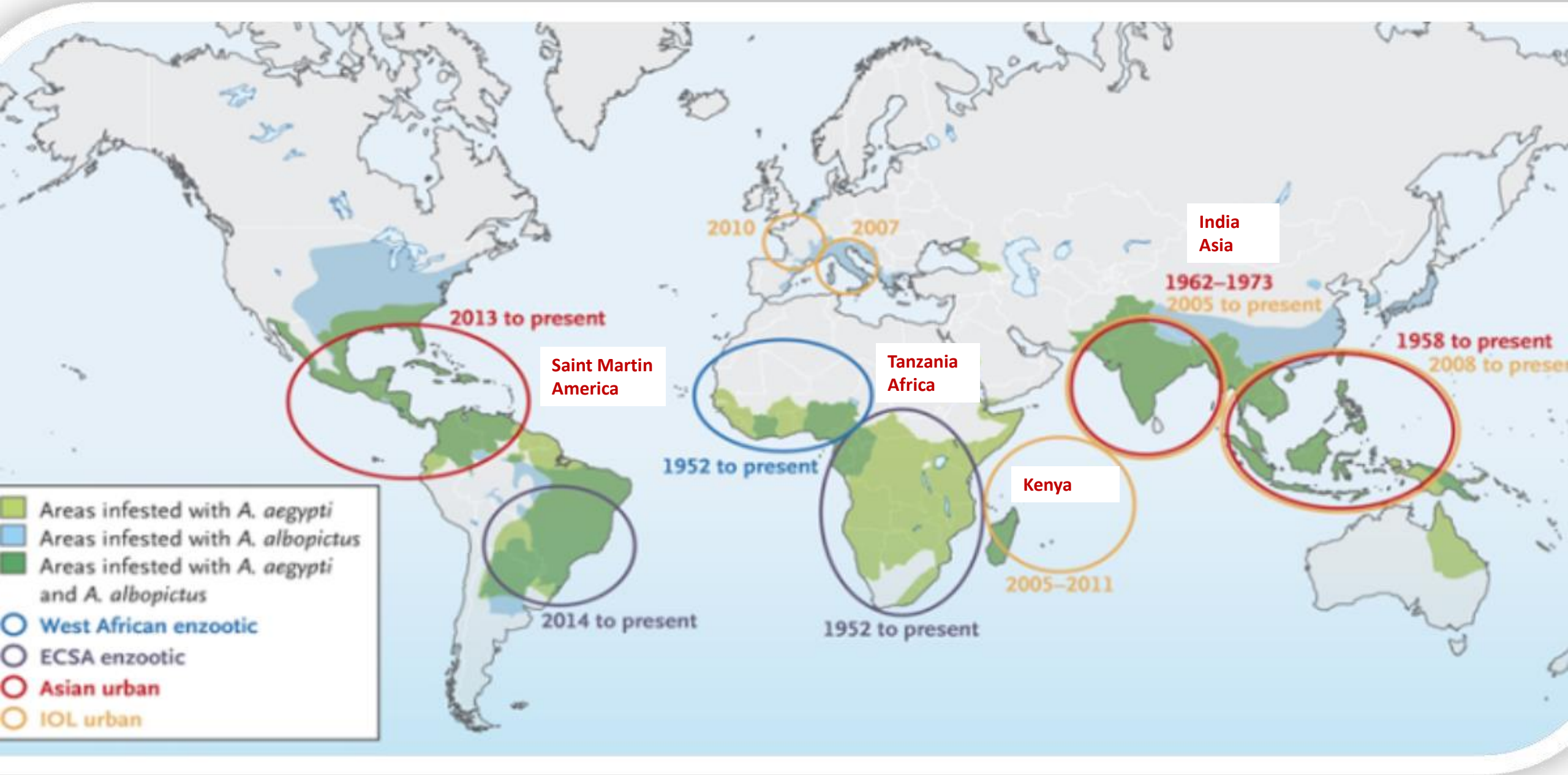
Chikungunya Virus



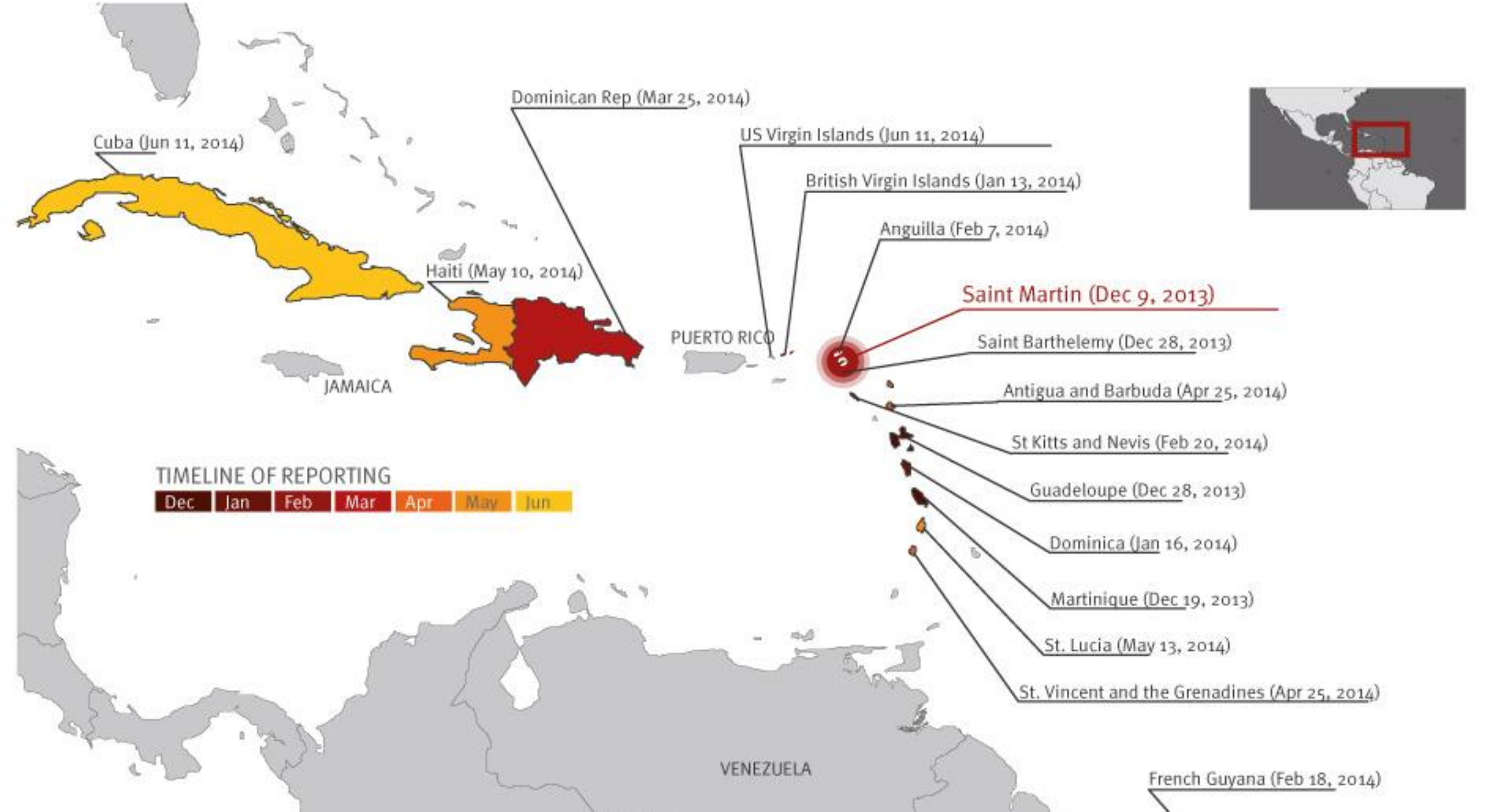


Chikungunya virus

- Genus: *Alphavirus*
- Vector: *Aedes aegypti* (primary) and *Aedes albopictus*
- Humans primary amplifying host during outbreaks
  - Sylvatic transmission in non-human primates in Africa
  - Role of other animals in maintaining the virus not known
- Other modes of transmission
  - Rarely: intrapartum from viremic mother to child, *in-utero* transmission resulting in miscarriage, percutaneous needle stick, laboratory exposure
  - Theoretical concern: blood transfusion and organ/tissue transplantation (chikungunya viremia can occur prior to onset of symptoms and infection can be asymptomatic)
  - No evidence of virus in breast milk.



Weaver SC, Lecuit M. N Engl J Med 2015;372:1231-1239


Dominican Rep (Mar 25, 2014)
US Virgin Islands (Jun 11, 2014)
British Virgin Islands (Jan 13, 2014)
Anguilla (Feb 7, 2014)
Cuba (Jun 11, 2014)
Haiti (May 10, 2014)
Saint Martin (Dec 9, 2013)
PUERTO RICO
Saint Barthelemy (Dec 28, 2013)
Antigua and Barbuda (Apr 25, 2014)
St Kitts and Nevis (Feb 20, 2014)
Guadeloupe (Dec 28, 2013)
Dominica (Jan 16, 2014)
Martinique (Dec 19, 2013)
St. Lucia (May 13, 2014)
St. Vincent and the Grenadines (Apr 25, 2014)
JAMAICA
TIMELINE OF REPORTING
Dec
Jan
Feb
Mar
Apr
May
Jun
VENEZUELA
French Guyana (Feb 18, 2014)

Chikungunya Virus

- Chikungunya is a global public health concern.
- Endemic in parts of West Africa (serosurveys → 35 to 50% of the population have Chikungunya antibodies).
- Local transmission has been reported widely in Puerto Rico, where serosurveys found nearly 25% of blood donors had been infected.
- Between 2014 and 2016, almost 4000 cases of chikungunya virus disease were reported in the United States among travelers; 92 percent were associated with travel in the Americas (most commonly the Dominican Republic, Puerto Rico, and Haiti).
- Dengue and Zika viruses are transmitted by the same mosquito vectors as chikungunya virus. The viruses can cocirculate in a geographic region, and coinfections have been documented.

Chikungunya Virus



Chikungunya virus can spread geographically via travel of infected individuals between regions with appropriate season/climate where competent mosquitoes exist for perpetuation of local transmission.

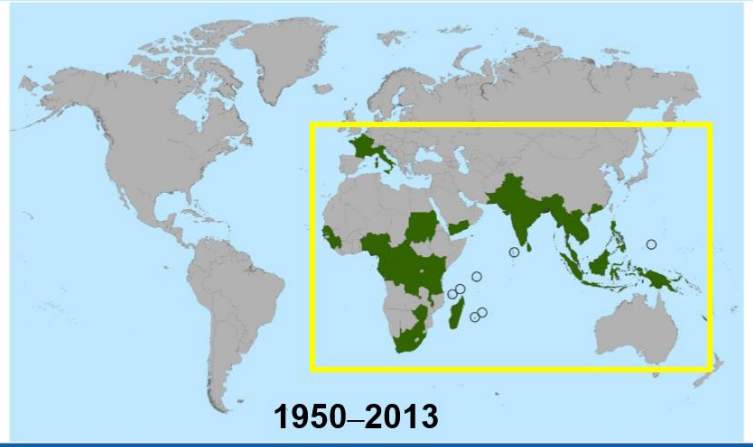


In addition, dissemination of mosquitoes can occur via transport of mosquito larvae and eggs by ships and air traffic to new areas with suitable environmental and climatic conditions.



Mutations in some strains of the chikungunya virus may shorten the extrinsic incubation period, allowing more mosquitoes to survive long enough to transmit virus

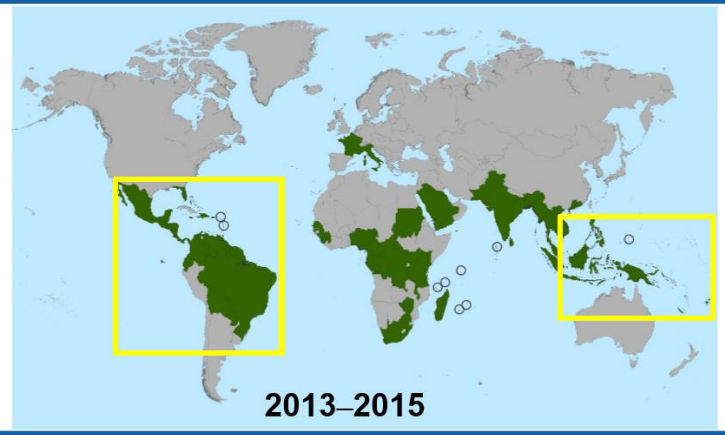
Chikungunya Virus: Approximate Geographic Distribution



1950–2013

Available at http://www.cdc.gov/chikungunya

Chikungunya Virus: Approximate Geographic Distribution

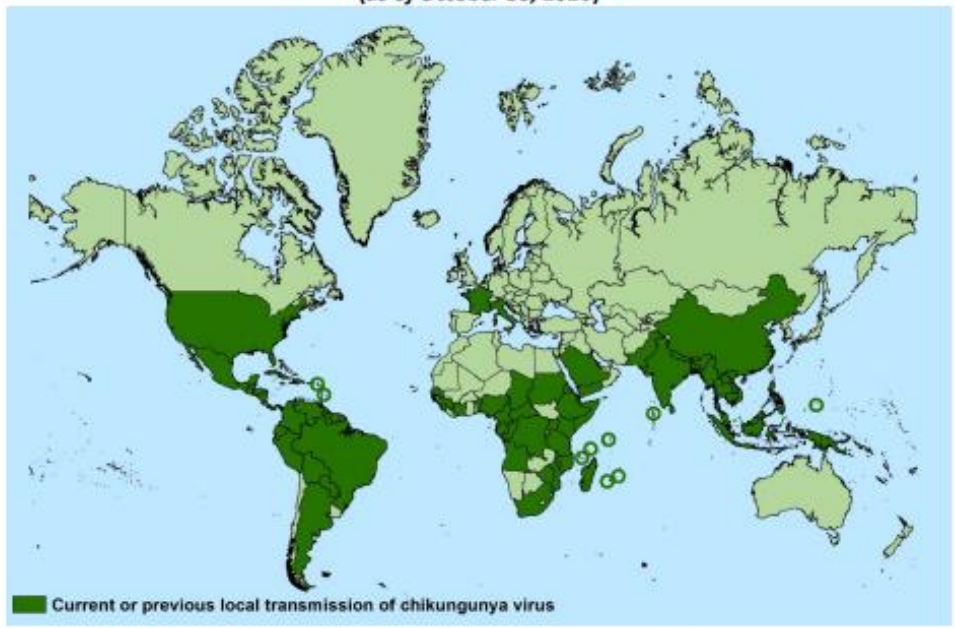


2013–2015

Available at http://www.cdc.gov/chikungunya

Countries and territories where chikungunya cases have been reported*

(as of October 30, 2020)

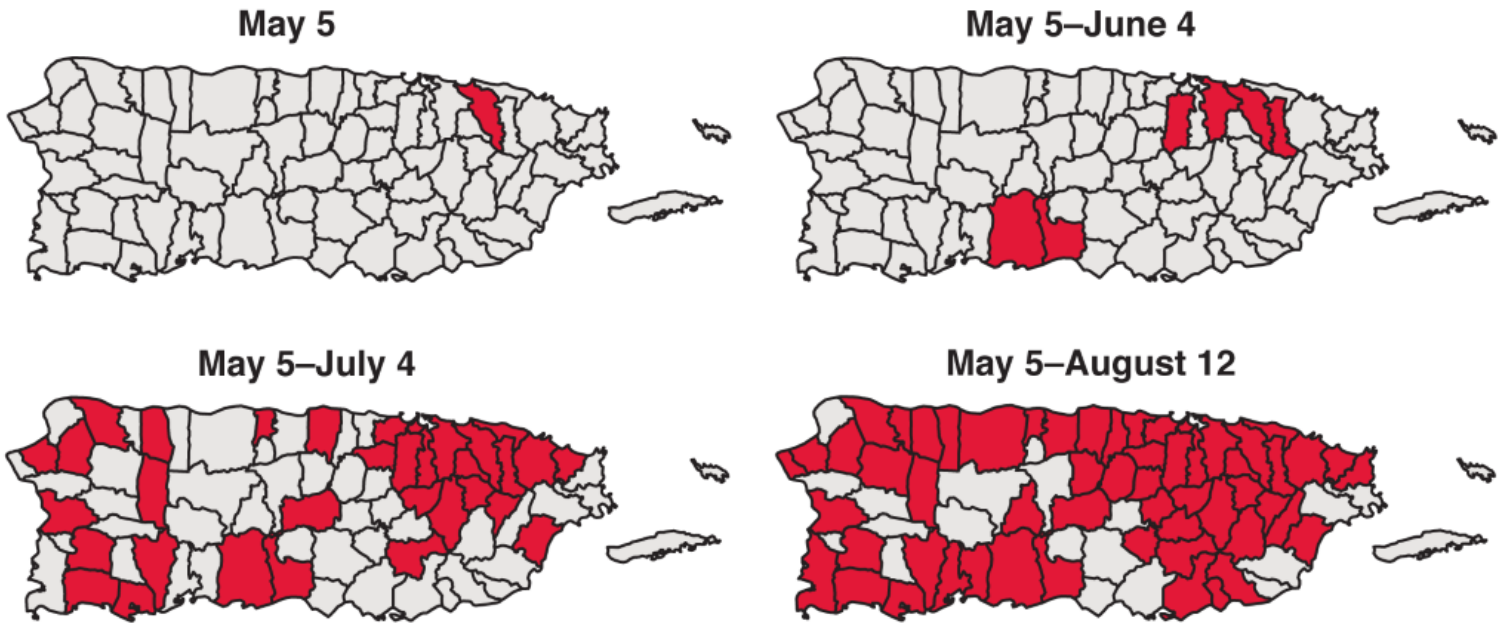


*Does not include countries or territories where only imported cases have been documented.

Data table: Countries and territories where chikungunya cases have been reported

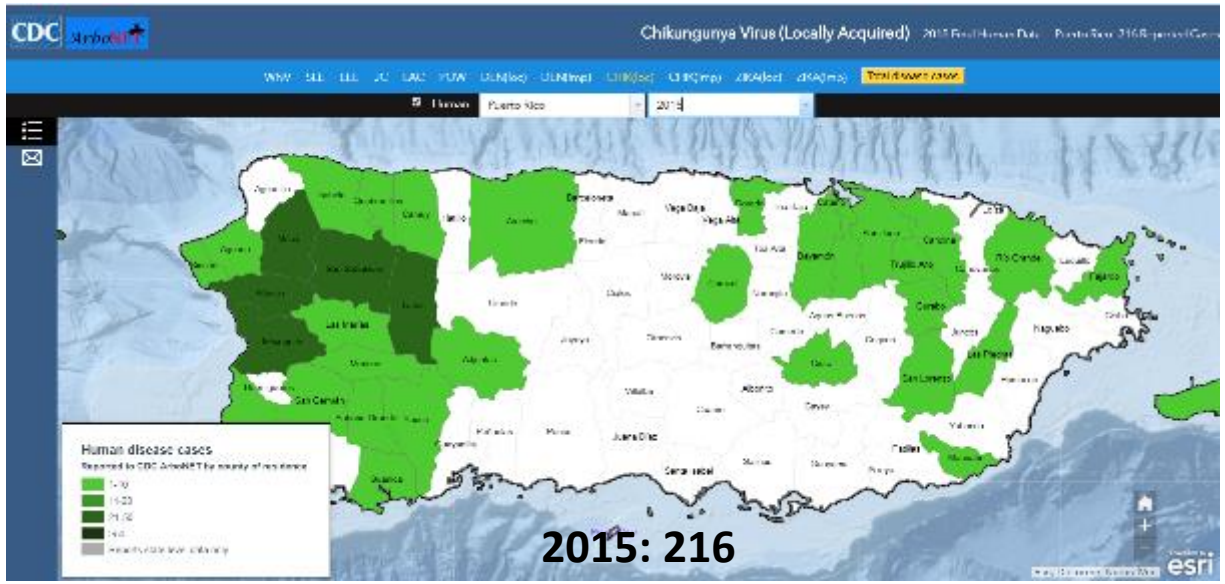
AFRICA	ASIA	AMERICAS	
Angola	Bangladesh	Anguilla	Panama
Benin	Bhutan	Antigua and Barbuda	Paraguay
Burundi	Cambodia	Argentina	Peru
Cameroon	China	Aruba	Puerto Rico
Central African Republic	India	Bahamas	Saint Barthelemy
Chad	Indonesia	Barbados	Saint Kitts and Nevis
Cote d'Ivoire	Laos	Belize	Saint Lucia
Dem. Republic of the	Malaysia	Bolivia	Saint Martin
Djibouti	Maldives	Brazil	Saint Vincent & the
Equatorial Guinea	Myanmar (Burma)	British Virgin Islands	Sint Maarten
Eritrea	Nepal	Cayman Islands	Suriname
Ethiopia	Pakistan	Colombia	Trinidad and Tobago
Gabon	Philippines	Costa Rica	Turks and Caicos Islands
Guinea	Saudi Arabia	Cuba	United States
Kenya	Singapore	Curacao	US Virgin Islands
Madagascar	Sri Lanka	Dominica	Venezuela
Malawi	Taiwan	Dominican Republic	
Mauritius	Thailand	Ecuador	
Mayotte	Timor-Leste	El Salvador	**OCEANIA/PACIFIC ISLANDS**
Mozambique	Vietnam	French Guiana	American Samoa
Nigeria	Yemen	Grenada	Cook Islands
Republic of the Congo		Guadeloupe	Federal States of Micronesia
Reunion		Guatemala	Fiji
Senegal	**EUROPE**	Guyana	French Polynesia
Seychelles	France	Haiti	Kiribati
Sierra Leone	Italy	Honduras	Marshall Islands
Somalia		Jamaica	New Caledonia
South Africa		Martinique	Papua New Guinea
Sudan		Mexico	Samoa
Tanzania		Montserrat	Tokelau

Geographic Distribution of Laboratory-Positive Chikungunya Cases — Puerto Rico, May 5-August 12, 2014

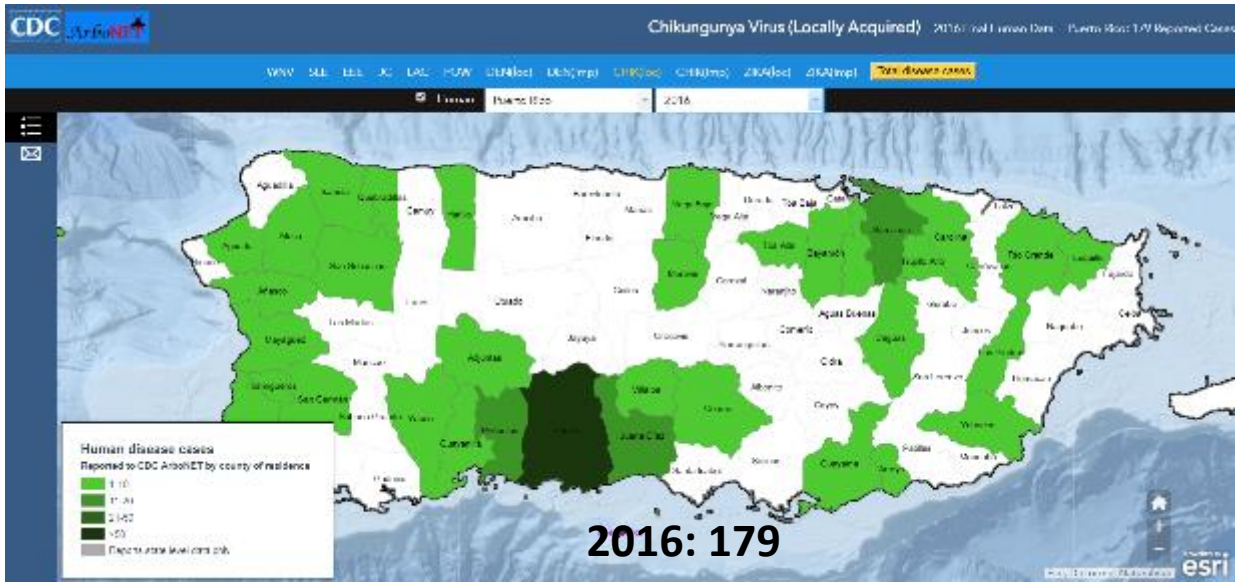


Source: *MMWR* 63: 1121, 2014.

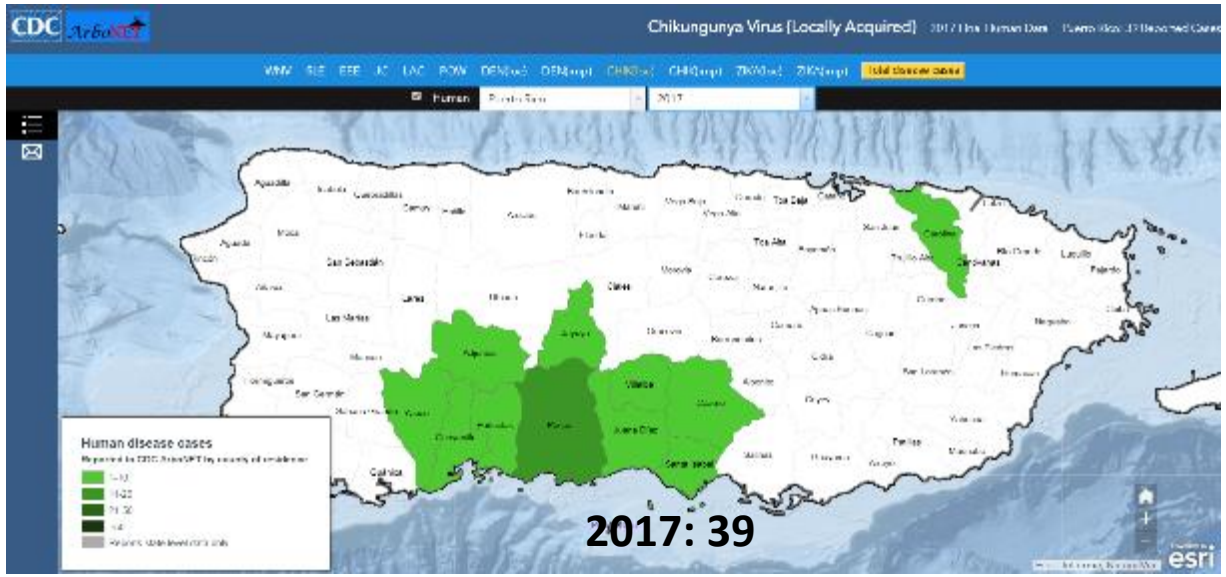
Chikungunya Cases in Puerto Rico 2015-2018



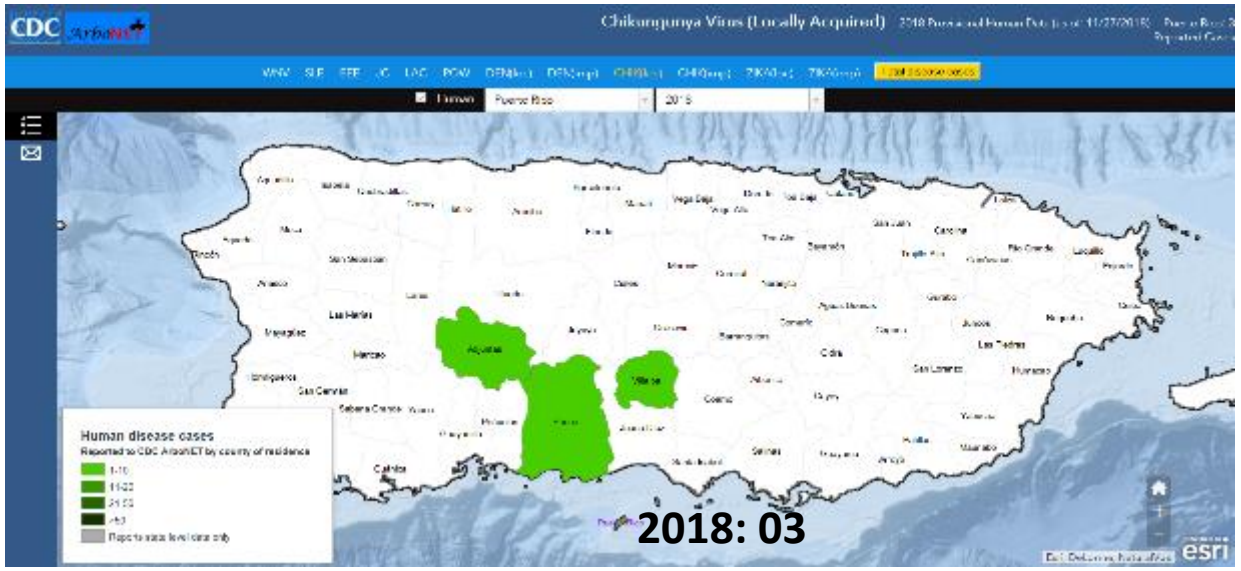
2015: 216



2016: 179

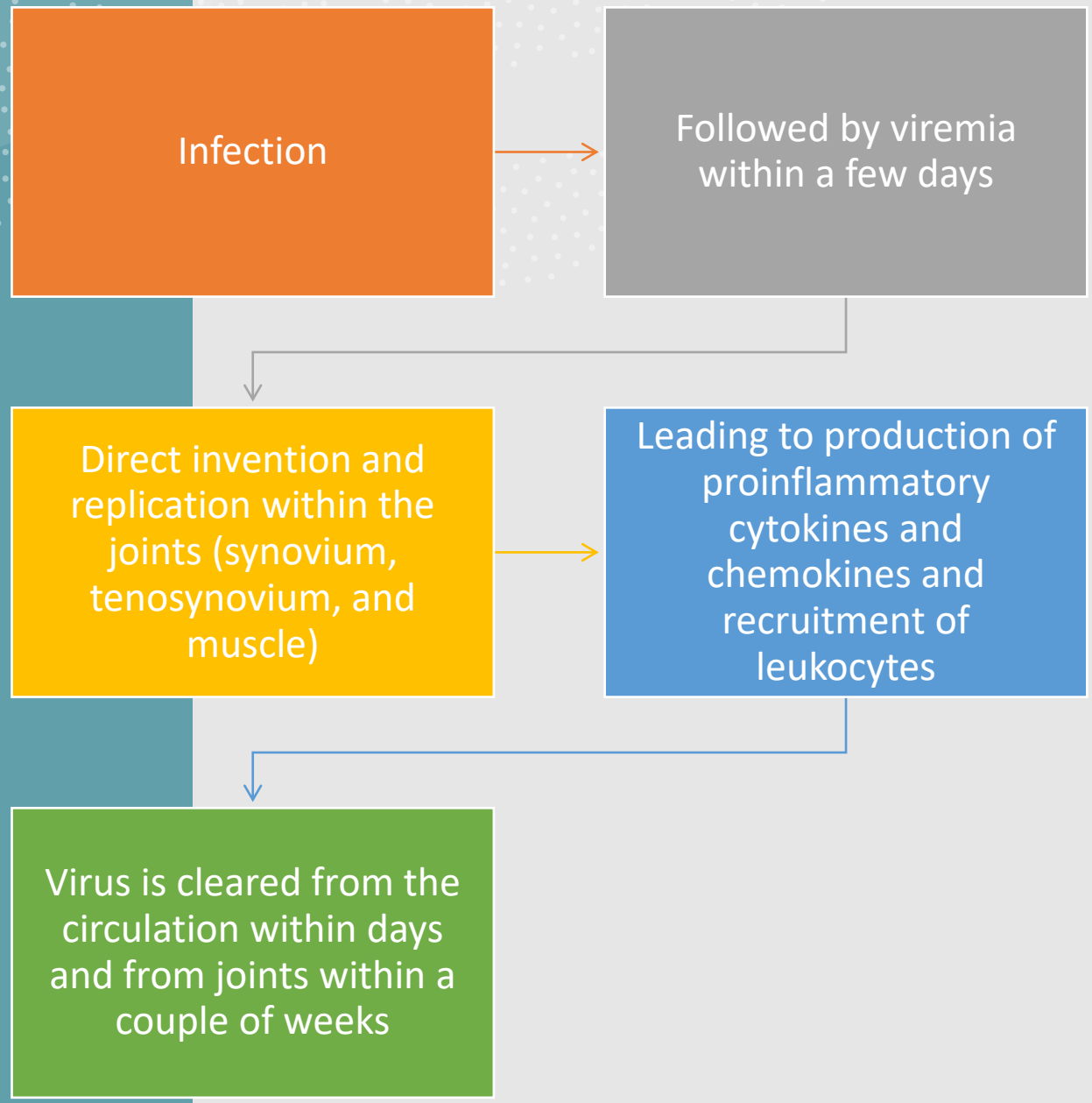


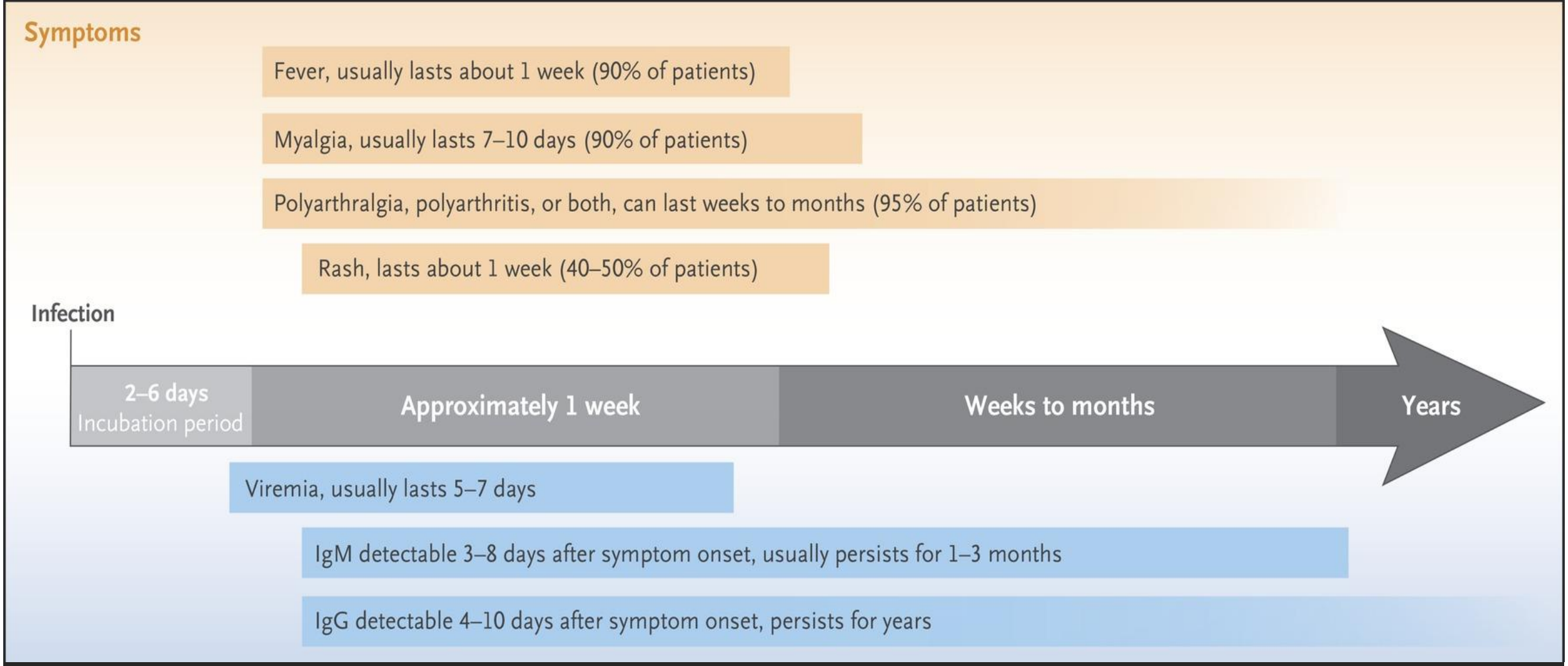
2017: 39



2018: 03

Pathogenesis





CHIKUNGUNYA FEVER

Timeline of Infection, Symptoms, and Biomarkers

COMPLICATIONS ASSOCIATED WITH CHIKUNGUNYA VIRUS

Reported atypical or severe disease manifestations of Chikungunya virus infection	
System	Clinical manifestations
Neurological	Meningoencephalitis, encephalopathy, seizures, Guillain-Barre syndrome, paresis, palsies, neuropathy
Ocular	Optic neuritis, iridocyclitis, episcleritis, retinitis, uveitis
Cardiovascular	Myocarditis, pericarditis, heart failure, arrhythmias, hemodynamic instability
Dermatological	Photosensitive, hyperpigmentation, intertriginous aphtous-like ulcers, vesiculobullous dermatosis.
Renal	Nephritis, acute renal failure
Other	Bleeding dyscrasias, pneumonia, respiratory failure, hepatitis, pancreatitis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), hypoadrenalism.

Clinical features of chikungunya virus infections compared to dengue virus infection		
Clinical Manifestations	**Chikungunya**	**Dengue**
Fever (>39 °C)	+++	++
Arthralgia	+++	+/-
Arthritis	+	-
Headache	++	++
Rash	++	+
Myalgia	+	++
Hemorrhage	+/-	++
Shock	-	+

Clinical Laboratory features of chikungunya virus infections compared to dengue virus infections

Laboratory		
Lymphopenia	+++	++
Neutropenia	+	+++
Thrombocytopenia	+	+++
Hemoconcentration	-	++

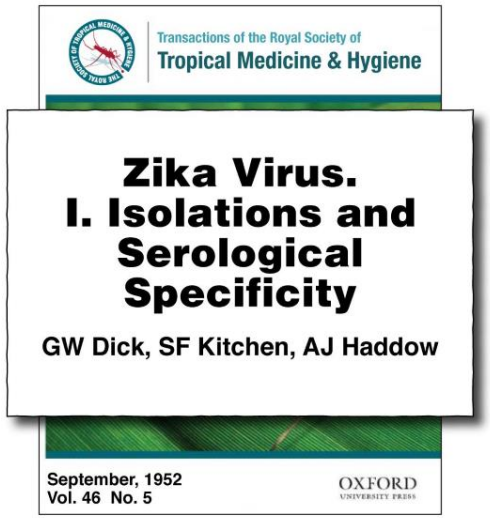
Treatment for Chikungunya

- No specific antiviral therapy; treatment is supportive.
- Assess hydration and hemodynamic status
- Evaluate for other serious conditions and treat or manage appropriately.
- Proper clinical management reduces mortality due to dengue.
- All suspected cases should be managed as if they have dengue until it has been ruled out.



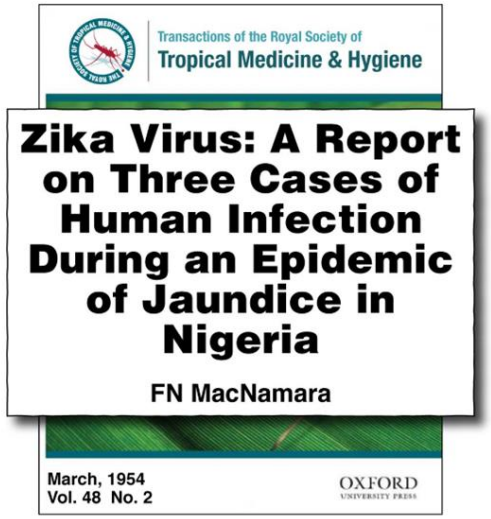


Zika Virus



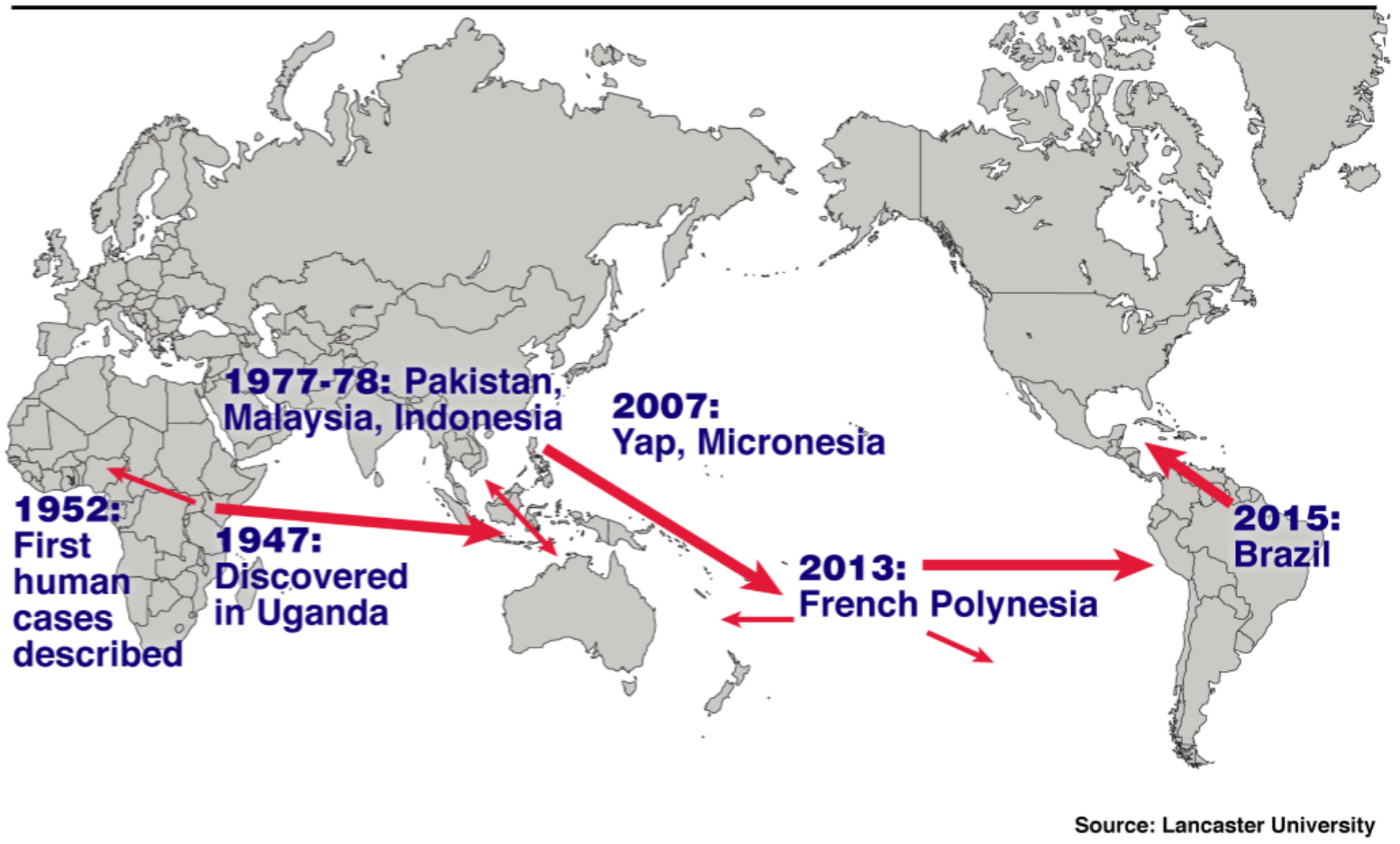


- Virus first isolated from a monkey in the Zika forest of Uganda in 1947





- First human cases reported in Nigeria in 1952



Zika Virus Spread 1947-2016





Arch Virol
DOI 10.1007/s00705-015-2695-5

BRIEF REPORT

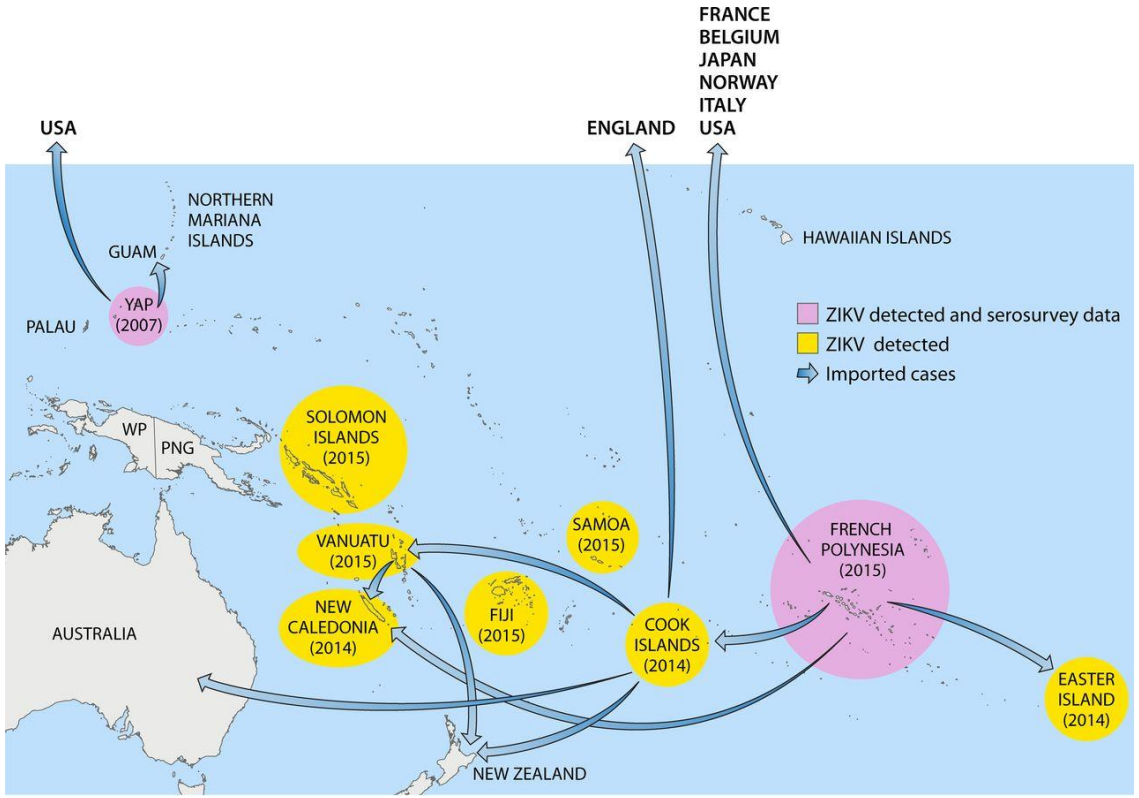
A report on the outbreak of Zika virus on Easter Island, South Pacific, 2014

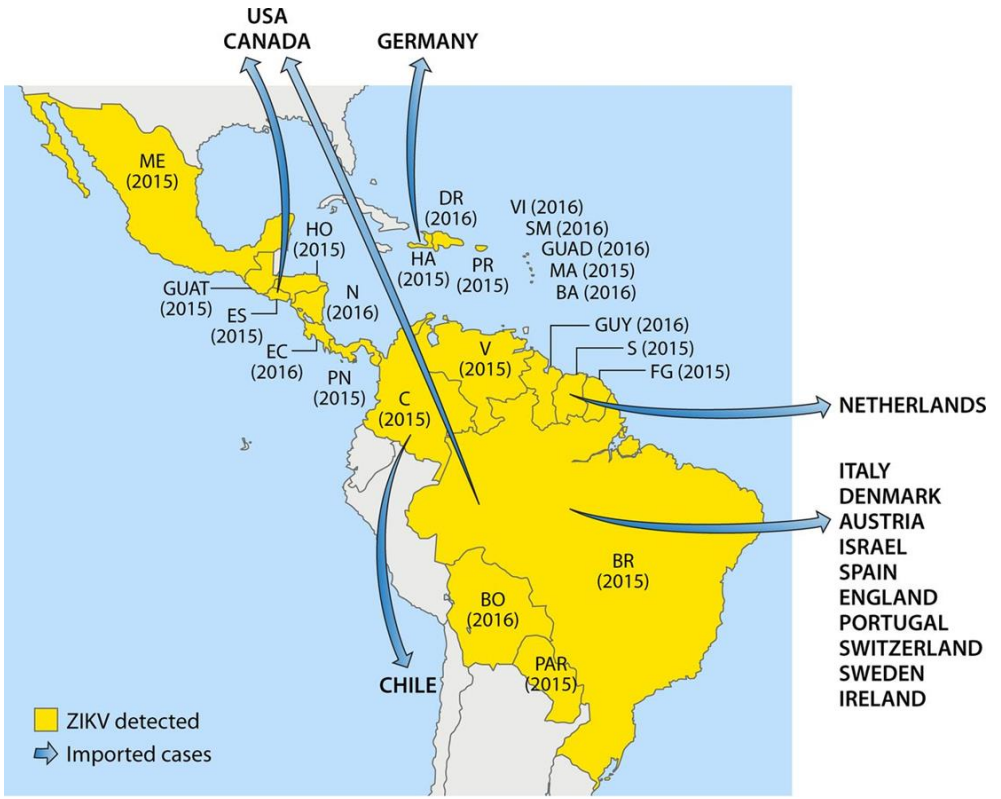
J. Tognarelli[1] · S. Ulloa[1] · E. Villagra[2] · J. Lagos[1] · C. Aguayo[1] · R. Fasce[3] · B. Parra[1] · J. Mora[2] · N. Becerra[2] · N. Lagos[2] · L. Vera[2] · B. Olivares[1] · M. Vilches[2] · J. Fernández[1]



Countries in which ZIKV circulation has been reported up to January 2016

Didier Musso, and Duane J. Gubler Clin. Microbiol. Rev. 2016;29:487-524

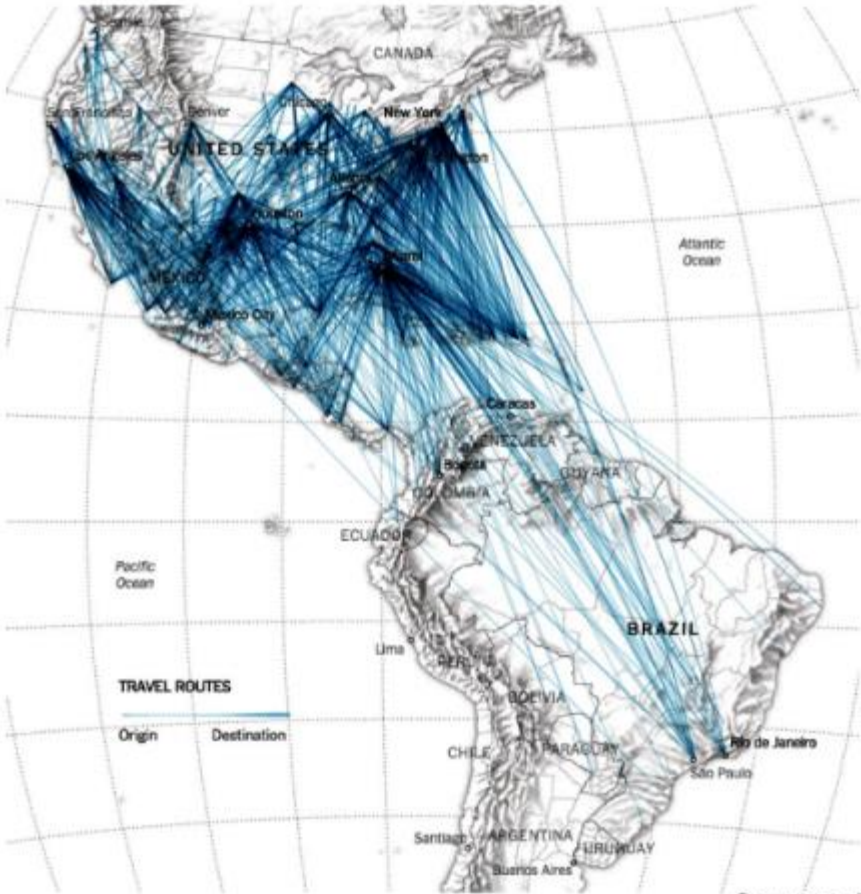




ZIKA VIRUS ENDEMIC AREAS IN THE AMERICAS



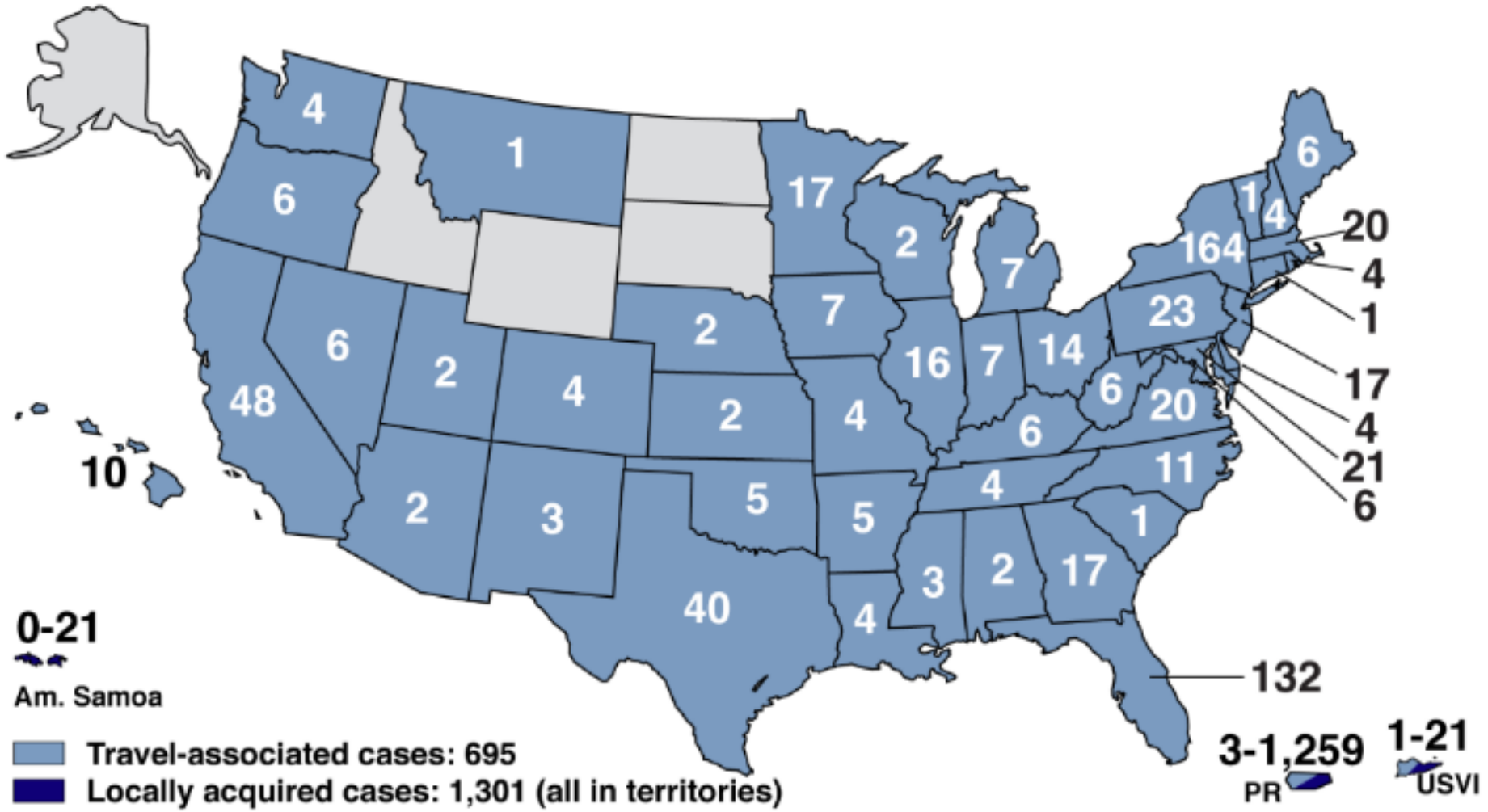
Potential for Imported Cases of Zika in the United States



- ~216 million passenger journeys to U.S. annually from areas with local Zika virus transmission
  - 34 M by air
  - 173 M by land
  - 9 M by sea

Sources: B Nelson et al. *PLoS Currents Outbreaks*, 5/31/2016; NY Times.

Zika Cases in the United States and U.S. Territories, 2015–2016



Zika Virus (Zika)

- Single stranded RNA virus
- Genus *flavivirus*, family *Flaviviridae*
- Closely related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses
- Primarily transmitted through the bite of an infected *Aedes* species mosquito (*Ae. aegypti* and *Ae. albopictus*)

Pathogenesis

Zika virus is a neurotropic virus that particularly targets neural progenitor cells.

Murine and human placental studies support the hypothesis that maternal infection leads to placental infection, followed by transmission of the virus to the fetal brain

-Kills neuronal progenitor cells

-Disrupts neuronal proliferation, migration, and differentiation, which slows brain growth and reduces viability of neural cells.

Zika virus is also associated with a higher rate of fetal loss throughout pregnancy, including stillbirths.

Placental insufficiency is the mechanism postulated to induce fetal loss later in pregnancy.

Transmission

- Bite of an infected mosquito
- Maternal-fetal transmission
- Sex (including vaginal, anal, and oral sex)
  - Semen: ZKV RNA clears after 3 months
  - Female genital tract secretions: ZKV detected on cervical mucus 14 days after onset of illness.
- Blood product transfusion
- Organ transplantation
- Laboratory exposure
- Zika virus has been detected in breast milk.
  - There are no reports of transmission of Zika virus infection through breastfeeding.
  - Based on available evidence, the benefits of breastfeeding outweigh any possible risk.

Incubation and viremia

Incubation period for Zika virus disease is 3 to 14 days.

Zika viremia ranges from a few days to 1 week.

Some infected pregnant women can have evidence of Zika virus in their blood longer than expected.

Virus remains in semen and urine longer than in blood.

Zika virus clinical disease course and outcomes

Clinical illness is usually mild.

Symptoms last several days to a week.

Severe disease requiring hospitalization is uncommon.

Fatalities are rare.

Research suggests that Guillain-Barré syndrome (GBS) is strongly associated with Zika; however only a small proportion of people with recent Zika infection get GBS.



Reported clinical symptoms among confirmed Zika virus disease cases

Symptoms	Number of patient (n =31)	%
Macular or popular rash	28	90
Subjective fever	20	65
Arthralgia	20	65
Conjunctivitis (non-purulent)	17	55
Myalgias	15	48
Headache	14	45
Retro-orbital pain	12	39
Edema	6	19
Vomiting	3	10

Clinical features: Zika virus compared to Dengue and Chikungunya

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

Clinical features: Zika virus compared to Dengue and Chikungunya

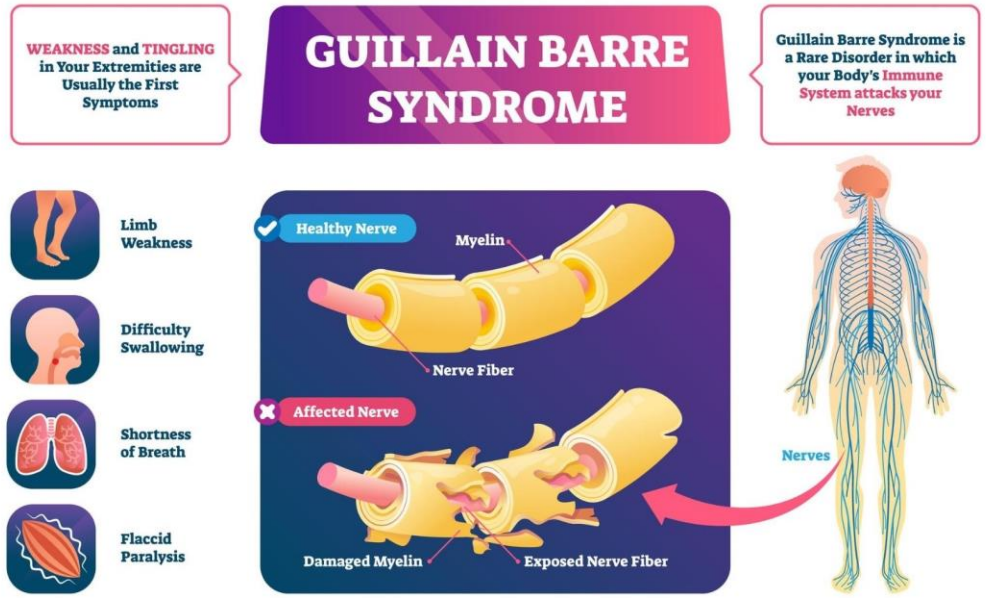
Features	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	-	-
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	+
Hemorrhage	-	++	-
Shock	-	+	-

THE LANCET

Published Online February 29, 2016

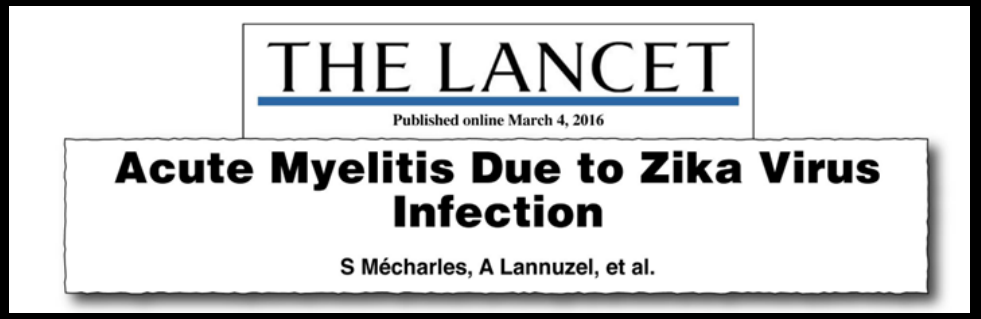
Guillain-Barré Syndrome Outbreak Associated with Zika Virus Infection in French Polynesia: A Case-Control Study

VM Cao-Lormeau, F Ghawché et al.



- From October 2013 to April 2014, French Polynesia experienced the largest Zika virus outbreak ever described (more than 32 000 patients were assessed for suspected Zika virus infection)
- During the same period, 42 cases of Guillain-Barré syndrome (autoimmune disease causing acute or subacute flaccid paralysis) were reported, in contrast to, contrasting with reports of five, ten, three, and three, in 2009, 2010, 2011, and 2012, respectively.

- **98% of 42 pts with GBS had anti-Zika virus IgM or IgG, and all (100%) had neutralizing antibodies against Zika virus compared with 56% of 98 pts in control group w/nAbs ($p<0.0001$)**
- **88% of 42 patients with GBS reported symptoms of Zika virus infection ~6 days before onset of neurological symptoms**
- **Based on attack rate for Zika virus of 66% in French Polynesia, risk of GBS in the general population during the outbreak was 24 /100,000 infections**





- Case report: In January 2016, a 15-year-old girl was admitted to a hospital in Pointe-a-Pitre, Guadaloupe, with left hemiparesis.
- Seven days previously presented to the emergency department with left arm pain, frontal headaches, and conjunctival hyperaemia, but no fever, signs of meningeal irritation, or sensory or motor deficits
- On day 2, she developed dysuria and urinary retention needing catheterisation, but no abnormal urinary frequency or urgency. The left-sided hemiparesis and pain worsened, and we noted loss of temperature sensation below the T2 dermatome.
- Spinal MRI showed lesions of the cervical and thoracic spinal cord. The cervical lesion was enlarged, suggesting of edema.
- High concentrations of Zika virus were detected on specific real-time reverse PCR in serum, urine, and cerebrospinal fluid on the second day of her admission.
- Zika virus infection should be considered in patients with acute myelitis living in or travelling from endemic areas, and further study should clarify the spectrum and incidence of neurological associations.

Testing Guidance: New Zika and Dengue Testing Guidance (November 2019) Testing Guidance | Zika Virus | CDC

Population	Asymptomatic pregnant women	Symptomatic pregnant patients	Pregnant women who have fetus with prenatal US findings consistent with congenital Zika virus infection who live in or traveled to areas with a risk of Zika	Symptomatic non-pregnant patients.
Whom to test?	• Zika: Routine test is not currently recommended (Living in or with recent travel to US and its territories • NAAT testing may still be considered up to 12 weeks after travel to an area with risk of Zika outside the US and its territories.	• Symptomatic after recent travel to areas with active dengue transmission and a risk of Zika. • Collect samples as soon as possible after the onset of symptoms and up to 12 weeks.		

Tests	• Zika virus serologic testing note recommended.
	  • IgM antibodies can persist for months to years following infection.
	  • Notable cross-reactivity between dengue IgM and Zika IgM antibodies
		• Collect at the same time: Dengue and Zika virus NAAT (serum) and Zika virus NAAT* on urine.
		• Dengue IgM antibody test is positive (no further testing).
		• Sex with someone who lives in or recently traveled to areas with a risk of Zika: only Zika NAAT (as above).
			• Zika virus NAAT and IgM testing on material serum/urine.
			• Zika virus NAATs are negative, and the IgM is positive, confirmatory PRNTs** should be performed against Zika and dengue
				• Zika testing is NOT currently recommended for this group based on the current epidemiology of these viruses.

**If the Zika NAAT is positive on a single specimen, the Zika NAAT should be repeated on newly extracted RNA from the same specimen to rule out false-positive NAAT results. If the dengue NAAT is positive, this provides adequate evidence of a dengue infection and no further testing is indicated.*

***PRNTs: Plaque reduction neutralization tests (PRNT) are quantitative assays that measure virus-specific neutralizing antibody titers. Confirmatory neutralizing antibody testing using PRNT is currently only available through a limited number of state health departments and CDC.*

How is Zika virus treated?

- There is no specific medicine or vaccine for Zika virus.
- Treat the symptoms.
- Get plenty of rest.
- Drink fluids to prevent dehydration.
- Take medicine such as acetaminophen (Tylenol®) to reduce fever and pain.
- Do not take aspirin and other non-steroidal anti-inflammatory drugs (NSAIDS) until dengue can be ruled out to reduce the risk of bleeding.
- If you are taking medicine for another medical condition, talk to your healthcare provider before taking additional medication.



Reporting of Zika in the United States

- Healthcare providers should report cases to their local, state, or territorial health department.
- State and territorial health departments are encouraged to report confirmed cases to CDC through ArboNET, the national surveillance system for arboviral diseases.
- Pregnant women with any lab evidence of possible Zika virus infection should be reported to the US Zika Pregnancy Registry.

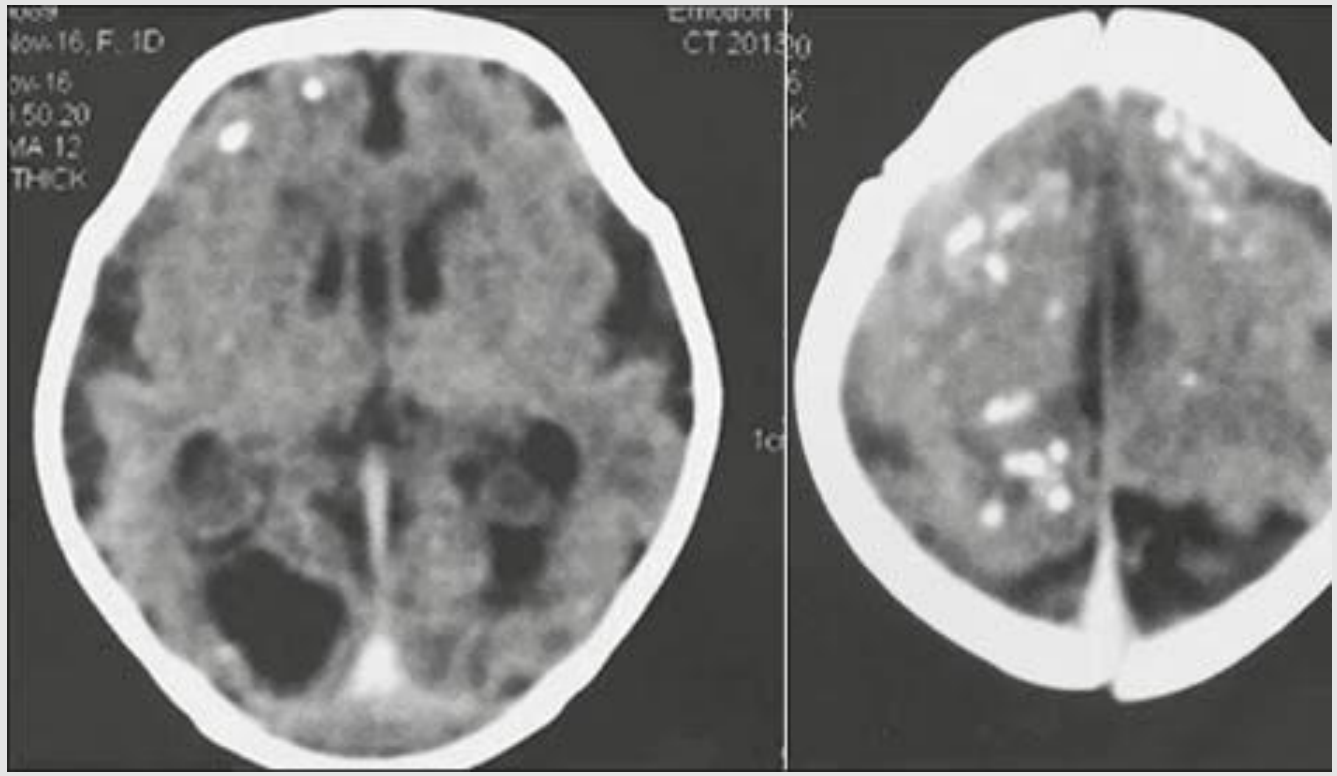


ArboNET



Congenital Zika Syndrome

- Severe microcephaly in which the skull has partially collapsed
- Decreased brain tissue with a specific pattern of brain damage, including subcortical calcifications.
- Damage to the back of the eye, including macular scarring and focal retinal pigmentary mottling.
- Congenital contractures, such as clubfoot or arthrogryposis.
- Hypertonia restricting body movement soon after birth
- Congenital Zika virus infection has also been associated with other abnormalities, including but not limited to brain atrophy and asymmetry, abnormally formed or absent brain structures, hydrocephalus, and neuronal migration disorders.



Histopathology

- Multiple congenital malformations:
  - Craniofacial malformations
  - Pulmonary hypoplasia
  - Fetal akinesia deformation sequence
  - Severe arthrogryposis.
- Histopathologic reports (brains of infants)
  - Tissue destruction
  - Calcifications
  - Gliosis
  - Necrosis
  - Loss of these cells early in development has been reported to substantially reduce the number of neurons generated.



Normal infant brain and head size



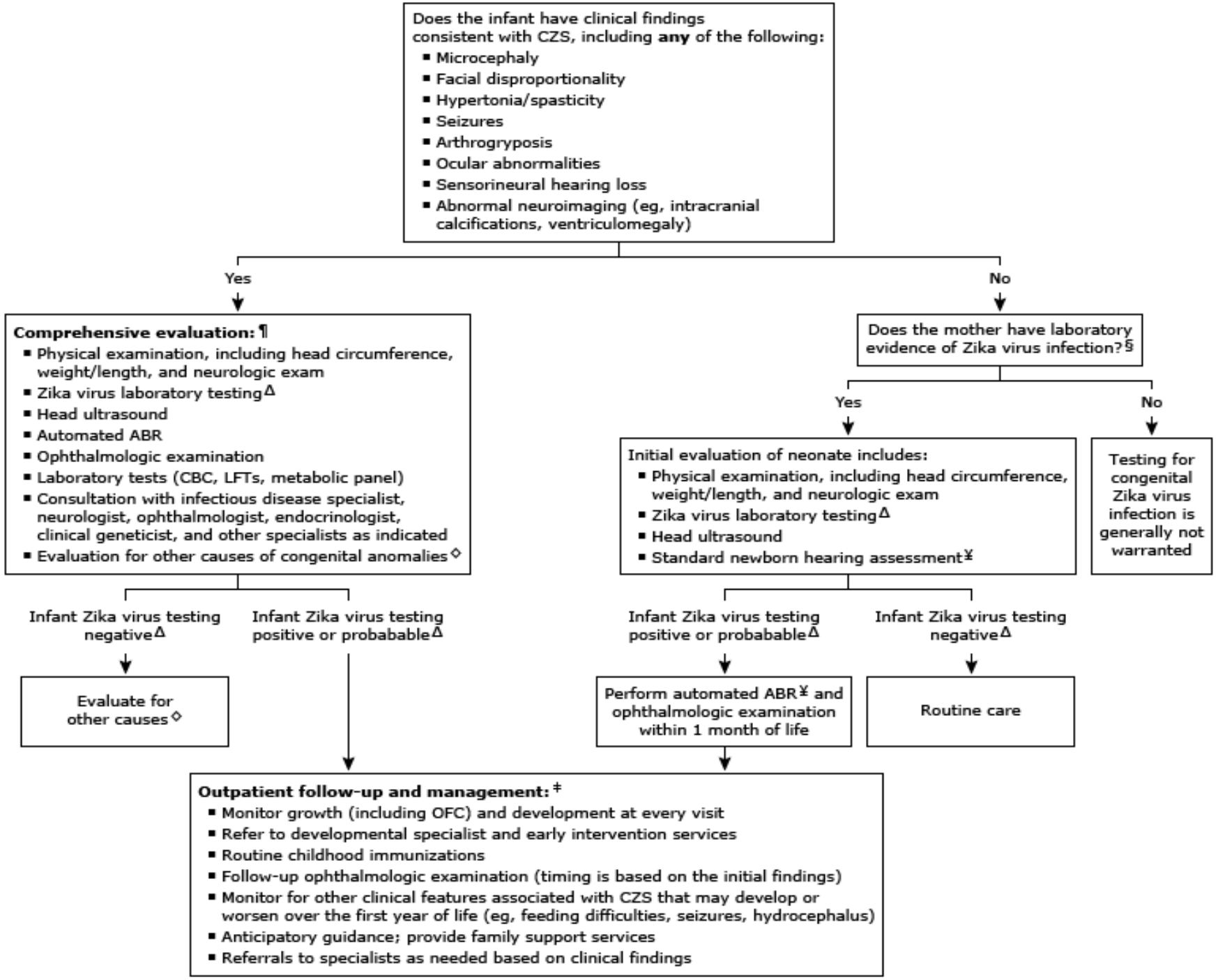
Microcephaly, Colombia 2015

Images: LatinAmericanScience.org

Microcephaly Attributed to Zika

- Microcephaly is a congenital malformation resulting in smaller than normal head size for age and sex.
- It has also been associated with other birth defects and neurologic conditions in children and adults.
- Neurologic sequelae may include seizures, vision or hearing problems, and developmental disabilities.
- There is now scientific consensus that Zika virus infection during pregnancy is a cause of microcephaly.
- It remains unknow, if a newborn who gets Zika virus infection around the time of birth will develop microcephaly after birth.

Evaluation


Does the infant have clinical findings consistent with CZS, including any of the following:
Microcephaly
Facial disproportionality
Hypertonia/spasticity
Seizures
Arthrogryposis
Ocular abnormalities
Sensorineural hearing loss
Abnormal neuroimaging (eg, intracranial calcifications, ventriculomegaly)
Yes
No
Comprehensive evaluation: ¶
Physical examination, including head circumference, weight/length, and neurologic exam
Zika virus laboratory testing Δ
Head ultrasound
Automated ABR
Ophthalmologic examination
Laboratory tests (CBC, LFTs, metabolic panel)
Consultation with infectious disease specialist, neurologist, ophthalmologist, endocrinologist, clinical geneticist, and other specialists as indicated
Evaluation for other causes of congenital anomalies ◇
Does the mother have laboratory evidence of Zika virus infection? §
Yes
No
Initial evaluation of neonate includes:
Physical examination, including head circumference, weight/length, and neurologic exam
Zika virus laboratory testing Δ
Head ultrasound
Standard newborn hearing assessment ¥
Testing for congenital Zika virus infection is generally not warranted
Infant Zika virus testing negative Δ
Infant Zika virus testing positive or probabable Δ
Infant Zika virus testing positive or probabable Δ
Infant Zika virus testing negative Δ
Evaluate for other causes ◇
Perform automated ABR ¥ and ophthalmologic examination within 1 month of life
Routine care
Outpatient follow-up and management: ‡
Monitor growth (including OFC) and development at every visit
Refer to developmental specialist and early intervention services
Routine childhood immunizations
Follow-up ophthalmologic examination (timing is based on the initial findings)
Monitor for other clinical features associated with CZS that may develop or worsen over the first year of life (eg, feeding difficulties, seizures, hydrocephalus)
Anticipatory guidance; provide family support services
Referrals to specialists as needed based on clinical findings

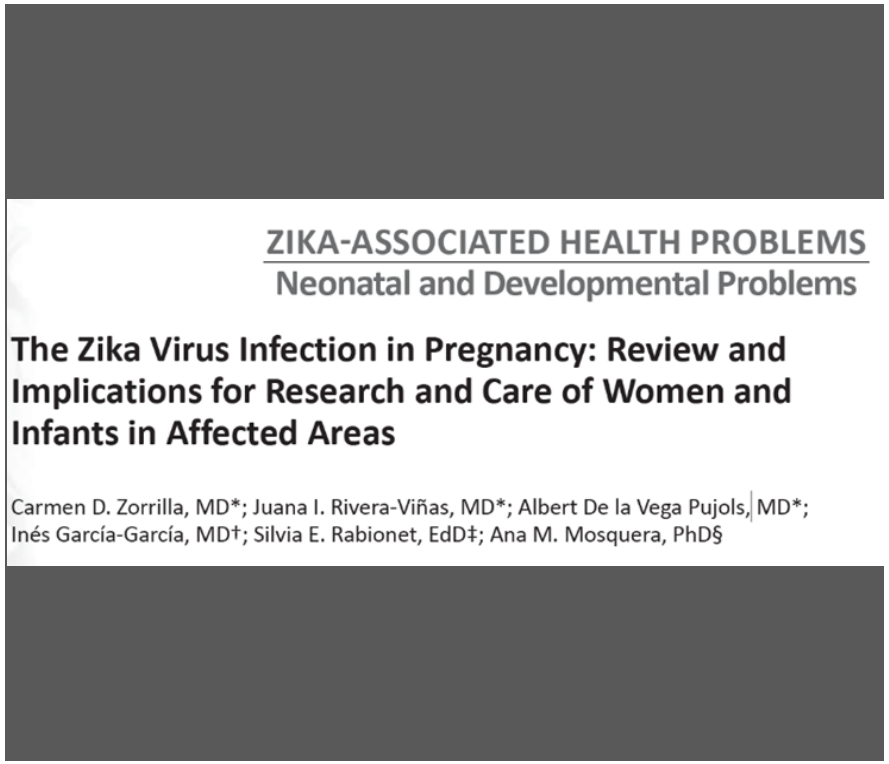
ZIKA-ASSOCIATED HEALTH PROBLEMS

Neonatal and Developmental Problems

The Zika Virus Infection in Pregnancy: Review and Implications for Research and Care of Women and Infants in Affected Areas

Carmen D. Zorrilla, MD*; Juana I. Rivera-Viñas, MD*; Albert De la Vega Pujols, MD*; Inés García-García, MD†; Silvia E. Rabionet, EdD‡; Ana M. Mosquera, PhD§

- Background:
  - Vanessa van der Linden, a neurologist in the Brazilian city of Pernambuco, saw (in August 2015) several babies with microcephaly whose mothers remembered having had a rash during their pregnancies.
  - In addition, her mother, Ana, another doctor, who works in Recife, saw 7 babies with microcephaly in 1 day. All of these mothers remembered having had a rash early in their pregnancies. Dr. Van der Linden alerted the Brazilian authorities of the increased number of cases of babies with microcephaly, subsequently Brazil Ministry of Health reviewed the birth certificates and alerted the WHO.
- Clinical manifestations
  - Incubation period: 3 to 14 days (no change in pregnant woman)
  - Maculopapular pruritic rash (44–93% of cases)
  - Conjunctivitis (35–58%)
  - Myalgia and arthralgia (39–64%)
  - Headache (53%)
  - Adenopathy (40%)
  - GBS: only one case was reported which suggests that the main target of this neurotopic virus during pregnancy might be the fetus's and not the mother's CNS.

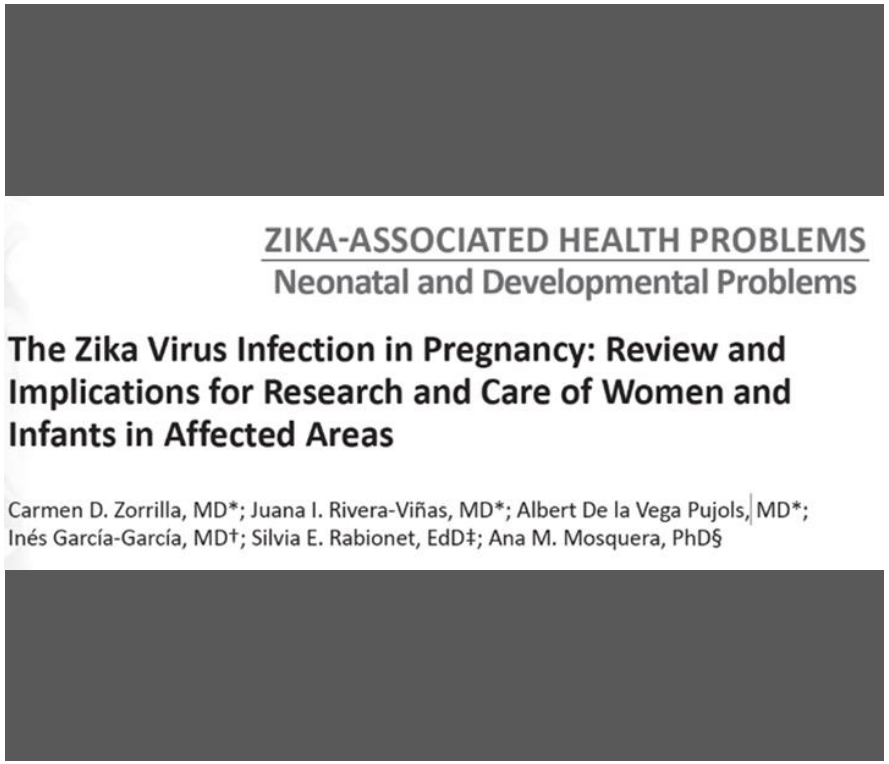


Data from Puerto Rico

- Official reported number of pregnant women with laboratory evidence of possible ZKV infection in Puerto Rico reached 3,300 by early 2017, the largest number of ZIKV-infected pregnant women in the USA.
- The CDC and the PR Department of Health carried out a survey (from August through December 2016) of 2,364 Puerto Rico residents having had a recent live birth (the Pregnancy Risk Assessment Monitoring System Zika Postpartum Emergency Response: PRAMS-ZPER).

Puerto Rico's response

- Plan included an awareness campaign, recommendations for vector control, guidance for the testing of pregnant women during, prenatal care (modified according to evidence), recommending ZIKV testing of all pregnant women during each trimester and acute testing for all symptomatic patients.
- Pregnant women be referred for ultrasound evaluation and care, the collection of infant blood and placental samples at delivery, a recommendation regarding the subspecialty evaluation of neonates, and recommending the longitudinal follow-up of the infants.
- Ob-Gyn Department of the University of Puerto Rico School of Medicine established, in collaboration with the Carlos Albizu University (CAU), a multidisciplinary clinic for pregnant women with ZIKV for dedicated care within the model of group prenatal care.



Brazil

- Cohort study of 345 pregnant women, of which 182 (53%) were ZIKV positive, there was a 10-times higher frequency of emergency cesarean sections during labor, mostly due to suspected fetal hypoxia (fetal distress).
- There were similar rates of fetal losses between ZIKV positive and negative.

Colombia

- Epidemic has so far been linked to relatively few pregnancy complications.
- The rate of term deliveries for the 616 women with a ZIKV diagnosis was 82%, and the rate of preterm birth was 8%; 2% of the infants.

Puerto Rico

- PR Zika Pregnancy Surveillance report (found on the PR Department of Health website), by the end of 2016, there had been 1,307 live births, and 1,203 women were still pregnant.
- The rate of pregnancy loss prior to 20 weeks was 2.8% (37/1307), and the number of pregnancy losses after 20 weeks was 13.
- These numbers seem to indicate a relatively low rate of pregnancy loss, but there might be a bias in reporting some of the outcomes.

Zika Pregnancy Registries

US Zika Pregnancy Registry



Zika Active Pregnancy Surveillance System (Puerto Rico)



Proyecto Vigilancia de Embarazadas con Zika (Colombia)














OFF!
DEEP WOODS
DRY
BURT'S BEES
CITRONELLA
Aromaflage
REPEL
LEMON EUCALYPTUS

Tropical Medicine and Infectious Disease

MDPI

Case Report

Fatal Dengue, Chikungunya and Leptospirosis: The Importance of Assessing Co-infections in Febrile Patients in Tropical Areas

Jaime A. Cardona-Ospina [1,2], Carlos E. Jiménez-Canizales [1,2,3], Heriberto Vásquez-Serna [3], Jesús Alberto Garzón-Ramírez [4], José Fair Alarcón-Robayo [5], Juan Alexander Cerón-Pineda [4] and Alfonso J. Rodríguez-Morales [1,6,*]

- Febrile patient from tropical areas, in which emerging arboviruses are endemic, represents a diagnostic challenge, and potential co-infections with other pathogens.
- An 87-year-old woman from Colombia (Junín, a rural area of the municipality of Venadillo, Tolima, Colombia, endemic for dengue, chikungunya and Zika) complained of upper abdominal pain, arthralgia, myalgia, reduction in appetite, malaise and intermittent fever accompanied with progressive jaundice.
- Hospital course
  - After her admission in ICU, she had one episode of hypoglycemia and her renal function gradually worsened.
  - Alongside supportive treatment, antibiotic therapy with cephazolin was initiated.
  - Her cardiac and pulmonary status quickly deteriorated after 24 hour.
  - She required ventilatory and vasopressor support. In the next hours, the patient evolved to pulseless electrical activity and died.
- Blood samples were tested at the Public Health Laboratory of Tolima.
  - Dengue IgM-antibodies (44.4% sensitivity, 99.1 specificity) and non-structural protein 1 (NS1) dengue protein through enzyme-linked immunosorbent assay (ELISA) (93.9% sensitivity, 97.4% specificity) were both positive.
  - Titers against Leptospira interrogans (serogroup Tarassovi, serovar Tarassovi, 1:400) were detected through non-paired microagglutination test (MAT) (93.8% sensitivity, 90.4% specificity).
  - Chikungunya infection was confirmed with reverse transcription polymerase chain reaction (RT-PCR) (90% sensitivity, 100% specificity).
  - Zika RT-PCR was negative.

Leptospirosis

Microbiology: spiral-shaped, highly motile aerobic spirochetes

Epidemiology: zoonotic disease, occurs in both temperate and tropical regions. Humans are infected incidentally after animal or environmental exposure.

Risk: occupational, recreational, household exposure, flooding/hurricane

IP: 6-26 days

Clinical manifestations: asymptomatic, self-limited, severe/fatal presentation.

Diagnosis: serology, molecular test, culture and antigen detection

Leptospirosis

Clinical Manifestations	Laboratories	Imaging	Treatment

• Fever
• Rigors
• Myalgias
• Headache
• Conjunctival suffusion
• Nausea, vomiting, diarrhea
• Nonproductive cough
• Muscle tenderness
• Splenomegaly
• Lymphadenopathy
• Pharyngitis
• Hepatomegaly
• Muscle rigidity
• Abnormal respiratory auscultation
• Skin rash
• Aseptic meningitis
• Weil's disease
  • ARDS
  • Renal failure
  • Jaundice
  • Pulmonary hemorrhage
	• Wbc: 3000 to 26,000
	• Thrombocytopenia
	• Hyponatremia
	• U/A: proteinuria, pyuria, microscopic hematuria.
	• Mild to moderate elevations of hepatic transaminases.
	• Serum bilirubin.
	• CSF
	  • Lymphocytic or neutrophilic pleocytosis
	  • Minimal to moderately elevated protein.
	  • Normal glucose concentration.
		CXR
		• Small nodular densities, which can progress to confluent consolidation or a ground-glass appearance
		• Infiltrates may represent alveolar hemorrhage, ARDS, or pulmonary edema.
			• Mild disease: doxycycline
			• Severe disease
			  • Ceftriaxone 1-2 gm IV daily.
			  • Cefotaxime 1g IV every 6 hours.
			  • Penicillin G 1.5 million units IV every 6 hours.


thank you
danke
謝謝
ngiyabonga
рахмат
teşekkür ederim
Баярлалаа
спасибо
gracias
dank je
tapadh leat
faafetai lava
vinaka
спасибі
blagodaram
misaotra
matondo
paldies
grazzi
mahalo
kiitos
dankie
nanni
nandri
dhanyavad
mauruuru
köszönöm
akun
dankon
ačiū
хвала
asante
manana
obrigada
tenki
bedankt
bayarlalaa
grâcie
hvala
enkosi
dziękuję
djiere dieuf
tau
mochchakkeram
murakoze
chokrane
дякую
mamnun
chnorakaloutioun
gratias ago
grâcies
sulpáy
go raibh maith agat
sukriya
kop khun krap
ţaiku
sagolun
sobodi
dēkuji
obrigado
mësi
didi madloba
ありがとう
arigatô
takk
dakujem
trugarez
najis tuke
tanemirt
grazie
rahmet
diolch
dhanyavadagalu
shukriya
mercé
мерси
terima kasih
kam sah hamnida
rahmat
ευχαριστώ
তোমাকে ধন্যবাদ
xièxie
감사합니다
merci