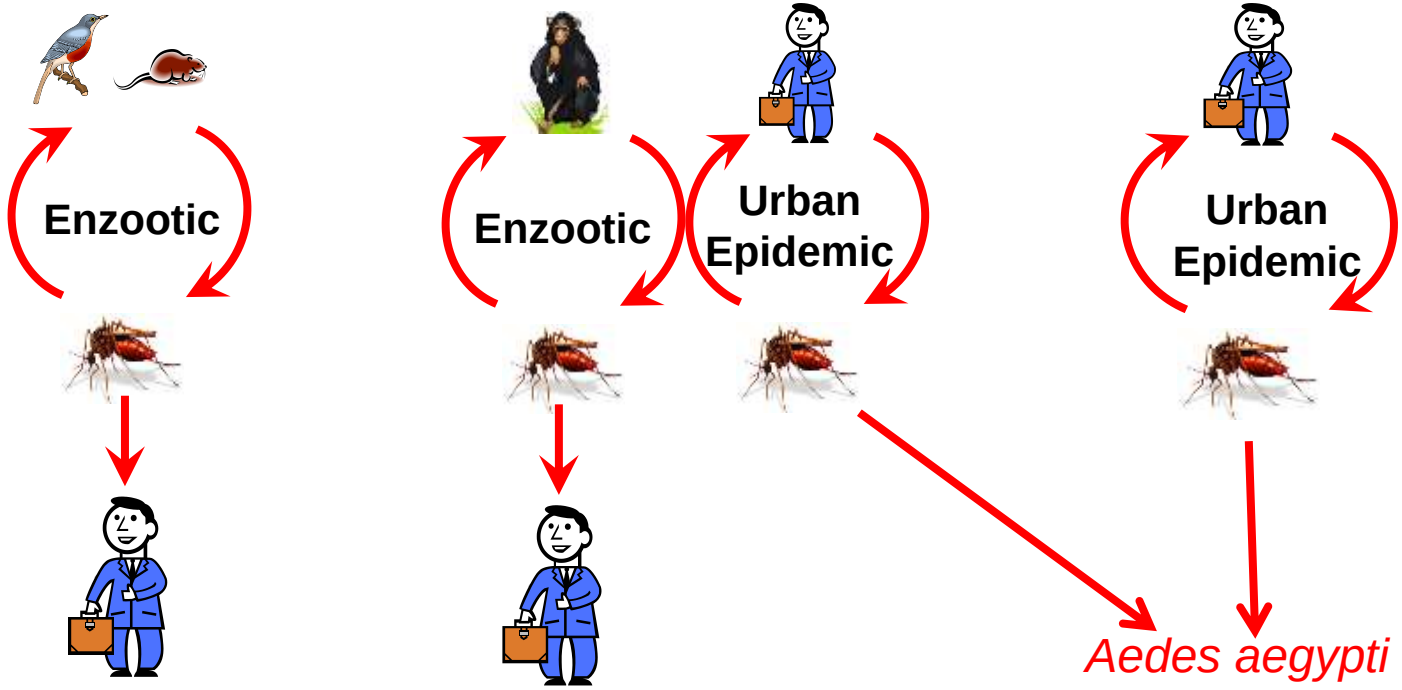
IPFA 23rd International Workshop

Epidemiology and Pathogenicity of Arbovirus Infections, with Focus on Zika Virus

May 26, 2016

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

General Patterns of Mosquito-Borne Arboviral Disease Transmission



Culex spp mosquitoes
West Nile virus
Japanese encephalitis

Aedes spp mosquitoes
Haemogogus spp mosquitoes
Yellow fever
Chikungunya
Zika

Aedes aegypti +/-
Aedes albopictus
Dengue
Urban yellow fever
Urban chikungunya
Urban Zika

Clinical Syndromes Associated with Arbovirus Infection

- Asymptomatic
  - Range from <10% to >70%
  - Often age-dependent
  - Often depends on immune status and underlying medical conditions
- Neuroinvasive disease
  - Meningitis
  - Encephalitis
  - Acute flaccid paralysis
- Hemorrhagic fever
- Fever, rash, arthralgia

Some degree of overlap occurs with these syndromes

Important Mosquito-Borne Flaviviruses

Pathogen	Enzootic Vector	Syndrome
Japanese encephalitis	*Cx. tritaeniorhynchus*	Encephalitis
West Nile virus	*Cx. pipiens, quinquefasciatus, tarsalis*	Encephalitis
St. Louis encephalitis	*Cx. pipiens, quinquefasciatus, tarsalis*	Encephalitis
Murray Valley encephalitis	*Cx. annulirostris*	Encephalitis
Yellow fever	*Ae. africanus* and others, *Haemogogus spp*	Hemorrhagic fever
Dengue	None*	Hemorrhagic fever
Zika	*Ae. africanus and others*	Fever, rash, birth defects

* Enzootic strains circulate in *Aedes* spp.

Important Alphaviruses

Pathogen	Enzootic Vector	Syndrome
Venezuelan equine encephalits	*Culex spp.*	Encephalitis
Eastern equine encephalitis	*Cs. melanura, morsitans*	Encephalitis
Western equine encephalitis	*Cx. tarsalis*	Encephalitis
O'nyong nyong	*Anopheles funestus* and *An. gambiae*	Fever, polyarthralgia
Chikungunya	*Aedes spp.*	Fever, polyarthralgia
Ross River	*Cx. annulirostris, Ae. vigilax, Ae. camptorhynchus*	Fever, polyarthralgia

Important Mosquito-Borne Bunyaviruses

Pathogen	Enzootic Vector	Syndrome
Rift Valley fever	*Aedes spp*., sandflies	Hemorrhagic fever
La Crosse encephalitis	*Ae. triseriatus*	Encephalitis

Viruses Transmitted by *Aedes aegypti* and *Aedes albopictus* Mosquitoes

Virus	*Aedes aegypti*	*Aedes albopictus*
Dengue 1–4	X	X
Chikungunya	X	X
Yellow fever	X	
Zika	X	X

Weaver SC. Antiviral Res 2010

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. Lancet Infect Dis 2014

Aedes aegypti: A Particularly Dangerous Vector

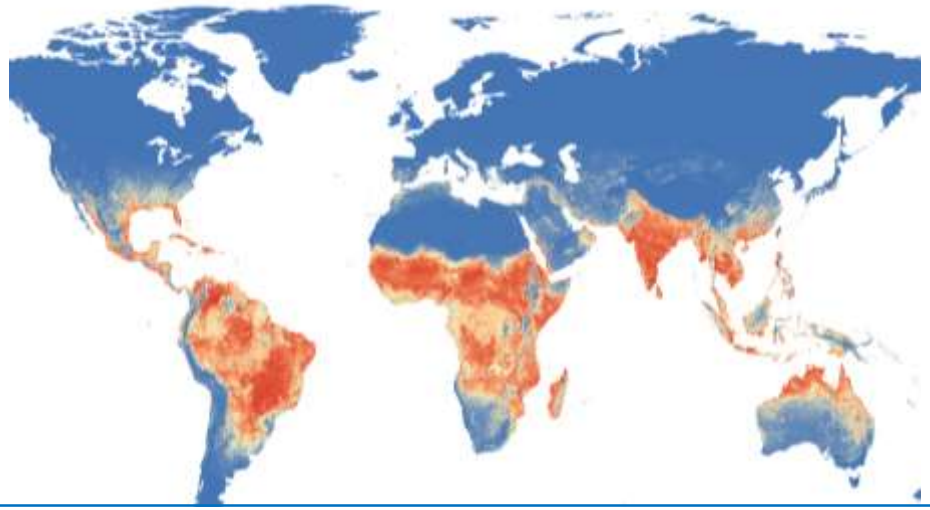
- **Also the primary vector of:**
  - Dengue
  - Yellow fever
  - Chikungunya
- **'Urban' mosquito; lives in close proximity to humans and prefers to bite humans**
- **Short flight range (typically 200m)**
- **Feeds on multiple hosts in a single gonotrophic cycle**
- **Erratic egg laying behavior**
- **Difficult to control**
  - No magic bullet

Aedes aegypti Control Strategies

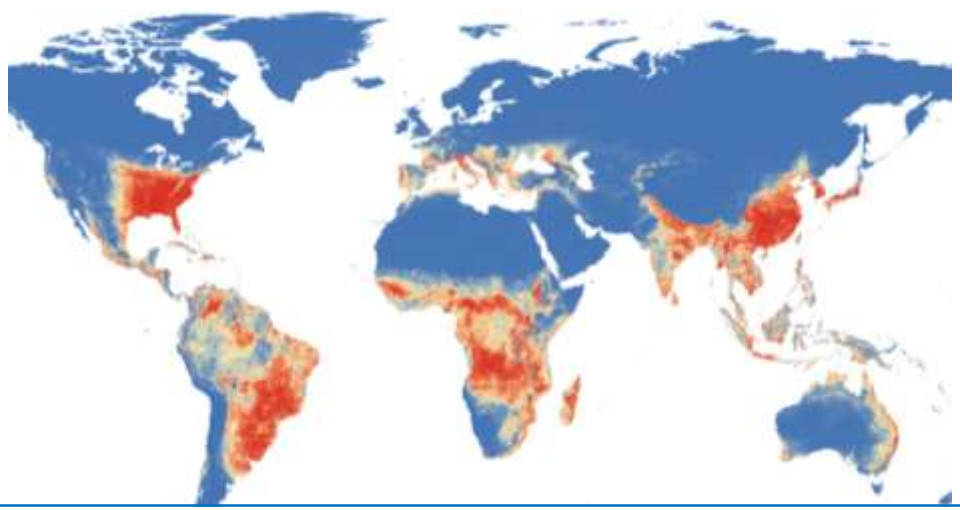
- Target immature stages
  - Oviposition traps
  - Larvicides
  - Source reduction
- Target adult mosquitoes
  - Hand-held or truck mounted spraying
  - Indoor/outdoor residual spraying
  - Aerial spraying

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

Aedes aegypti



Aedes albopictus



Dengue Virus Types 1–4: Approximate Geographic Distribution

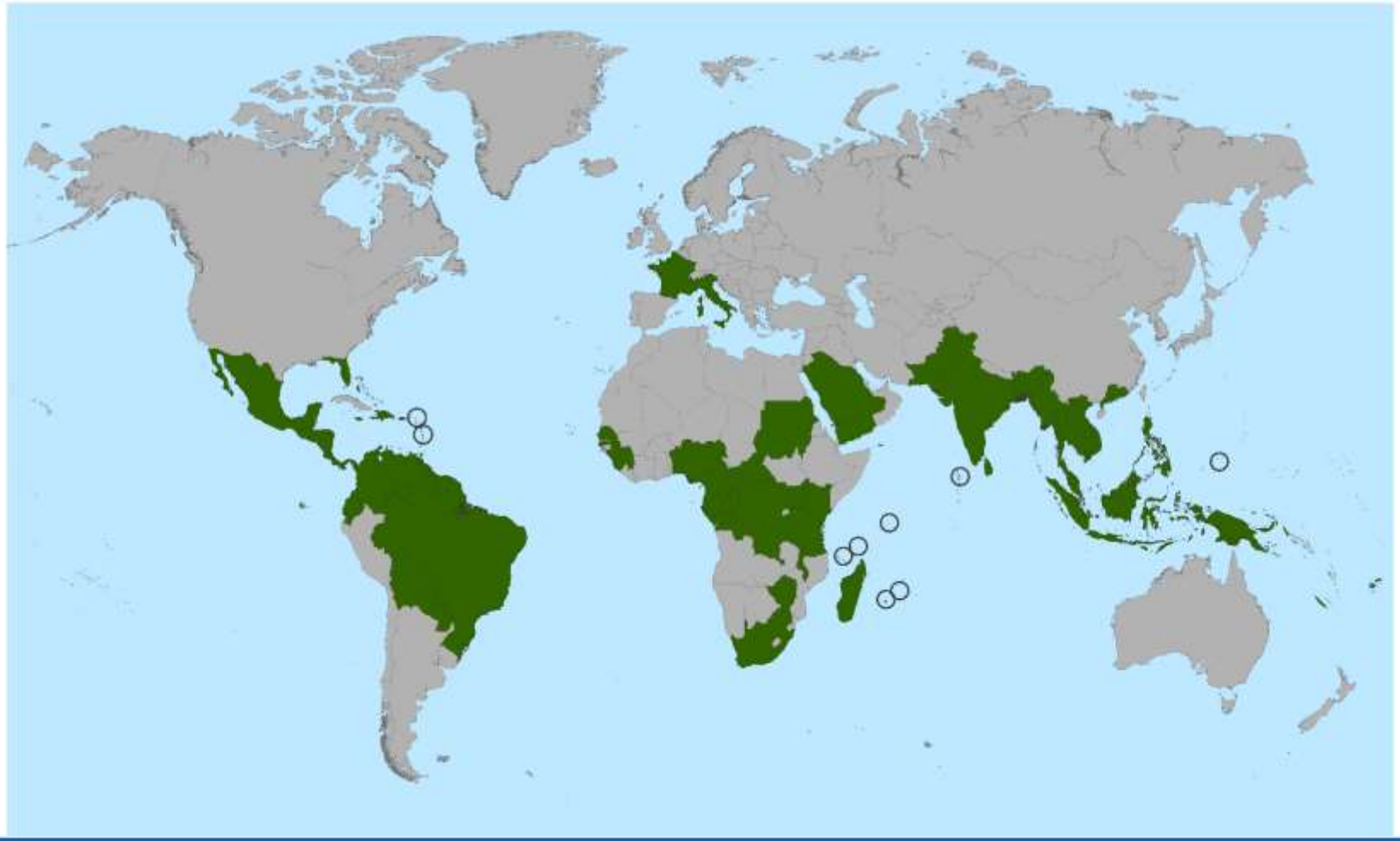
Bhatt S. Nature 2013

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. Nature 2013

Chikungunya Virus: Approximate Geographic Distribution



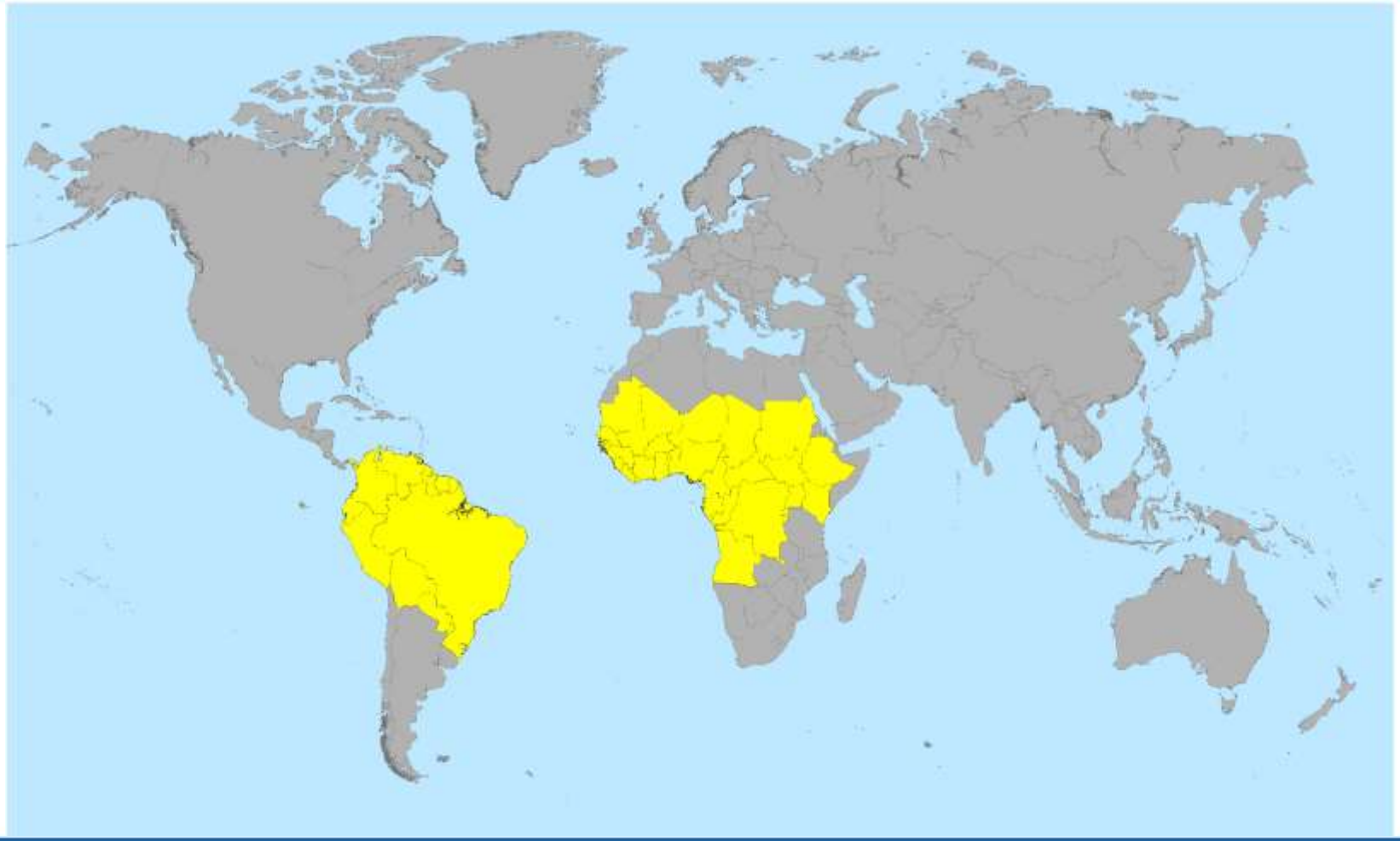
Available at http://www.cdc.gov/chikungunya

Chikungunya Virus Epidemiology

- **Large outbreaks with high infection rates (≥30%)**
- **Majority (72%–97%) of infected people symptomatic**
- **Over 1 million suspected cases reported in 2014**
  - Mostly in the Caribbean, and Central and South America

Staples JE. N Engl J Med 2014

Yellow Fever Virus: Approximate Geographic Distribution



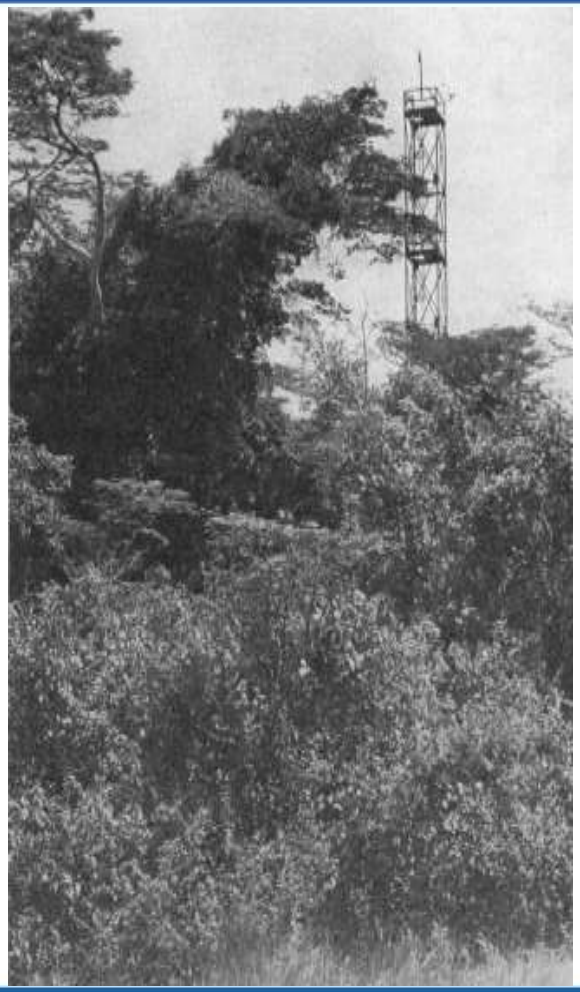
Jentes ES. Lancet Infect Dis 2011

Yellow Fever Virus Epidemiology

- 30% of population infected during urban outbreaks
- 10%–20% infected people develop clinical disease
- 85% of reported cases from sub-Saharan Africa
- First large urban outbreak in Africa in 2 decades now occurring

MMWR 2010;59(RR-7)

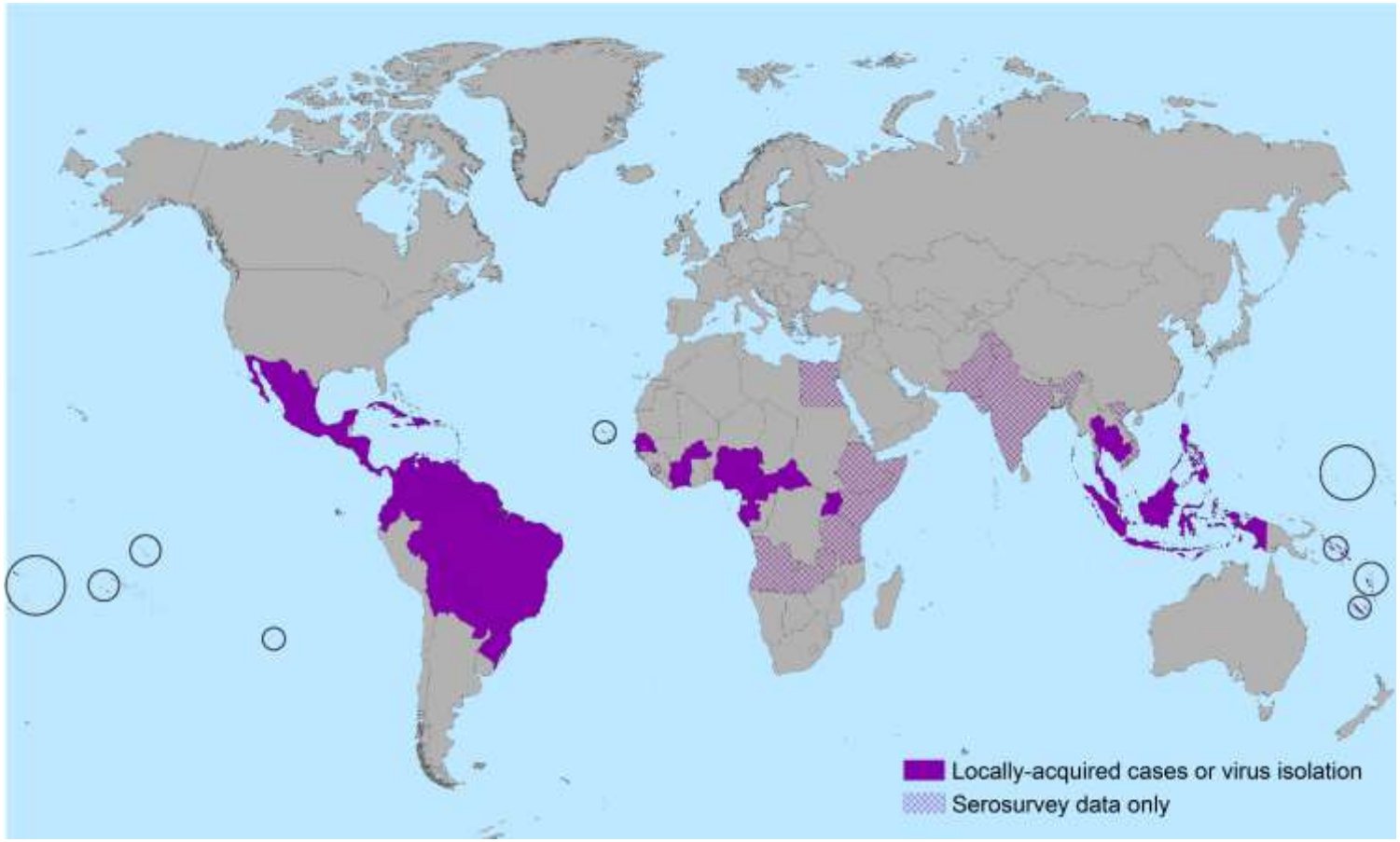
Zika Forest, Kisubi, Uganda



Zika Virus Disease Epidemiology

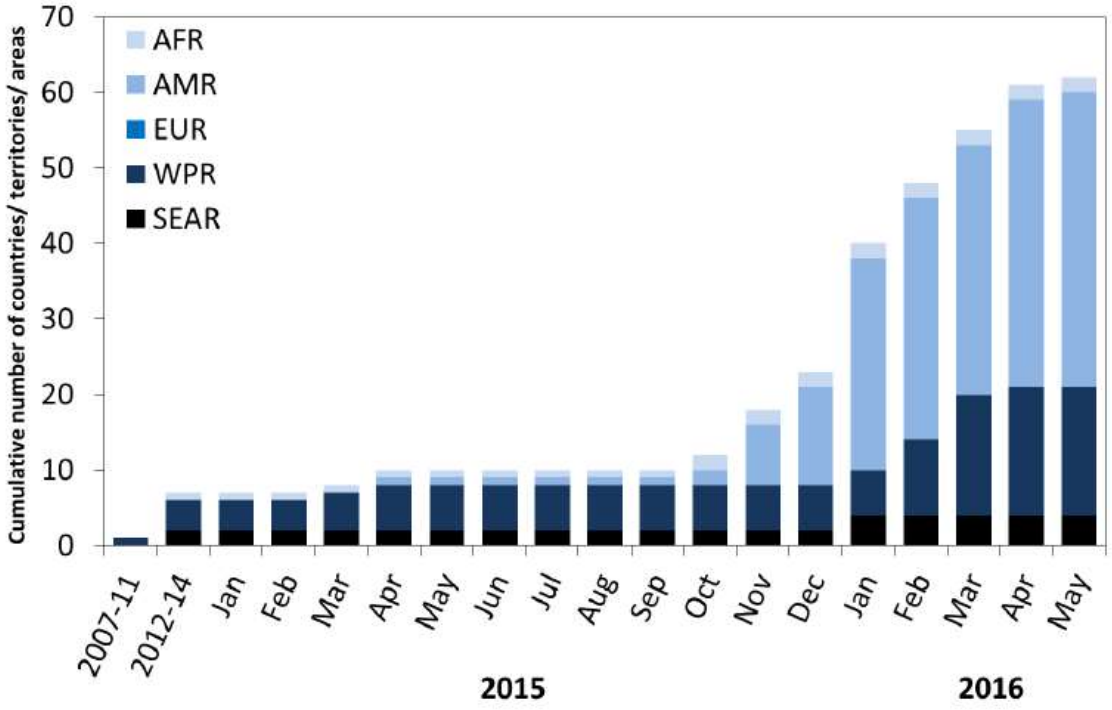
- First isolated from a monkey in 1947
- Before 2007, only sporadic human disease cases reported from Africa and southeast Asia
- 2007 outbreak in Yap resulted in an estimated 900 cases (population 7,391); estimated attack rate 73%
- In 2014–2015, >30,000 suspected cases reported from French Polynesia and other Pacific islands

Countries or Territories with Reported Local Transmission of Zika Virus (as of April 2016)

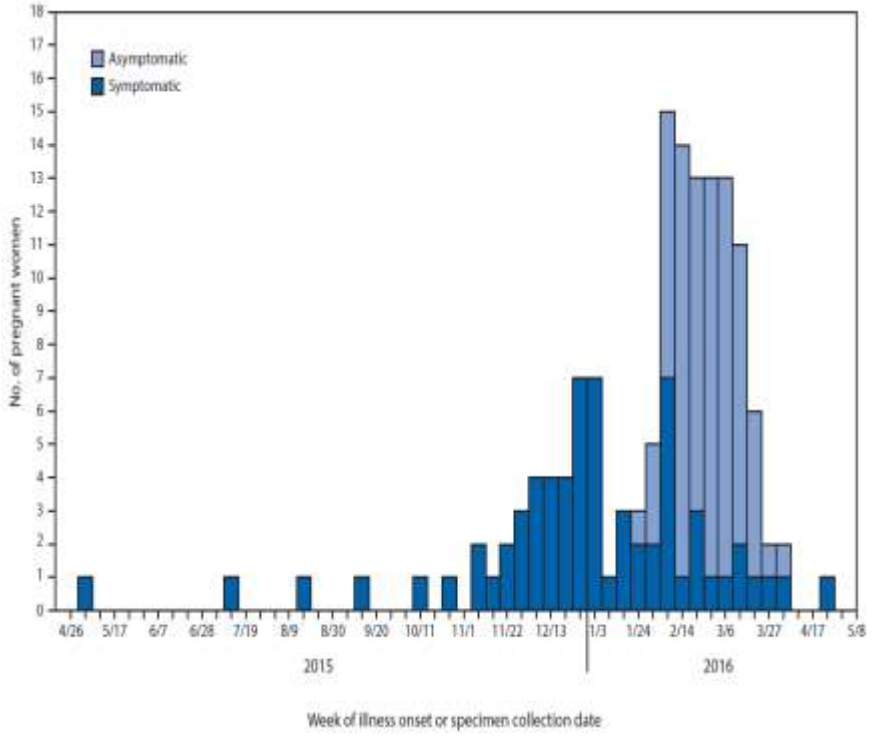


Cumulative Number of Countries, Territories, and Areas by WHO Region Reporting Mosquito-Borne Zika Virus Transmission

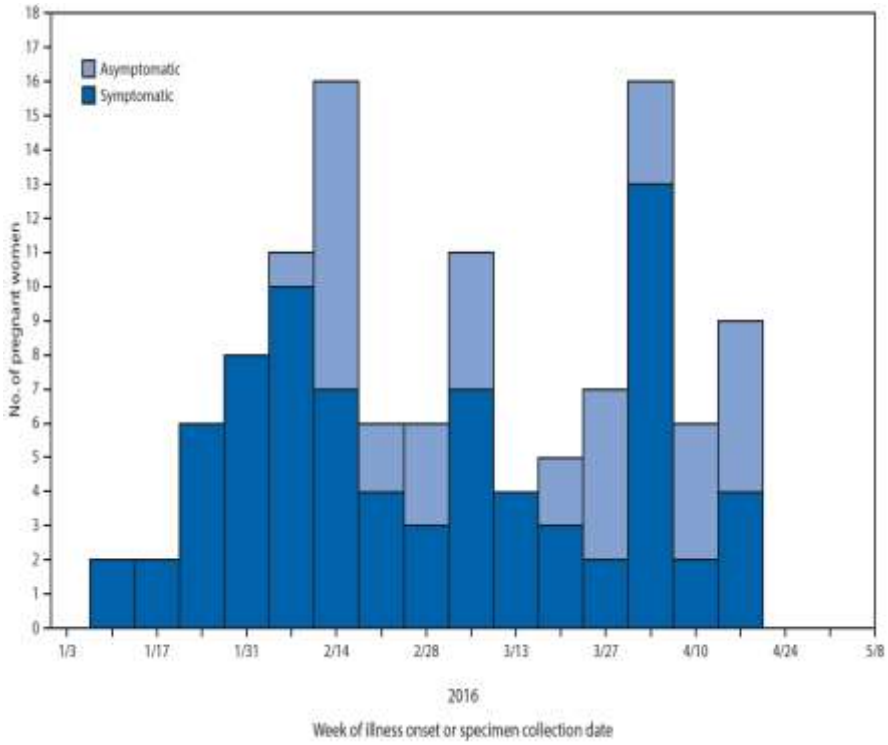
- 58 countries report continuing transmission
- 45 experienced a first outbreak since 2015
- 9 countries reported sexual transmission
- All current outbreaks associated with Asian genotype



Zika Virus in Pregnant Women in the US States and Territories, by Date of Symptom Onset or Identification



50 US States & DC,
August 1, 2015 – May 12, 2016, N = 157



US Territories,
January 3, 2016–May 12, 2016, N = 122

Non-Mosquito Modes of Transmission

- Documented
  - Intrauterine
  - Intrapartum from viremic mother to newborn
  - Sexual
  - Laboratory exposure
  - Blood transfusion
- Possible
  - Organ or tissue transplantation
  - Breast milk

Sexual Zika Virus Transmission

- What is known
  - To date: man to woman or man to man
  - All published reports to date have been from symptomatic men
  - Transmission can occur before symptom onset
  - Most transmissions have occurred during or shortly after symptoms
  - Virus present in high titer in semen
  - Viral RNA can persist in semen for at least 62 days after symptom onset
- What is not known
  - Duration of risk
  - Absolute risk
  - Female to male transmission

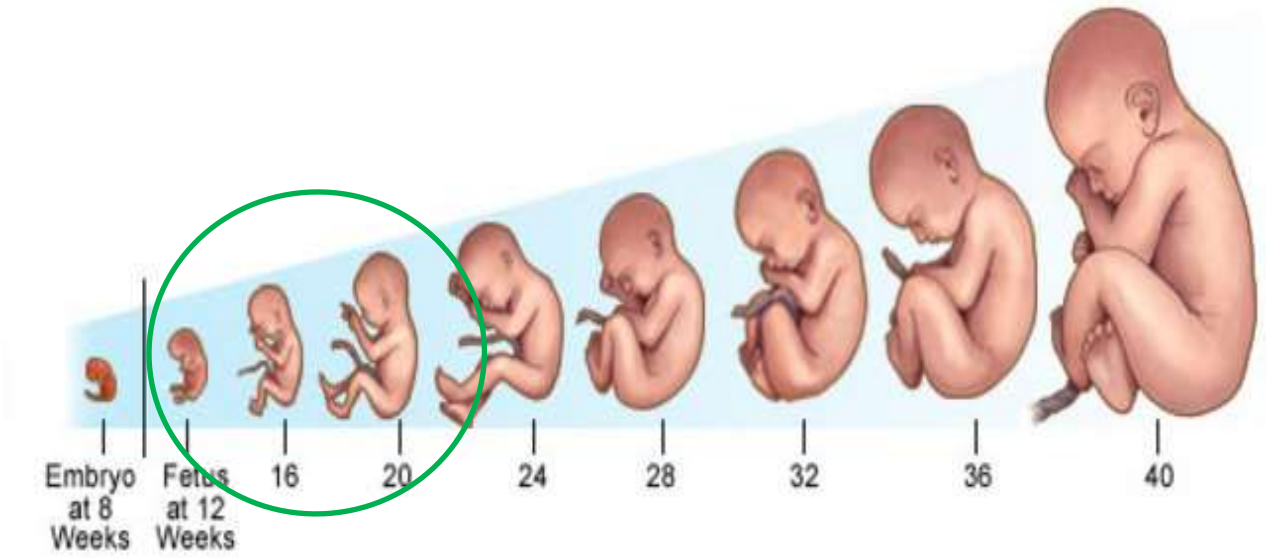
Zika Virus – Acute Disease

- Symptomatic proportion
  - 18% Yap outbreak serosurvey
  - 26% French Polynesia blood donors
- Symptoms (Yap outbreak)
  - Rash (90%), fever (65%), arthralgia (65%), conjunctivitis (55%), myalgia (48%), headache (45%)
- Rash is maculopapular and pruritic
- Case reports
  - Hematospermia, hearing changes, swelling hands and ankles, subcutaneous bleeding
  - Thrombocytopenia common; sometimes severe (ITP?)

Zika Virus: Newly Identified Clinical Manifestations

- Fetal loss
- Microcephaly and other congenital anomalies
- Guillain-Barré syndrome or other neurological disease manifestations
- Thrombocytopenia

Severe Microcephaly and Timing of Prenatal Zika Virus Infection



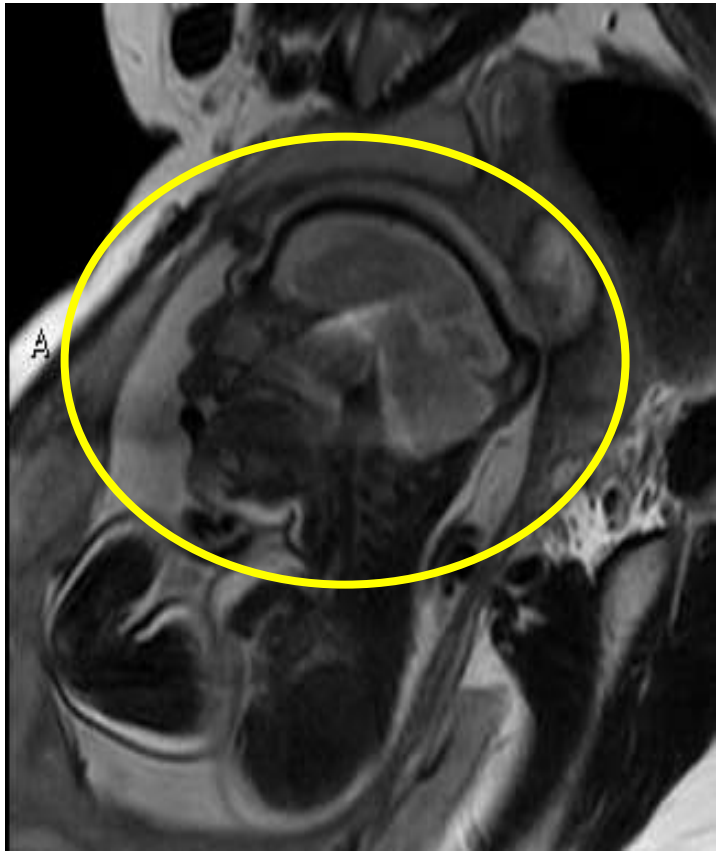
CNS development //

Young adulthood

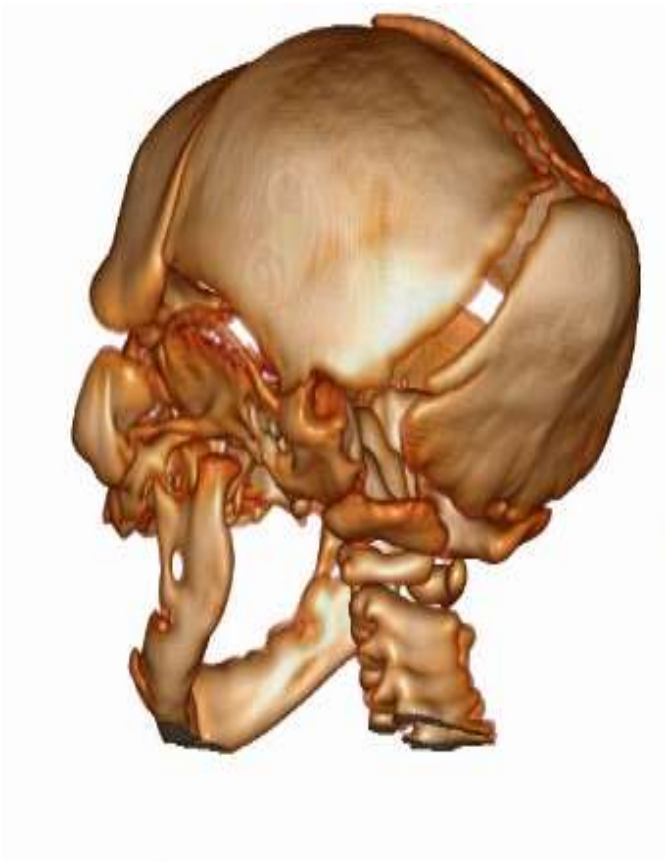
Prenatal Zika Virus Infection – Cranial Morphology
Fetal Brain Disruption Sequence

Courtesy of Dr. Bill Dobyns & Dr. André Pessoa

Prenatal Zia Virus Infection – Cranial Morphology Intrauterine and Postnatal Imaging

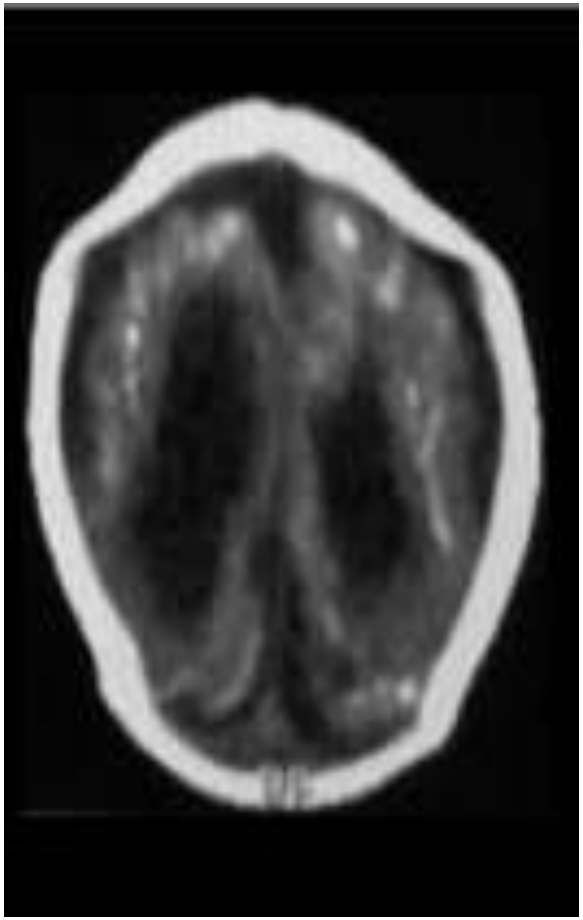


Fetal MRI at 31 weeks gestation



3D CT reconstruction at 3 months of age

Prenatal Zika Virus Infection – Brain and Eye Defects



Images courtesy of Dr. Bill Dobyns & Dr. André Pessoa

Fundus of presumed Zika syndrome Ventura et al.

Prenatal Zika Virus Infection – Congenital Contractures

Photos courtesy of Dr. André Pessoa

Unknowns: Zika and Birth Defects

- Risk of microcephaly
- Full spectrum of illness
- Co-factors that may increase or decrease risk
- Risk, if any, of pre-conception infection
- Persistent RT-PCR positivity in pregnant women

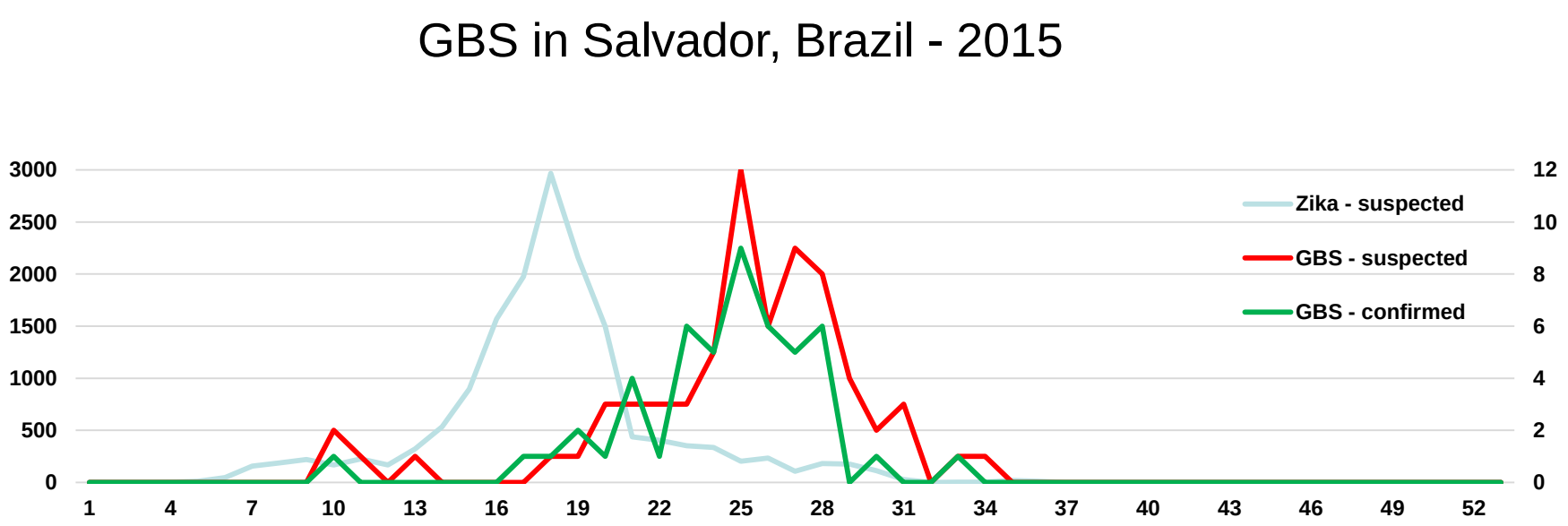
Zika Virus and Neurological Disease

- GBS in French Polynesia: Case-control study
  - 100% of GBS and 56% had neutralizing Abs to Zika
  - 88% of GBS had transient illness median 6 days previously
  - Acute motor axonal neuropathy (AMAN) type; although anti-ganglioside Abs rarely present
  - Rapid evolution of disease

- 13 Central/S. American, Caribbean countries with increased reports of GBS following introduction of Zika virus

- Case reports of other neurologic illnesses associated with Zika virus
  - Encephalitis
  - Anterior Myelitis
  - Acute Disseminated Encephalomyelitis [ADEM]

Strong Geo-Temporal Association between Zika and GBS



Case-Control Study: GBS in Salvador, Brazil

	Odds Ratio	95% CI
Preceding illness	**18.1**	**6.9-47.5**
Rash	15.7	5.8-42.4
Conjunctivitis	7.4	2.2-25.1
Nausea/vomiting	7.4	2.2-25.1
Pruritus	6.8	2.6-17.8
Headache	6.5	2.8-15.0
Retro-orbital pain	6.4	2.4-17.5
Myalgia	6.4	2.7-15.5
Fever	5.8	2.5-13.6
Arthralgia	4.8	2.0-11.3
Diarrhea	3.7	1.2-11.3

Summary Zika and Neurological Disease

- GBS
  - Frequency unknown; 1:5000
  - Increasing evidence of an association with Zika
  - Unusual characteristics
    - Short interval from acute illness to GBS
    - Rapid progression to clinical nadir
    - Paresthesias
- Other syndromes – unclear association
  - Encephalitis
  - Acute disseminated encephalomyelitis
  - Anterior myelitis

Thank You

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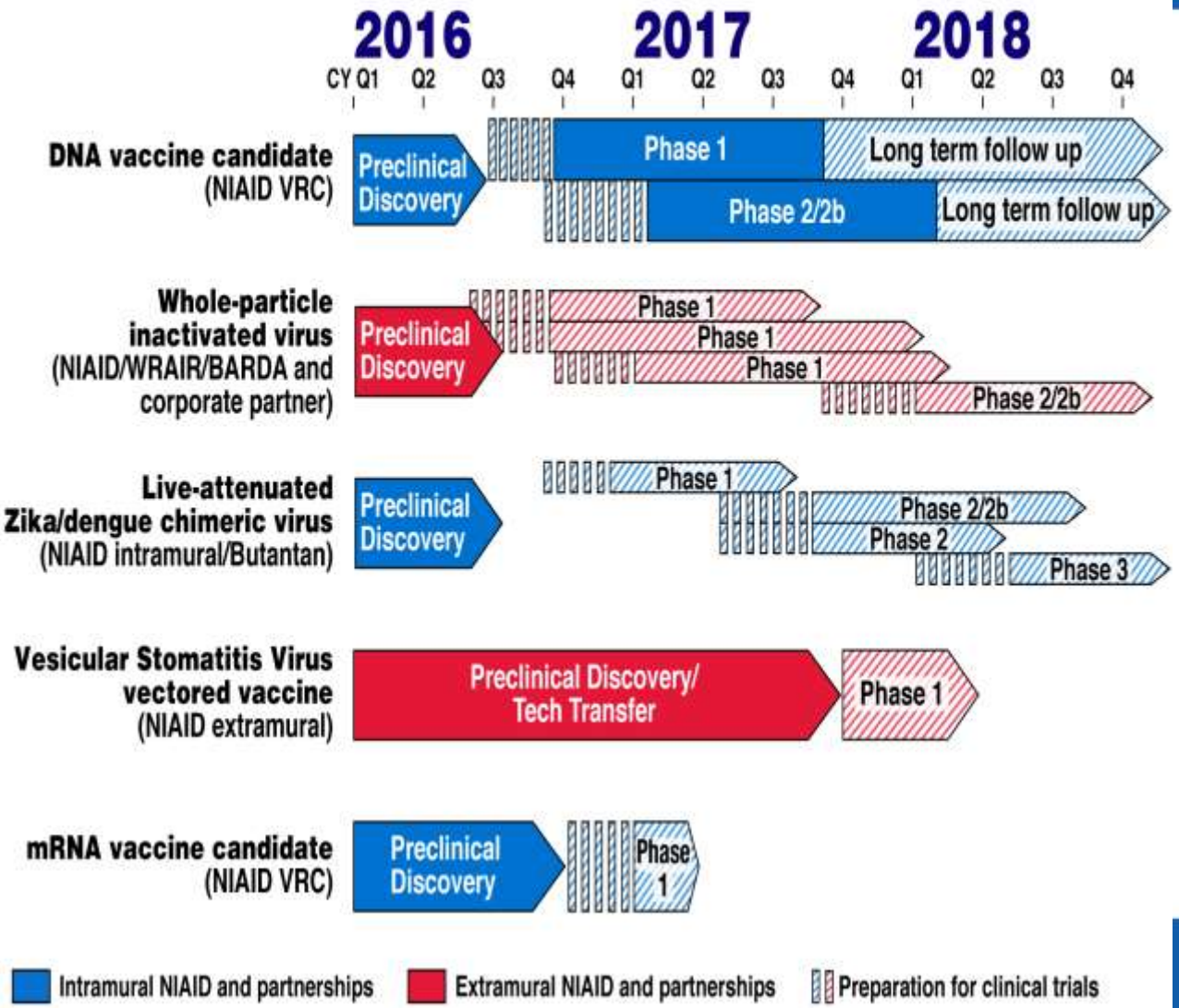
Centers for Disease Control and Prevention

Zika Virus Diagnostic Testing

- **Symptomatic persons**
  - **Serum RT-PCR within 7 days after onset**
  - **Urine RT-PCR <14 days after onset**
  - **IgM in anyone with negative RT-PCR or RT-PCR not done**
- **Asymptomatic pregnant women at risk (live in area of active transmission) but without symptoms**
  - **IgM at initiation of prenatal care and mid-second trimester**

RT-PCR: Reverse transcription-Polymerase chain reaction

Zika Virus Diagnostic Testing

- **Asymptomatic pregnant women who have traveled to an area of active transmission**
  - **IgM 2-12 weeks after return**
- **RT-PCR or immunohistochemical staining on autopsy tissues**
- **Unclear significance:**
  - **RT-PCR in amniotic fluid**
  - **RT-PCR in IgM positive pregnant women**

Zika Vaccine Development Timeline