Zika Virus Clinician Forum 2017

Infectious Disease Perspective

May 24, 2017

Costi D. Sifri, MD

University of Virginia School of Medicine

Division of Infectious Diseases & International Health

Disclosures

- None to Declare

Case Presentation

March 2015

- 19 y/o student presents with fevers and rash 3 days after returning from **São Paulo, Brazil** for Spring Break
- 10 day mission trip, working outside building a school
- Slept outside on a roof, numerous **mosquito bites**, saw **rats** on the roof
- Ate **local food**, **swam** in local river, 1 day trip to **Amazon River Basin**
- Vaccines up to date, including
  - hepatitis A, typhoid, HBV, influenza, MMR, meningococcus
- No malaria chemoprophylaxis

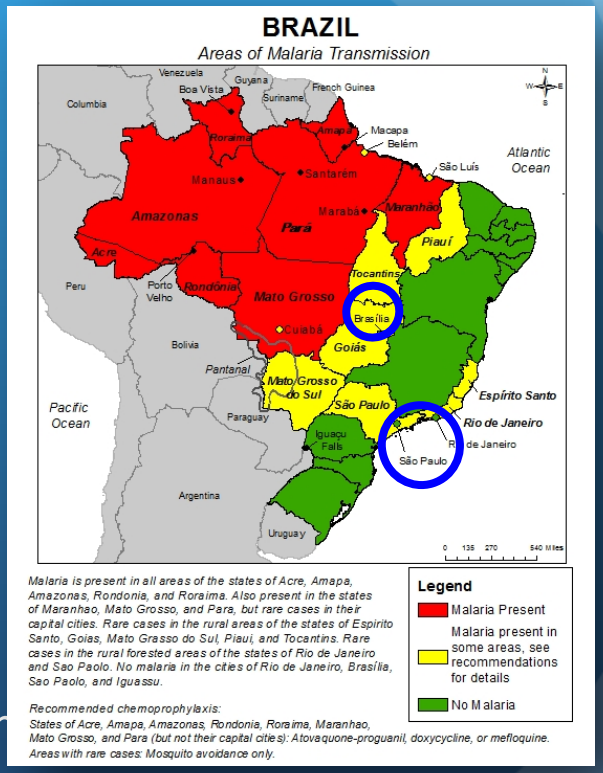
Case Presentation

- Acute onset **fever** one day earlier, **Tm 103°F**
- **Pruritic rash** started on neck, **arthralgias**
- Additional sx: **myalgias**, retro-orbital **headache**
- No abdominal pain, nausea, vomiting, diarrhea, dysuria
- A few other students had similar, milder illness
- Exam: nontoxic, normal conjunctivae and oropharynx, supple neck, normal chest/abdomen, maculopapular rash most prominent over shoulders
- Labs: WBC 12.2 (78^{S} 12^{L} 9^{M} 1^{E}), HGB 14.1 mg/dL, PLT 189, Cr 0.8 mg/dL, normal LFTs, CXR NAD

Case Presentation

Differential Diagnoses

1. *Chikungunya virus
2. *Dengue virus¶
3. *Malaria
4. Typhoid fever
5. Acute schistosomiasis
6. Leptospirosis
7. Hantavirus virus
8. Acute HIV
9. Tick borne illness (e.g. rickettsial infection
10. Acute EBV (mononucleosis)



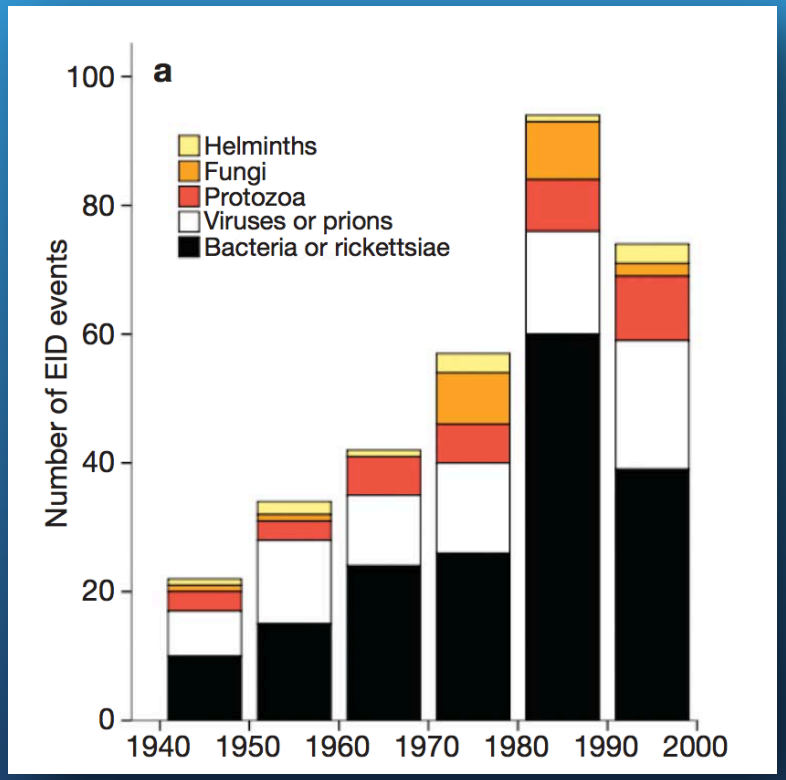
Malaria transmission in Brazil

¶ Recent reports of dengue outbreak in Brazil

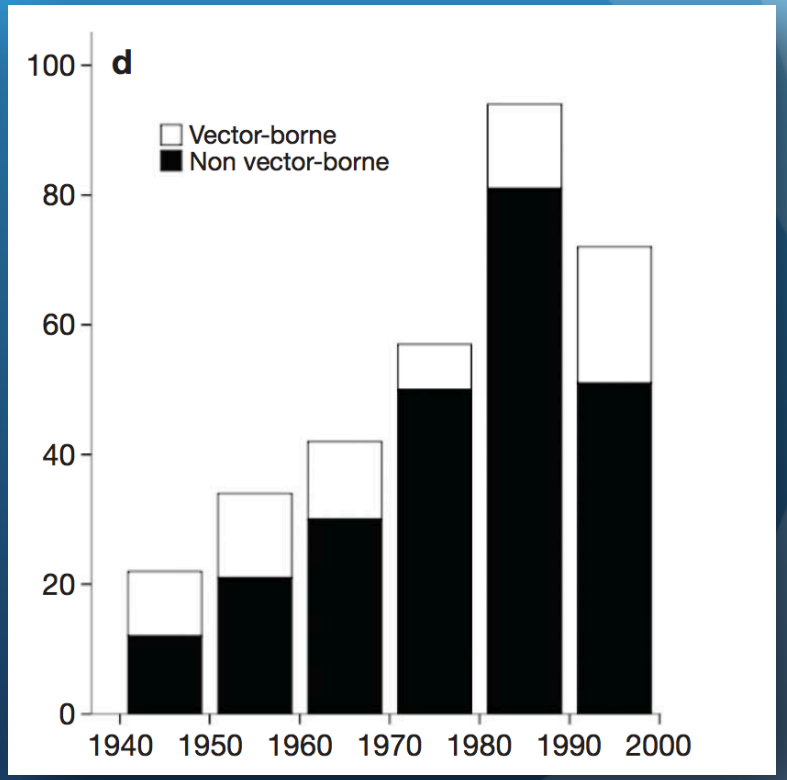
Emerging infectious disease 1940-2004

~1/3 viruses, ~1/3 vector borne

Pathogen class



Vector vs non-vector



Jones KE, et al. *Nature* 2008;451:990-3

A Connected World

The world is growing ever more connected

Daily Flight Paths

http://contrailscience.com

A Connected World

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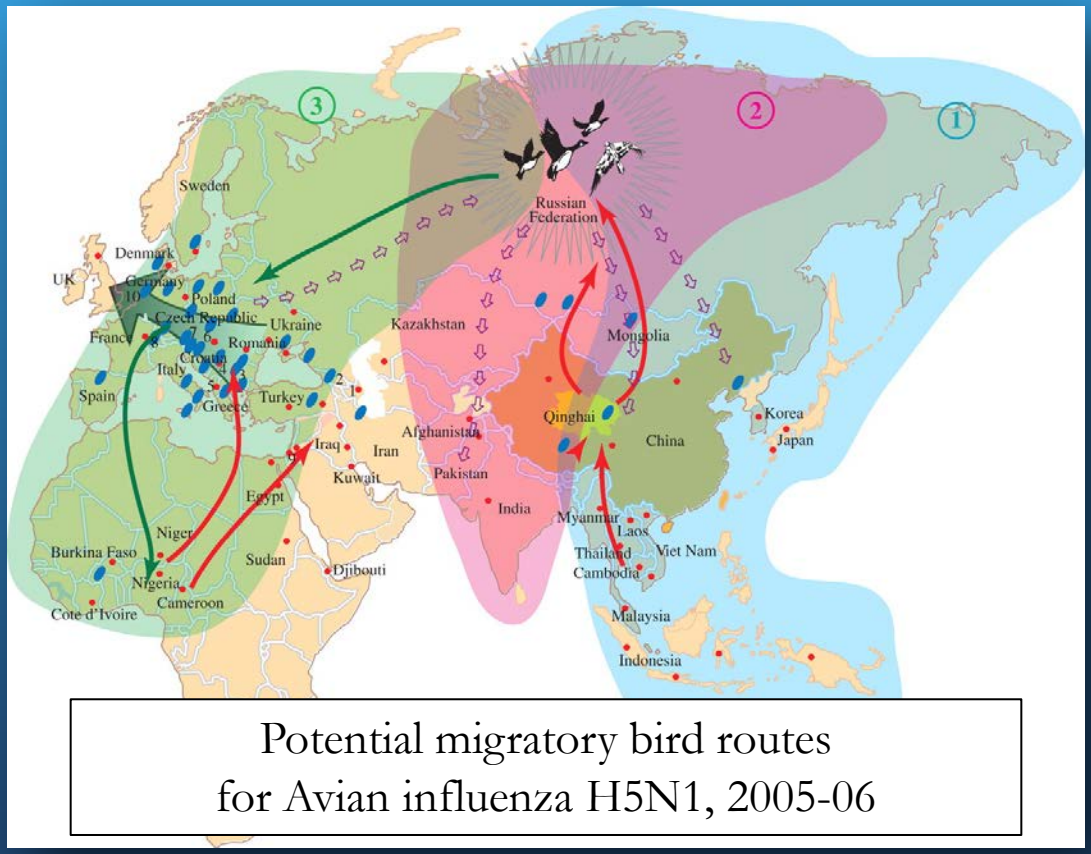


Potential migratory bird routes
for Avian influenza H5N1, 2005-06

Ma Y, et al. *Philos Trans R Soc Lond B Biol Sci*. 2009;364:2725-37

Dengue and Chikungunya

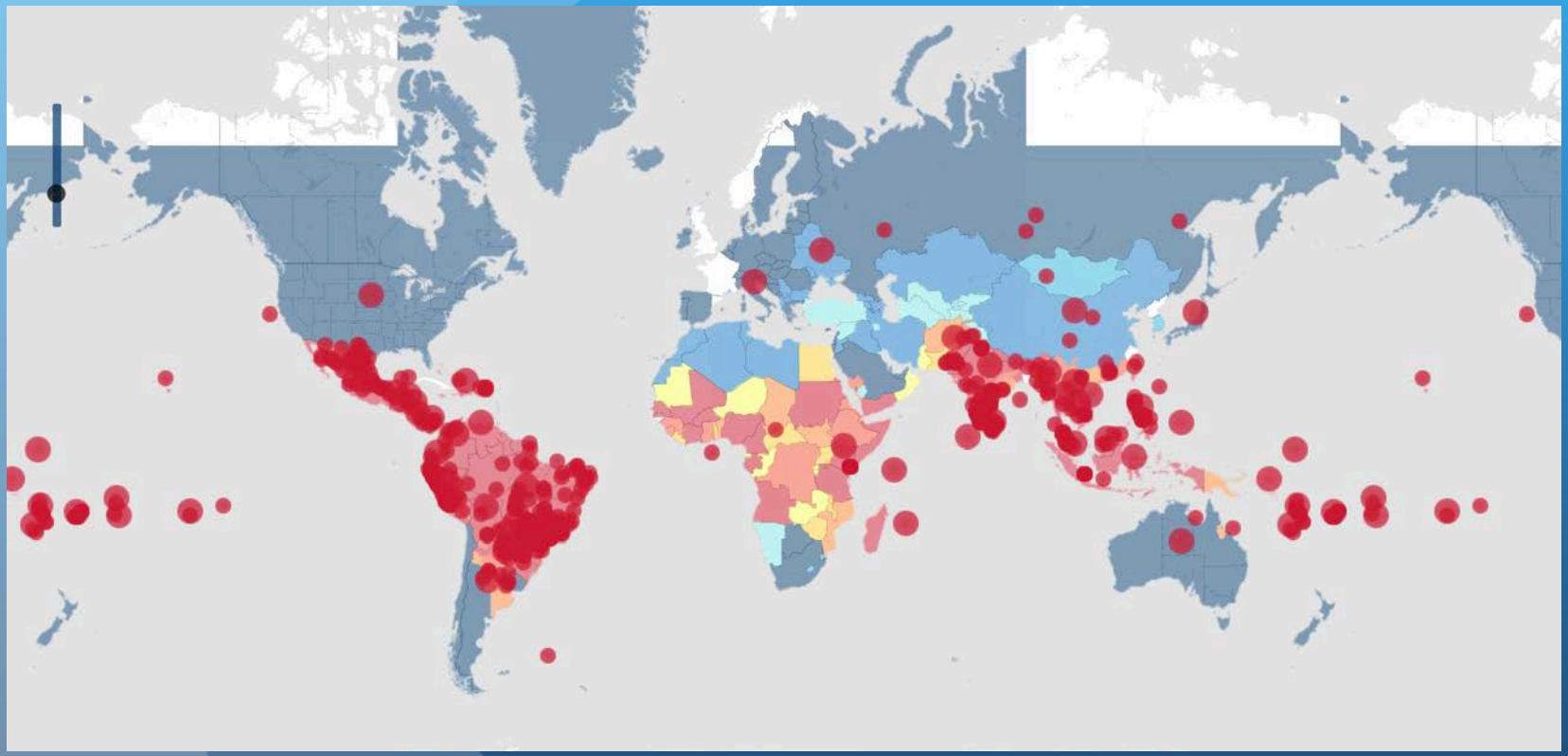
Dengue

- Mosquito-borne flavivirus that causes fever, headache, arthralgia/myalgia, mild rash, mild to severe bleeding
- Explosive growth 1980-90s (>100 countries)
- Four serotypes (DENV-1 to DENV-4)
  - Long term homotypic immunity
  - Heterotypic immunity wanes, thought to lead to "immune enhancement" – up to 100-fold increased risk of dengue hemorrhagic fever and dengue shock syndrome
- 50-100 million cases and 22,000 deaths annually

Chikungunya

- Mosquito-borne alphavirus that causes fever and severe polyarthralgia
- 1st locally-acquired cases in the Caribbean, Dec 2013
- Explosive growth in the Americas: 56,000 cases in the first 6 months (R_0 5.2)
- >1.7 million cases worldwide

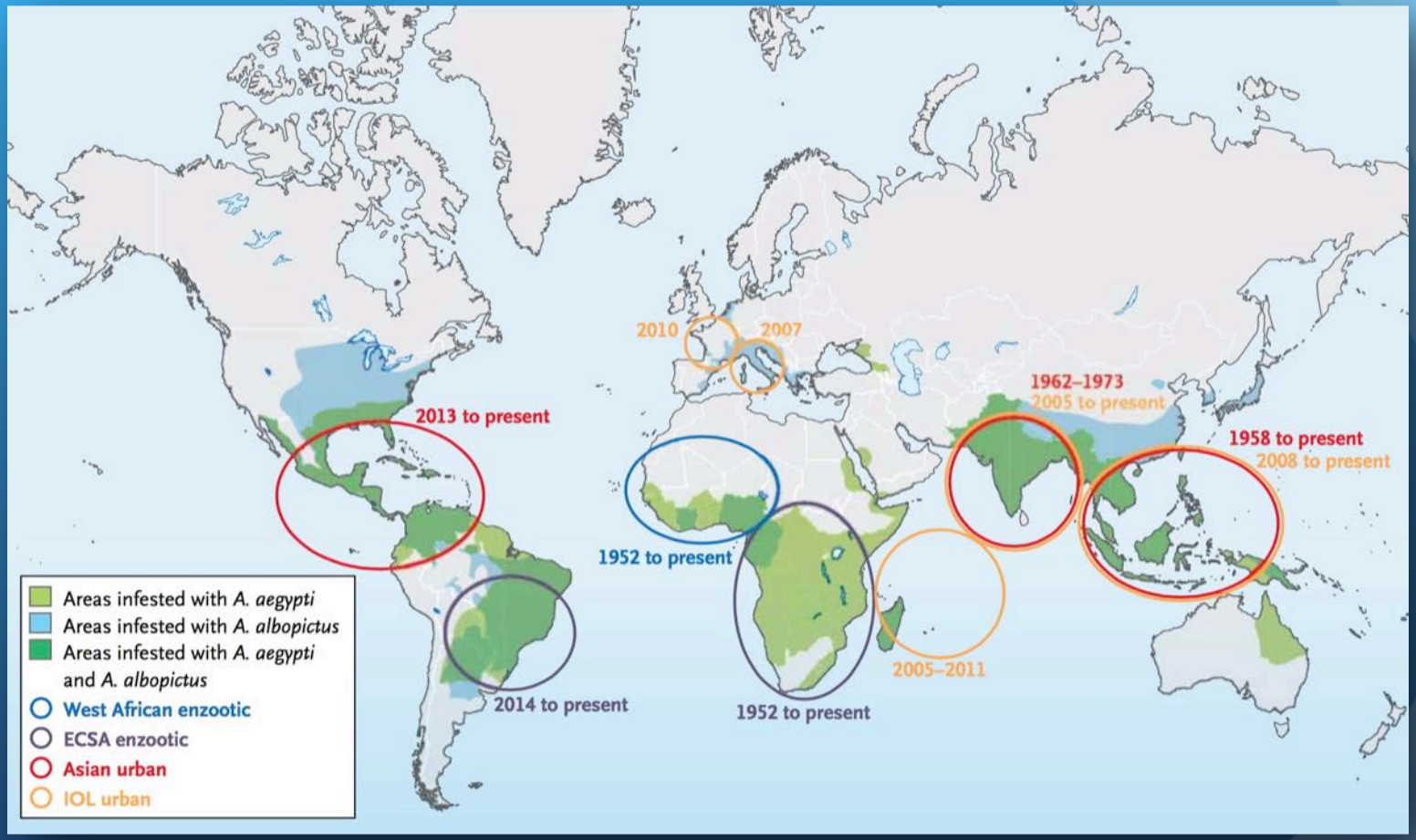
Dengue



Dengue alerts for the last 30 days

http://www.healthmap.org/dengue/en/ (accessed May 10, 2017)

Chikungunya



Weaver CW, et al. *N Engl J Med* 2015; 372:1231-9

Chikungunya vs. Dengue

- Broad clinical overlap, shared vectors, co-circulation, occasional co-infection
- Treatment approaches differ, distinguishing is important
- Diagnostic evaluation through Public Health (serology, PCR, culture)

	Chikungunya	Dengue
Mosquito	*A. aegypti* *A. albopictus*	*A. aegypti* *A. albopictus*
Median incubation period	3-4 days	4-7 days
Fever (>39°C)	+++	+
Arthralgia	+++	+/-
Arthritis	+	-
Myalgia	+	++
Rash	Maculopapular	Petechial (& maculopapular)
WBC	Lymphopenia	Neutropenia
Thrombocytopenia	+	+++
Hemoconcentration	-	++
Hemorrhage	+/-	++
Shock	-	+

Staples JE, et al. *N Engl J Med* 2014; 371:887-9. Weaver CW, et al. *N Engl J Med* 2015; 372:1231-9.

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Aedes Mosquito Geographic Distribution – Global

Aedes aegypti

Yellow fever mosquito

Aedes albopictus

Asian tiger mosquito

Aedes Mosquito Geographic Distribution – U.S.

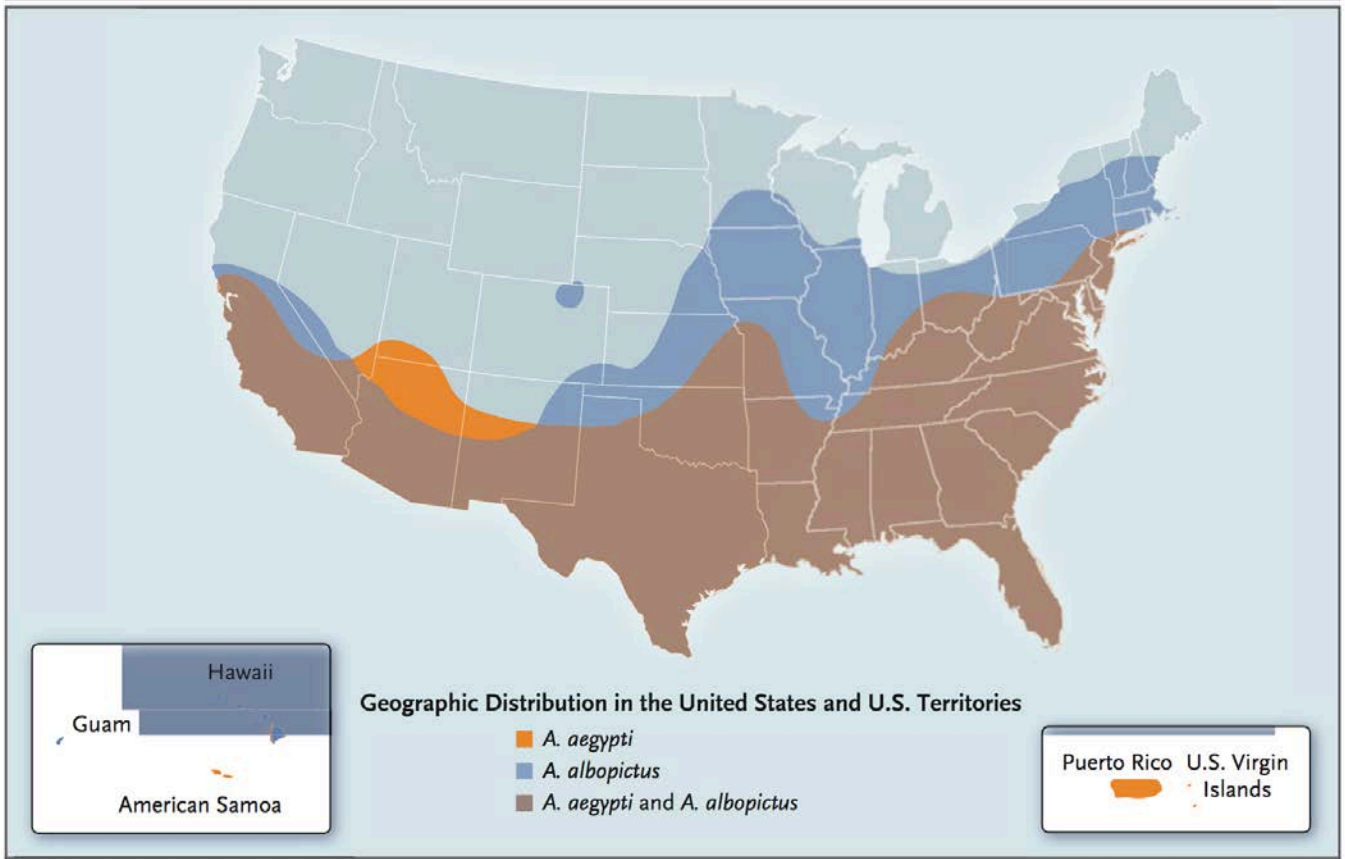


Figure 3. Approximate Ranges of *A. aegypti* and *A. albopictus* in the United States (as of March 2016).
These mosquitoes may not be present in all areas, and vector density may vary considerably within these ranges.

Petersen L, et al. *N Engl J Med*. 2016;374:1552-63

Case Presentation

19 y/o student with fever, rash, and arthralgia after 10 day trip to São Paulo, Brazil in March 2015

Diagnosis	Test
Chikungunya	Negative acute anti-CHIKV IgM/IgG Negative convalescent anti-CHIKV IgM/IgG
Dengue	Negative acute anti-DENV IgM/IgG Negative convalescent anti-DENG IgM/IgG
Malaria	Negative BinaxNOW, Negative thick/thin Giemsa smears

Case Presentation

19 y/o student with fever, rash, and arthralgia after 10 day trip to São Paulo, Brazil in March 2015

Diagnosis	Test
Schistosomiasis	Negative anti-MAMA Ab
Leptospirosis	Negative Leptospira Ab
Hantavirus	Negative IgM/IgG serology
Acute HIV	Negative ELISA, negative p24, Negative HIV NAT
Influenza	Negative influenza nasopharyngeal PCR
EBV	Negative monospot
Tick borne illness	doxycycline x 7d
Typhoid fever (bacterial infection)	ceftriaxone x 2d

"Brazil had more than 224,000 cases of dengue by March"

R7 R7.COM

R7 TV NOTÍCIAS ENTRETENIMENTO ESPORTES RECORD TV SERVIÇOS

Acessibilidade

R7 NOTÍCIAS

FEBRE AMARELA DOENÇAS DO AEDES AEGYPTI FALA SAÚDE DIABETES AVANÇOS DA MEDICINA

12/3/2015 às 15h11

Brasil teve mais de 224 mil casos de dengue até março

FACEBOOK TWITTER GOOGLE + PÁGINA INICIAL ALTO CONTRASTE -A +A

EFE

Brasília, 12 mar (EFE).- O número de casos de dengue no Brasil entre 1º de janeiro e 7 de março foi de 224.100, o que representa um aumento de 162,4% em comparação com o mesmo período no ano passado, quando foi de 85.401, informou nesta quinta-feira o Ministério da Saúde. "Nós temos um número de casos

"The first case [of Zika] in São Paulo was detected on May 19, 2015 … It is possible that Zika has been circulating for a few months."

Zika Virus


DON'T GIVE ZIKA A BITING CHANCE.
Learn how to protect yourself at TexasZika.org.
TEXAS
LAMAR

Return to the past

… the last time an infectious pathogen (rubella virus) caused an epidemic of congenital defects was more than 50 years ago …

Lyle Petersen, MD MPH & colleagues
Director, Vector Borne Diseases
NCEZID, CDC
New Engl J Med - May 16, 2016

First time in history

Never before in history has there been a situation where a bite from a mosquito could result in a devastating malformation.

Tom Frieden, MD MPH
Director, CDC
Fortune - April 13, 2016

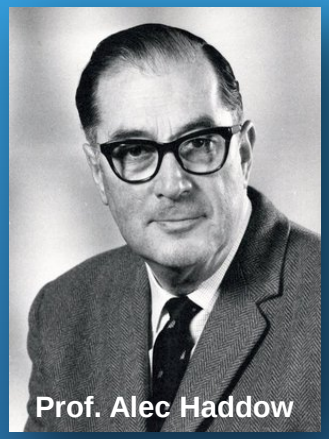
What is Zika Virus

- Single-stranded RNA virus (**flavivirus**)
- Several dozen mosquito-borne flaviviruses including **dengue**, **yellow fever**, **Japanese encephalitis**, and **West Nile viruses**
- Primarily transmitted by two type of *Aedes* mosquitoes
  - *Aedes aegypti* (primary) and *Aedes albopictus* (secondary)
- Additional modes of transmission
  - Intrauterine and perinatal transmission (mother to fetus)
  - Sexual transmission (M>F, M>M, F>M)
  - Laboratory exposure
  - Blood transfusion

Petersen L, et al. *N Engl J Med*. 2016;374:1552-63

Zika Virus

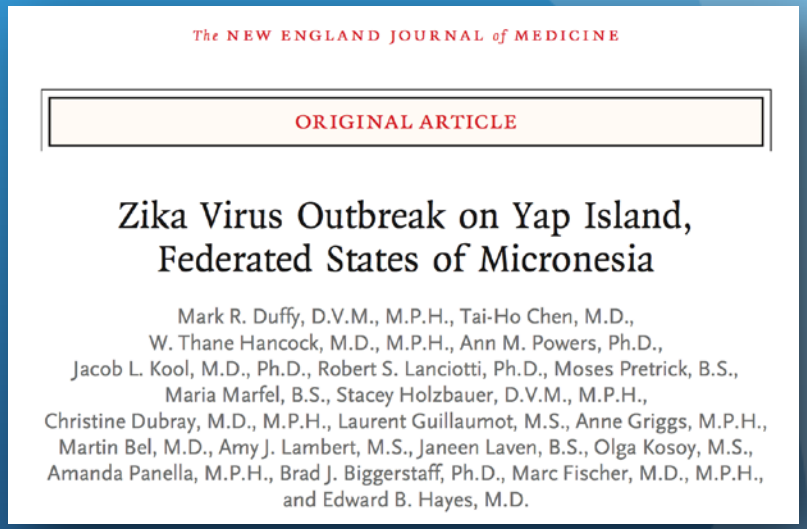
- 1947: first isolated from a macaque, Zika Forest
- 1952-2006: only 14 sporadic human disease cases reported from Africa and SE Asia


Prof. Alec Haddow

http://www.universitystory.gla.ac.uk

Zika Virus

- 2007: First outbreak, Yap, Federated States of Micronesia (population 7391)
  - Attack rate 73%
  - Only 20% symptomatic
  - Asian genotype
- 2013-14: >30,000 suspected cases reported from French Polynesia and other Pacific Islands



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Zika Virus Outbreak on Yap Island, Federated States of Micronesia

Mark R. Duffy, D.V.M., M.P.H., Tai-Ho Chen, M.D., W. Thane Hancock, M.D., M.P.H., Ann M. Powers, Ph.D., Jacob L. Kool, M.D., Ph.D., Robert S. Lanciotti, Ph.D., Moses Pretrick, B.S., Maria Marfel, B.S., Stacey Holzbauer, D.V.M., M.P.H., Christine Dubray, M.D., M.P.H., Laurent Guillaumot, M.S., Anne Griggs, M.P.H., Martin Bel, M.D., Amy J. Lambert, M.S., Janeen Laven, B.S., Olga Kosoy, M.S., Amanda Panella, M.P.H., Brad J. Biggerstaff, Ph.D., Marc Fischer, M.D., M.P.H., and Edward B. Hayes, M.D.

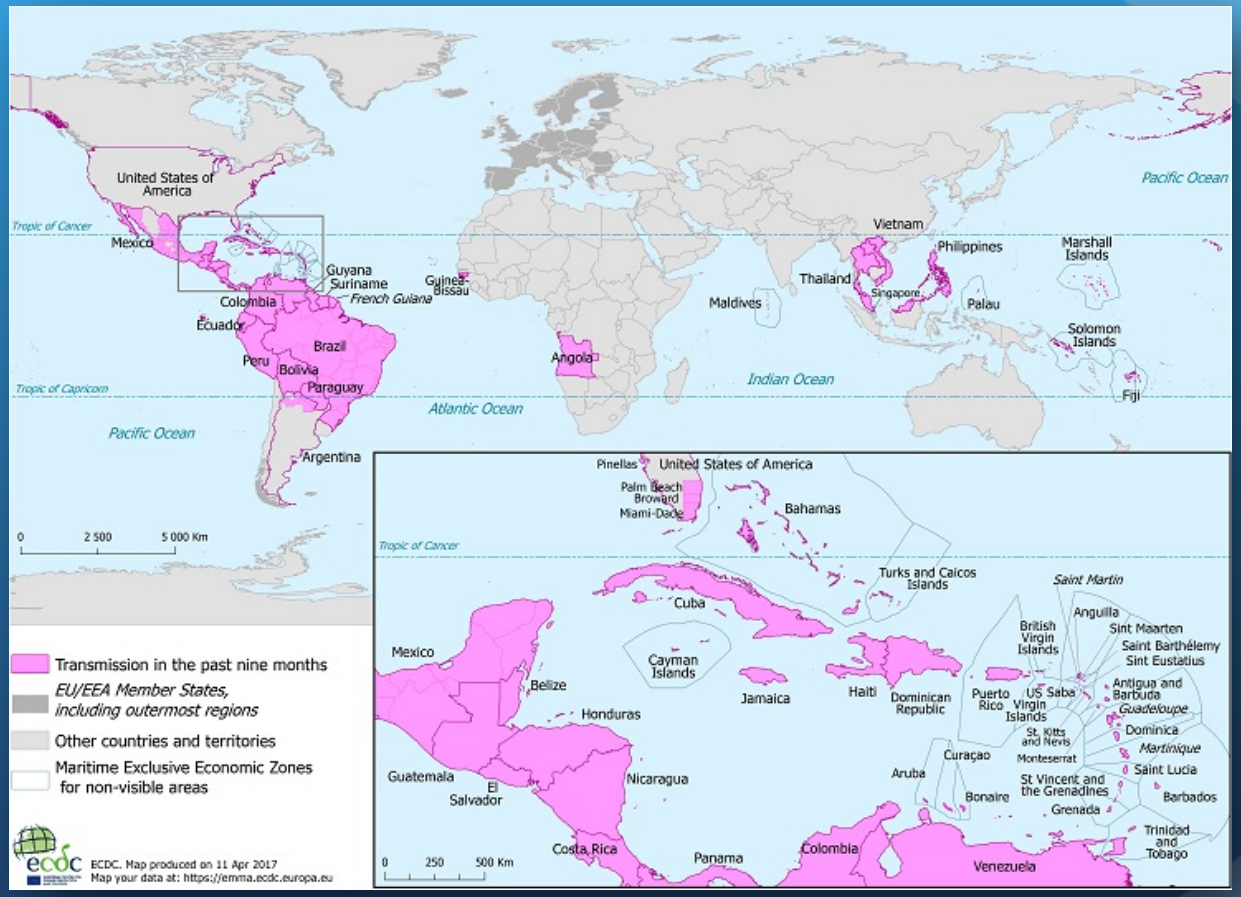
Duffy MR, et al. *N Engl J Med* 2009;360:2536-43. Cao-Lormeau VM, et al. Emerg Infect Dis. 2014;20:1085-6.

Zika virus arrives in the Americas

- Mar 2015. Brazil report mild febrile rash illness (7000 cases) to WHO from NE Brazil; 13% Dengue positive
  - Negative Chikungunya, enterovirus, parvovirus B19, measles
- Apr 2015. First cases of Zika virus infection identified in NE Brazil
- May 2015. First confirmed case of Zika virus infection in São Paulo, Brazil
- Oct 2015. Brazil HD informs WHO of increased number of infants with microcephaly in NE Brazil
- Feb 2016. Increased microcephaly noted found after retrospective review in French Polynesia

http://www.paho.org

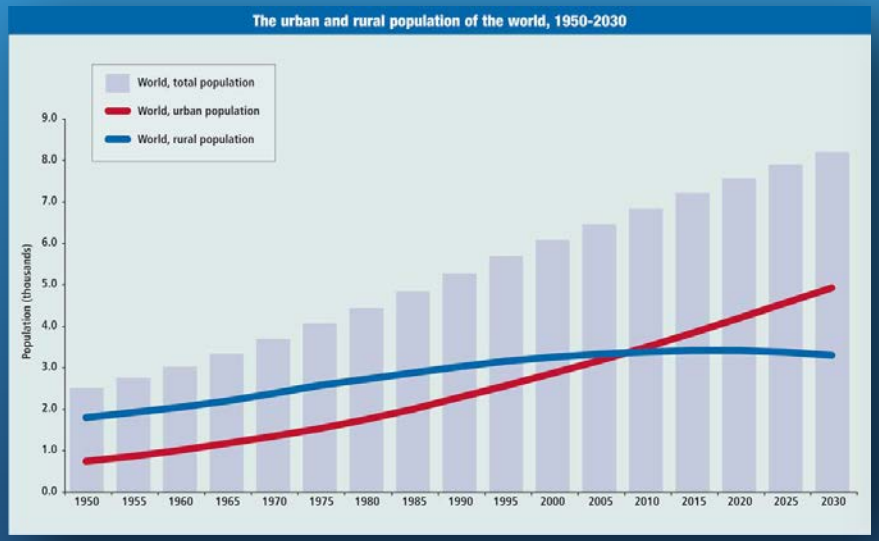
Countries & territories with active Zika virus transmission



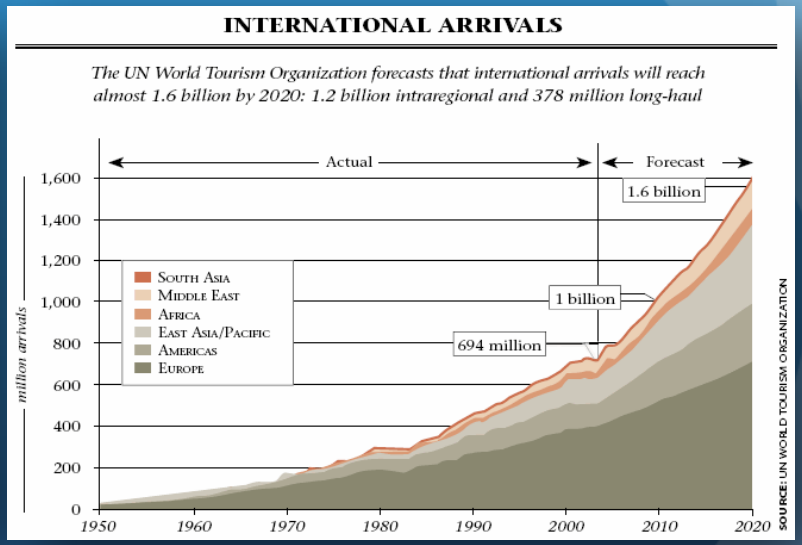
http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/zika-outbreak.aspx

Why is Zika spreading now?

Urban vs Rural Population Growth



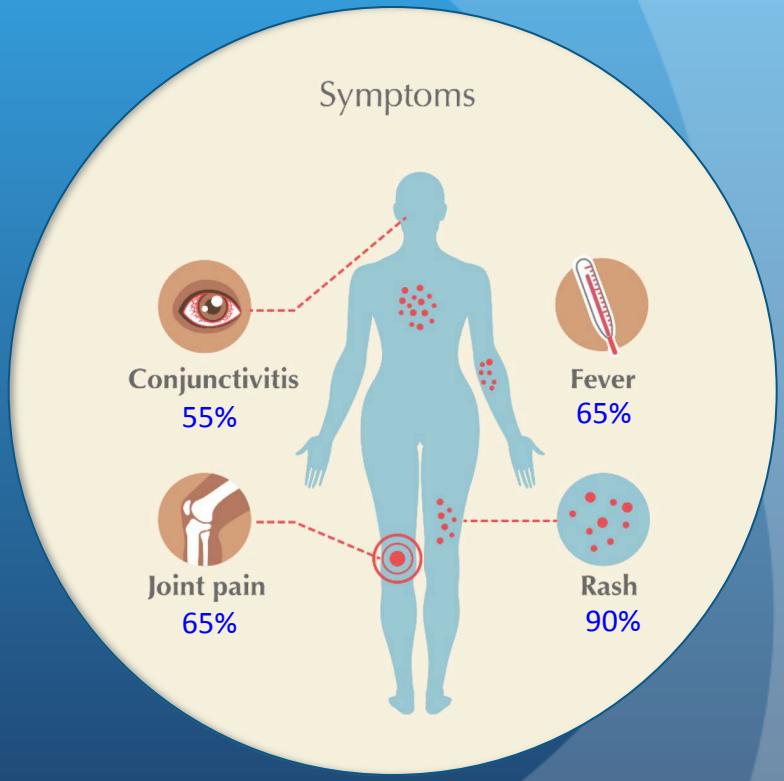
International Travel



www.un.org

Zika clinical presentation

- Only 20% symptomatic
  - typically mild illness
- Incubation period ~6 days
  - (range 3-12 days)
- Blood, urine, semen, vaginal fluids, saliva
- Illness lasts ~5-7 days
- Severe disease is uncommon, death is rare
- Likely lifelong immunity after recovery



Petersen L, et al. *N Engl J Med*. 2016;374:1552-63

Zika clinical presentation

Figure 1. Conjunctival injection.

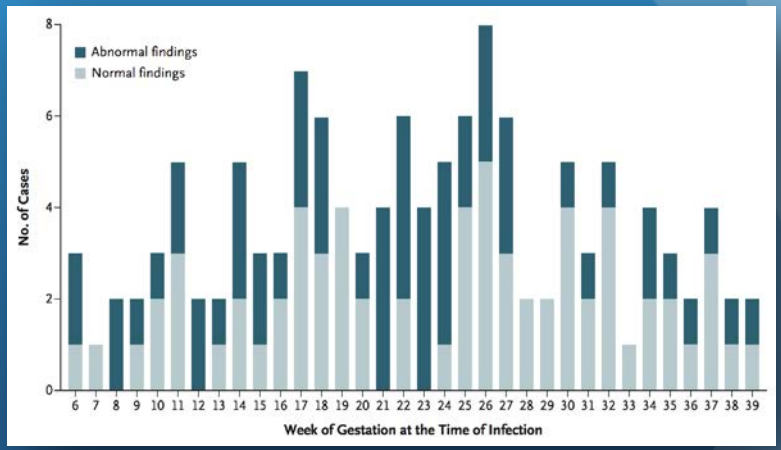
Figure 2. Rash on torso.

Macesic N, et al. *Clin Infect Dis*. 2015;61:1445

Zika virus and pregnancy

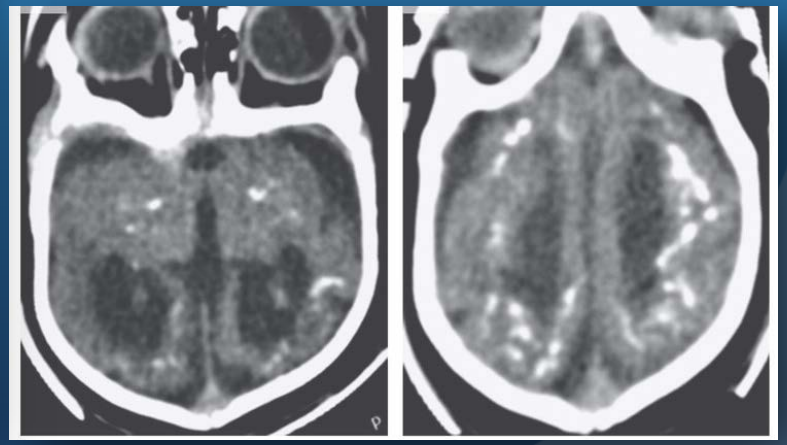
- Pregnant women can be infected
  - Through the bite of an infected mosquito
  - Through sex without a condom with an infected partner
- Zika can be passed to the fetus during pregnancy or around the time of birth
- Infection can occur in any trimester
  - The clinical course is similar to that in non-pregnant people
- Transmission rate ~6%
  - ~11% in the first trimester

Week of gestation at time of infection and risk of ultrasound abnormalities

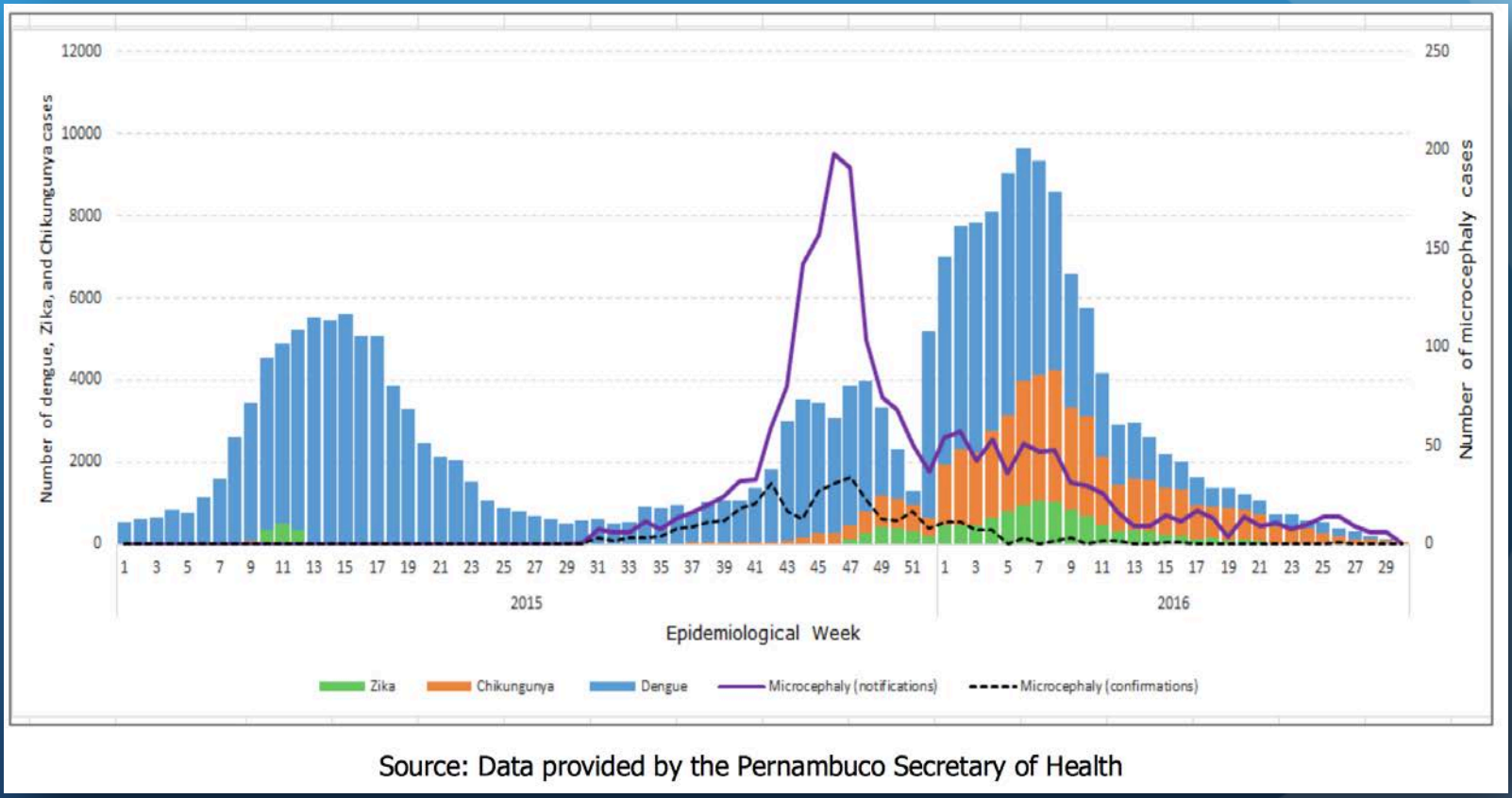


Brasil P, et al. *N Engl J Med*. 2016;375:2321-34

Zika virus congenital syndrome



Chikungunya, dengue, Zika and microcephaly cases in the state of Pernambuco, Brazil



Source: Data provided by the Pernambuco Secretary of Health

Zika and Guillain–Barré syndrome

- Guillain–Barré syndrome
  - Frequency 1:5000 infections
  - Short interval from acute illness to GBS
  - Rapid progession
- Other syndromes
  - ADEM, encephalitis, anterior myelitis

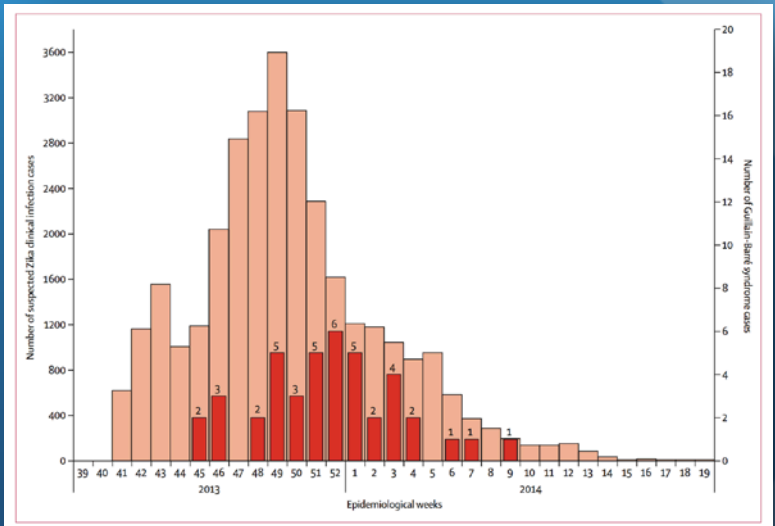


Figure: Weekly cases of suspected Zika virus infections and Guillain-Barré syndrome in French Polynesia between October, 2013, and April, 2014

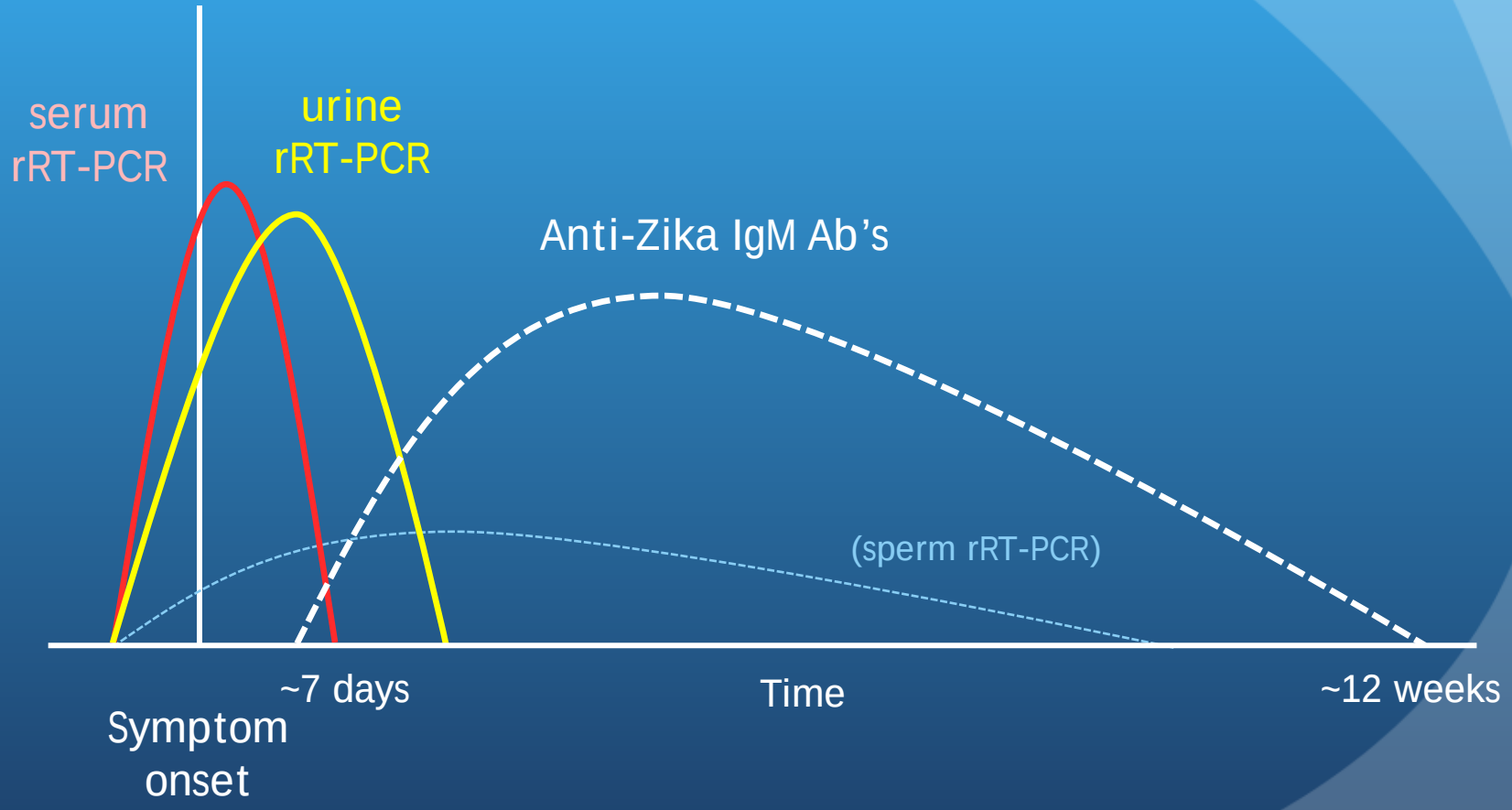
Cao-Lormeau VM, et al. *Lancet* 2016;387:1531-9

Zika diagnostic testing

- Molecular rRT-PCR
  - Trioplex rRT-PCR (ZIKV, DENV, CHIKV)
  - Serum: typically up to 7 days, longest time 13 days non-pregnant, 62 days pregnant)
  - urine: typically up to 14 days
- Serology (up to 3 months)
  - Zika IgM enzyme-linked immunosorbent assay (MAC ELISA)
  - Plaque reduction neutralization test (PRNT) to detect neutralizing antibodies (only available through CDC)
- Immunohistochemistry

Zika diagnostic testing

Testing approach depends on indication and timing



Adapted from Dr. Lyle Petersen, CDC

Sexual transmission of Zika virus

- Viral RNA in semen persists in most men up to 60 days
  - 5 men have had detectable RNA in semen 60-188 days
- High viral loads compared to serum
- Replication competent virus for up to 69 days (usually less than 24 days)
- Transmission has been within the first 20 days of travel thus far

Petersen EE, et al. MMWR 2016;65;1077-81

Guidance for pregnant women

- Use condoms consistently or abstain from sex for the duration of the pregnancy

Petersen EE, et al. MMWR 2016;65;1077-81

Guidance for couples trying to conceive

- Women
  - Wait at least 8 weeks after symptom onset or after the last possible exposure
- Men
  - Wait at 6 months after symptom onset or after the last possible exposure
- Both
  - avoid nonessential travel to areas with Zika virus transmission
  - use of mosquito bite prevention strategies while attempting pregnancy and during pregnancy if travel to areas with Zika virus transmission is unavoidable

Petersen EE, et al. MMWR 2016;65;1077-81

Case conclusion

- Checked Zika IgM more than 12 months after his acute illness
  - Negative
  - No stored serum
- No commercial available Zika IgG test
  - Cross reactive with other flaviviruses
- The student made a complete recovery

Costi D. Sifri, MD
csifri@virginia.edu
434-924-0260