



Zika: Global Updates

A Dynamic Epitome of the Interdependence of an
Emerging Infection, Health and Human Rights

Elizabeth A. Talbot MD
Assoc Professor, ID and International Health
Deputy State Epidemiologist, NH



GEISEL
— SCHOOL OF —
MEDICINE
AT DARTMOUTH

Zika is Not a New Virus

- An RNA flavivirus in Spondweni group
- First isolated in
 - 1947 from rhesus monkey in Zika forest, Uganda
 - 1948 in mosquitoes (*Aedes africanus*) same forest
 - 1953 in human in Nigeria



Petersen LR et al. N Engl J Med 2016;374:1552-1563

Historically Zika was Widespread

- Serosurveys in Uganda suggest 6.1% of population had Zika virus infection
- Additional serosurveys indicate broad geographic distribution of human infection
 - Egypt, East Africa, Nigeria, India, Thailand, Vietnam, Philippines, and Malaysia
- Before 2007, sporadic in Africa and Southeast Asia: no large outbreaks, mild disease with no hospitalizations or deaths
 - “Dumb cousin of dengue”

Dick GW. Epidemiological notes on some viruses isolated in Uganda. . . Zika vi ruses. Trans R Soc Trop Med Hyg 1953; 47: 13-48.; Petersen LR et al. N Engl J Med 2016;374:1552-1563



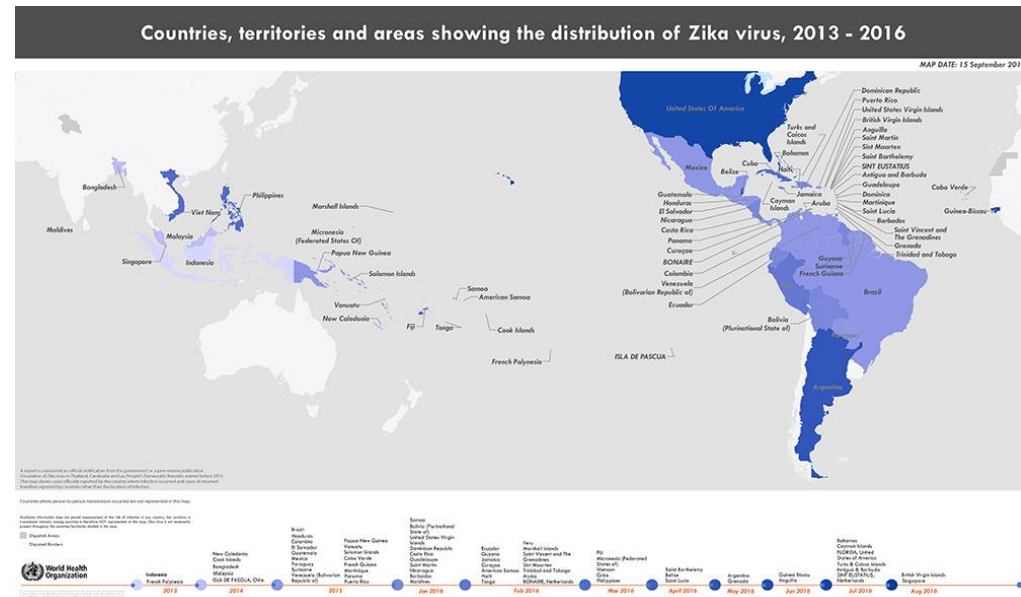
Major Emergence in 2007

- April to July 2007, outbreak on Yap Island
 - Affected 73% of population of ~12,000
- 2013 - 2015 several outbreaks in Pacific
 - French Polynesia: ~32,000 of 270,000 population
 - Observed association with Guillain-Barre syndrome



2014: South and Central America

- March 2015 spread in Americas
 - Suspect source case attended FIFA World Cup
- Feb 2016 Public Health Emergency of International Concern
- ~3–4 million cases in 70 countries in 2016



<http://www.cdc.gov/zika/geo/active-countries.html>;

<http://www.who.int/emergencies/zika-virus/situation-report/Zika-timeline-15Sept.jpg?ua=1>

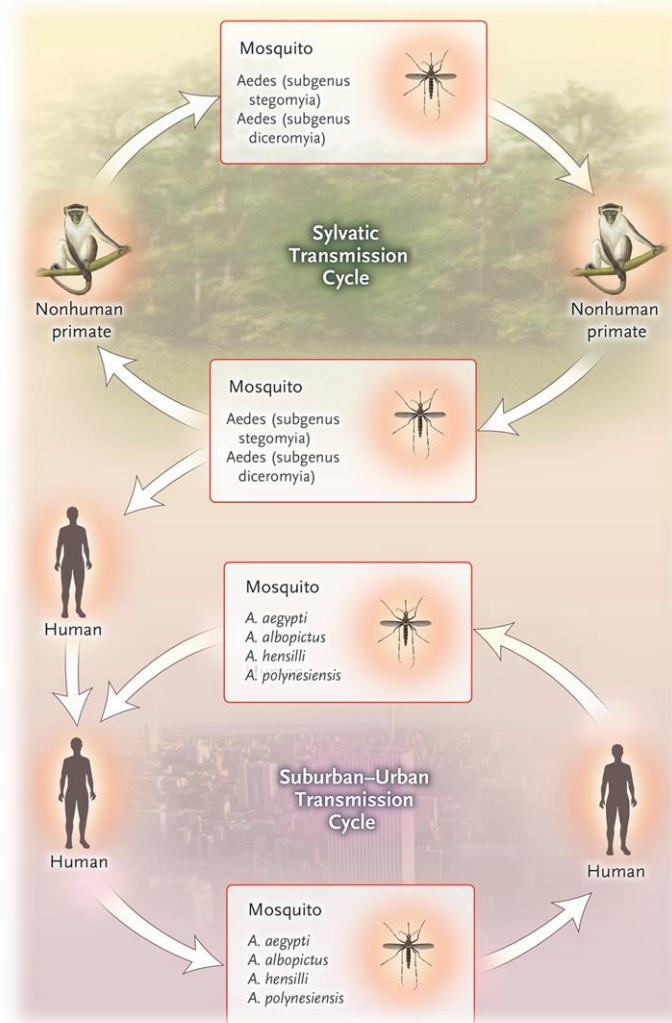


Why is Zika Emerging Now?

- Increases in dengue, chikungunya, and Zika (sharing *A. aegypti* as primary vector) suggest common underlying mechanisms
 - Globalization, urbanization, climate change
 - Introduction to previously unexposed populations
- Recognition of GBS and microcephaly may reflect
 - Change in viral virulence – **no evidence**
 - Increased incidence of infection in settings with more resource for surveillance
 - In Africa and Asia, exposure may occur in childhood, when GBS is less likely and then later immune to infection during pregnancy



Zika Has Typical Arbovirus Cycle

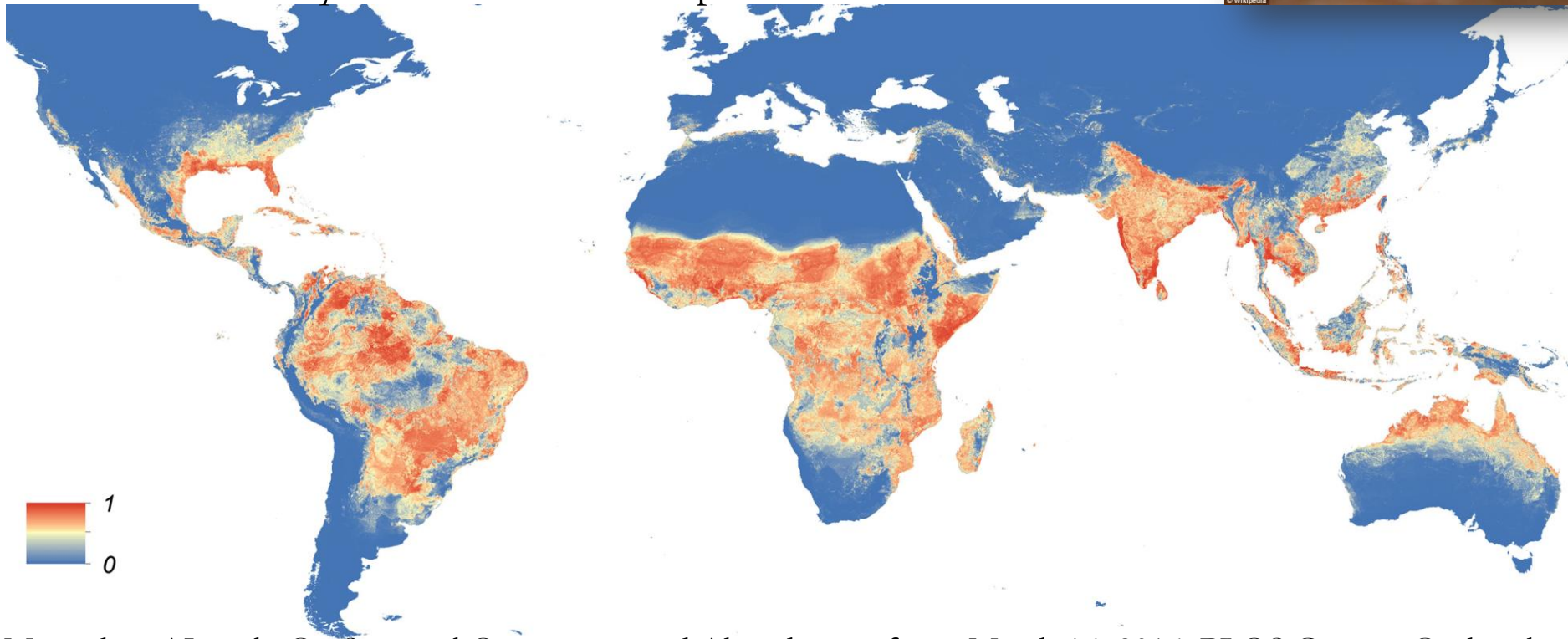


Petersen LR et al. N Engl J Med 2016;374:1552-1563



Vast Proportion of Transmission

- Major urban/suburban vector is *A. aegypti*
 - Dengue, chikungunya, Zika, JEV, yellow fever
 - *A. albopictus* much less “competent”



Monaghan AJ et al. On Seasonal Occurrence and Abundance of . . . March 16, 2016, PLOS Current Outbreaks
<http://currents.plos.org/outbreaks/article/on-the-seasonal-occurrence-and-abundance-of-the-zika-virus-vector-mosquito-aedes-aegypti-in-the-contiguous-united-states/>



Additional Transmission Modes?

- Identified in multiple body fluids: uncertain if can transmit
 - Breastmilk: risk benefit favors breastfeeding
 - Organ transplantation and blood transfusion: likely
 - Urine, saliva, CSF
- Transmission documented
 - 2 lab accidents
 - Placental transmission or during delivery
 - Sexual transmission reported as early as 2011
 - Scientist who visited Senegal contracted



Zika RNA Persistence in Secretions

Secretion	Duration of Detection
Serum	
Nonpregnant	>8 weeks
Pregnant	10 weeks
Urine	13 weeks
Saliva	13 weeks
Breastmilk	>1 year
Female genital secretions	11 days
Semen (sperm)	27 weeks

- Male to female transmission: +/- symptoms
- Female to male*
- Nonsexual
 - Caregiver to Zika patient with high viral load**

Summarized using UpToDate: ©2016 UpToDate, Inc.; *Prisant N et al. Lancet ID 2016; doi:10.1016/S1473-3099(16)30193-1. *Davidson A, et al. MMWR 2016; mm6528e2. **Brent C, et al. MMWR 2016;



Clinical Features

- Incubation ~3-12 days after bite
- 80% of infections asymptomatic
- Symptoms usually mild, self-limiting febrile illness of 4–7 days duration without complications
 - Pruritic maculopapular rash (90%), acute fever (65%), arthralgia of small joint hands and feet (65%), non-purulent conjunctivitis/conjunctival hyperemia (55%), headache (45%), retro-orbital pain (39%)
 - GI signs rare
 - Meningoencephalitis and acute myelitis reported
 - Among children postnatally infected, no developmental complications observed



The Real Catastrophe of Zika

- Nov 2013 in French Polynesia first association made with Guillain Barre syndrome (GBS)
 - Over course of that Zika outbreak, national incidence of GBS increased 20-fold
 - 1/1000 cases
 - No doubt in Americas
- Adverse fetal outcomes

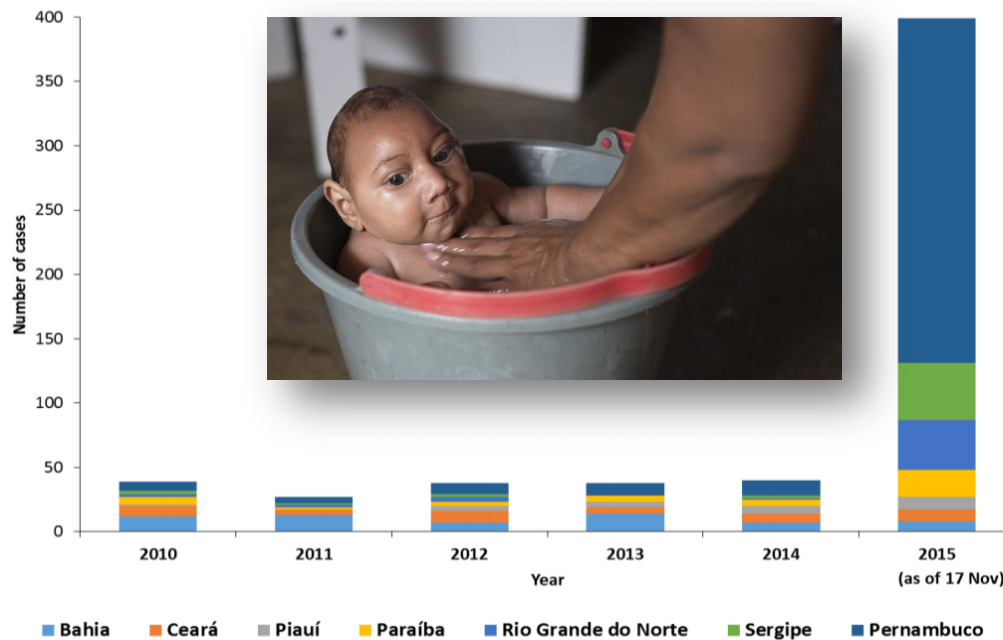
Musso D et al. Rapid Spread of emerging Zika in Pacific Area. Clin Micro and Infect. 2014; 20(10):595.



Microcephaly Detected in Brazil

- Through Dec 2015, >1,248 cases of microcephaly reported among newborns in Brazil
 - 20-fold rate increase exactly coincident with Zika

Figure 2. Number of cases of microcephaly reported annually in the seven Brazilian states reporting an unusual increase of microcephaly, 2010–2015



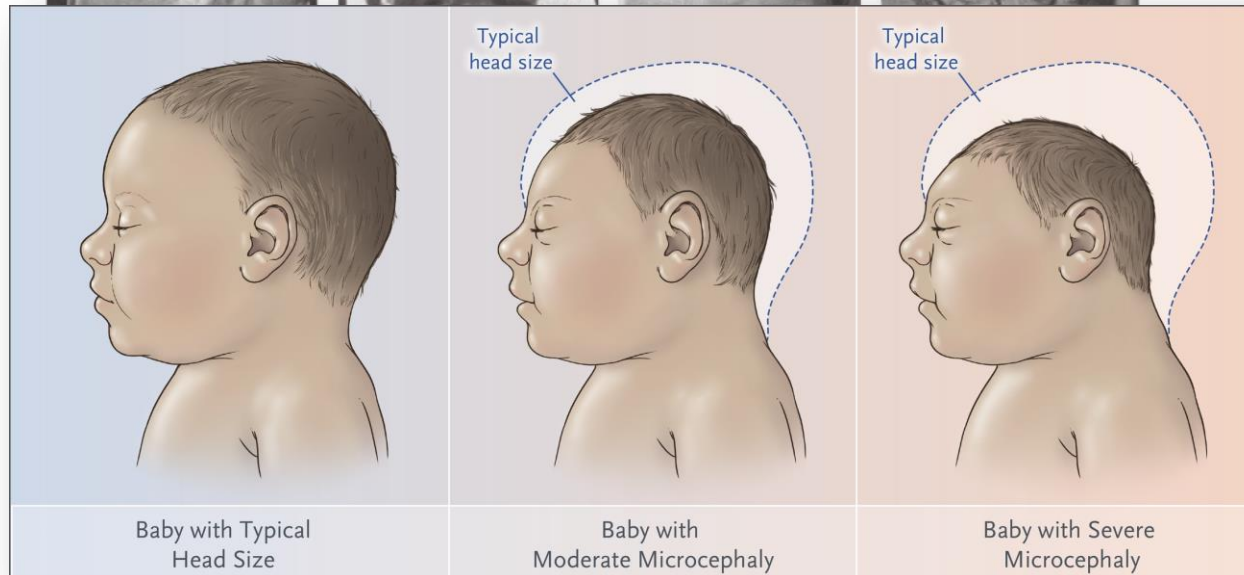
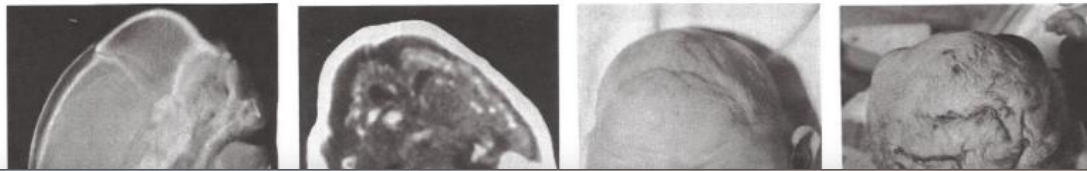
<http://ecdc.europa.eu/en/publications/publications/zika-microcephaly-brazil-rapid-risk-assessment-nov-2015.pdf>



Microcephaly From Zika

Fetal Brain Disruption Sequence

- First described in 1984 but noted in earlier literature
- Brain destruction resulting in collapse of the fetal skull, microcephaly, scalp rugae and neurologic impairment
- Photos and x-ray from 1990 series*; phenotype appears to be present in affected babies in Brazil

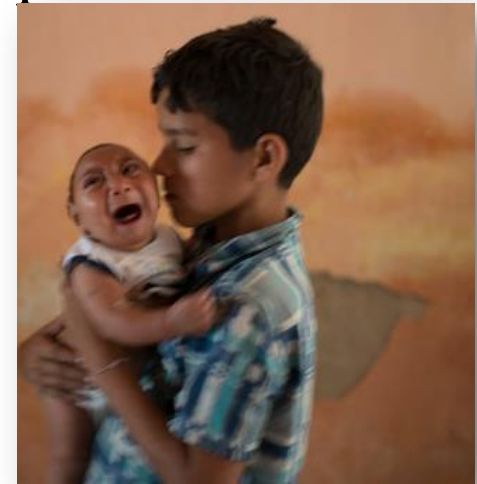


Petersen LR et al. N Engl J Med 2016;374:1552-1563



Congenital Zika Syndrome

- As of June 4, 7,830 microcephaly in Brazil
- Ultrasonographic fetal abnormalities present in 29% of women with zika in Brazil
 - Microcephaly ($<3^{\text{rd}}$ percentile)
 - Ocular abnormalities in 35%
- Surveillance for head size may underestimate magnitude of epidemic impact
- Noting late developmental effects



Franca GVA, et al. Lancet 2016; doi 10.1016/S0140-6736(16)30902-3



Global Response

- Jan 28, WHO DG Margaret Chan said Zika virus “spreading explosively” in Americas, was “deeply concerning. . . Rapidly changed risk profile of Zika from mild threat to one of alarming proportions. The increased incidence of microcephaly is particularly alarming, as it places a heart-breaking burden on families and communities.”
- Feb 1 Public Health Emergency of International Concern
- Vector control, diagnostics, drugs, vaccine development



Whistleblower News

- Dr. Robert Lanciotti, chief of CDC lab, developed Singleplex PCR test for 2007 outbreak
- CDC implemented Trioplex for Zika, dengue, chikungunya
- Lanciotti found Trioplex 40% less sensitive
 - Independent laboratory came to similar conclusion
 - Study by CDC lab in Puerto Rico found no difference in sensitivity
- Mid-April Dr. Lanciotti sent out unauthorized email to 30 state labs saying his lab at Fort Collins was continuing to use the Singleplex; demoted because CDC officials told Lanciotti his email “created more trouble and confusion than it clarified.”
- July filed Whistleblower claim and reinstated

Washington Post Sept 28, 2016



Zika Vaccines: GLS-5700

- GeneOne Life Science (S Korea) and Inovio (PA, US)
 - Ebola experience of 18m development
- Synthetic DNA plasmid that encodes premembrane and envelope (prM-Env) proteins
- 3 doses separated by 1 month, 1 or 2 mg
- Mouse and rhesus studies completed and led to FDA IND
- June 28 Phase 1 trial began for safety, tolerability and immunogenicity in Miami, Phili and Canada
 - Goal side effects, binding antibody titers, neutralizing antibodies, T cell response
 - Expected completion among 40 volunteers in Q4 2016
 - Larger next phase trial in early 2017



Zika Vaccines: 2 Tested Together

- Developed by WRAIR through NIAID
 - Another DNA vaccine which also targets prM-Env and envelope proteins
 - Translating DNA vaccine to humans
 - “ZPIV”: purified inactivated with or without adjuvant
- In mice, both 100% protective with single dose
- Placebo controlled 16 monkeys vaccinated and boosted at one month had 100% protection against infection
- Partnering with Sanofi Pasteur, phase I begins October and phase II anticipated in December
- WHO says at least 15 others in pipeline

Abbink et al., Science 10.1126/science.aah6157 (2016).

Larocca et al. Nature 10.1038/nature18952 (2016). Medline doi:10.1038/nature18952



Pipeline Tracking

Institution	Technology	Status & timelines	Collaboration
Bharat	Inactivated purified virus as priority project ; VLP with pRME protein	Preclinical work ongoing, GMP lots 3Q2016	
Bio-Manguinhos / Fiocruz	Inactivated purified ; YF17DD chimeric ; VLP ; DNA	Work initiated	Under consideration
Butantan	Live dengue recombinant ; inactivated purified	Work initiated	Collaboration with US NIH
US CDC	DNA plasmid expressing VLP ; live recombinant adenovirus	Work initiated	
Hawaii Biotech	Insect cell line produced recombinant proteins plus Alhydrogel or proprietary adjuvant fom collaborator	Work initiated. GMP lots 4Q2016	Under discussion
InOvivo/GeneOne	DNA – electroporation; work initiated	Preclinical work initiated	
Institut Pasteur	Lentivirus-vectored, measles vectored	Work initiated	Measles vectored work in collaboration with Themis
NewLink	Purified Inactivated virus	Work initiated, clinical evaluation 2018	
US NIH	Zika targeted mutation live attenuated (longer-term), DNA, live VSV recombinant	Work initiated	Various
Novavax	E protein – nanoparticles	Preclinical work initiated	
Replikin	Synthetic replikin peptides	Preclinical work initiated	
Sanofi	ChimeriVax (YF17D) ; other undisclosed technologies	Work initiated	Under consideration
Themis Bioscience	Measles vaccine virus vector (live)	Work initiated	Institut Pasteur
Valneva	Purified inactivated vaccine	Work initiated	

In addition, the following institutions have communicated about their active consideration of the field or have committed planning/discovery stage activities: CureVac, Geovax, GlaxoSmithKline, Institut Pasteur, Johnson & Johnson, Merck, Oxford University, Pax Vax, Pfizer, Profectus Biosciences, Protein Sciences, Sementis, Sinergium, Takeda.

Preclinical work refers to animal studies

<http://www.who.int/csr/research-and-development/zika-rd-pipeline.pdf>



Other Approaches

- Two drugs developed to protect neurons
- Multiple drugs that may stop viral replication
 - Amodiaquine, chloroquine, ribavirin
 - BCX4430, GS-5734, NITD008
- Monoclonal antibodies



Sept 28 Funding Package

- \$394M for CDC for vector control, technical assistance, international response activities
 - \$44M to reimburse states for PHEP funding transferred for Zika
- \$397M for NIH for Zika research, vaccine, and diagnostic tests
- \$75M to reimburse healthcare provided in states and territories with Zika transmission for those without private health insurance
- \$40M for Community Health Centers in PR and other U.S. territories
- \$6M for NHS Corps in PR and other territories
- \$20M for Maternal and Child Health special projects of regional and national significance in PR and other territories



Zika's Myriad Ethical Issues

- Fate of Olympics and Paralympics
- Vector control
 - Mosquito genetic modification, irradiation, Wolbachia infection
 - Larvicides in water, aerial spraying
- Expediting vaccine development, esp pregnant women
- Access to personal protection against vectors
 - Clothing, bednets, repellents, environment modification

Zika Ethics Consultation: Ethics Guidance on Key Issues Raised by the Outbreak
Pan American Health Organization Washington, D.C., April 6-7, 2016



Women's Privileged Access

- Information
- Personal protection
 - Vector avoidance
 - Condoms
- Diagnostics
- Reproductive options
 - Birth control
 - Pregnancy termination
- Support for adverse pregnancy outcome



Zika Virus Epidemiology and Recommendations

Benjamin P. Chan, MD, MPH

September 30, 2016

NH Division of Public Health Services

Outline

- Updated Epidemiology
- Management of Pregnant Women
- Management of infants
- Reproductive Planning

Current Active Zika Transmission



Case Counts: U.S. States

- Travel-associated cases reported: 3,565
- Laboratory acquired cases reported: 1
- Locally acquired mosquito-borne cases reported: 59 (All in Florida)
- Total: 3,625
 - Guillain-Barré syndrome: 12
 - Sexually transmitted: 30 (including 1 in NH)

Travel Associated U.S. Cases

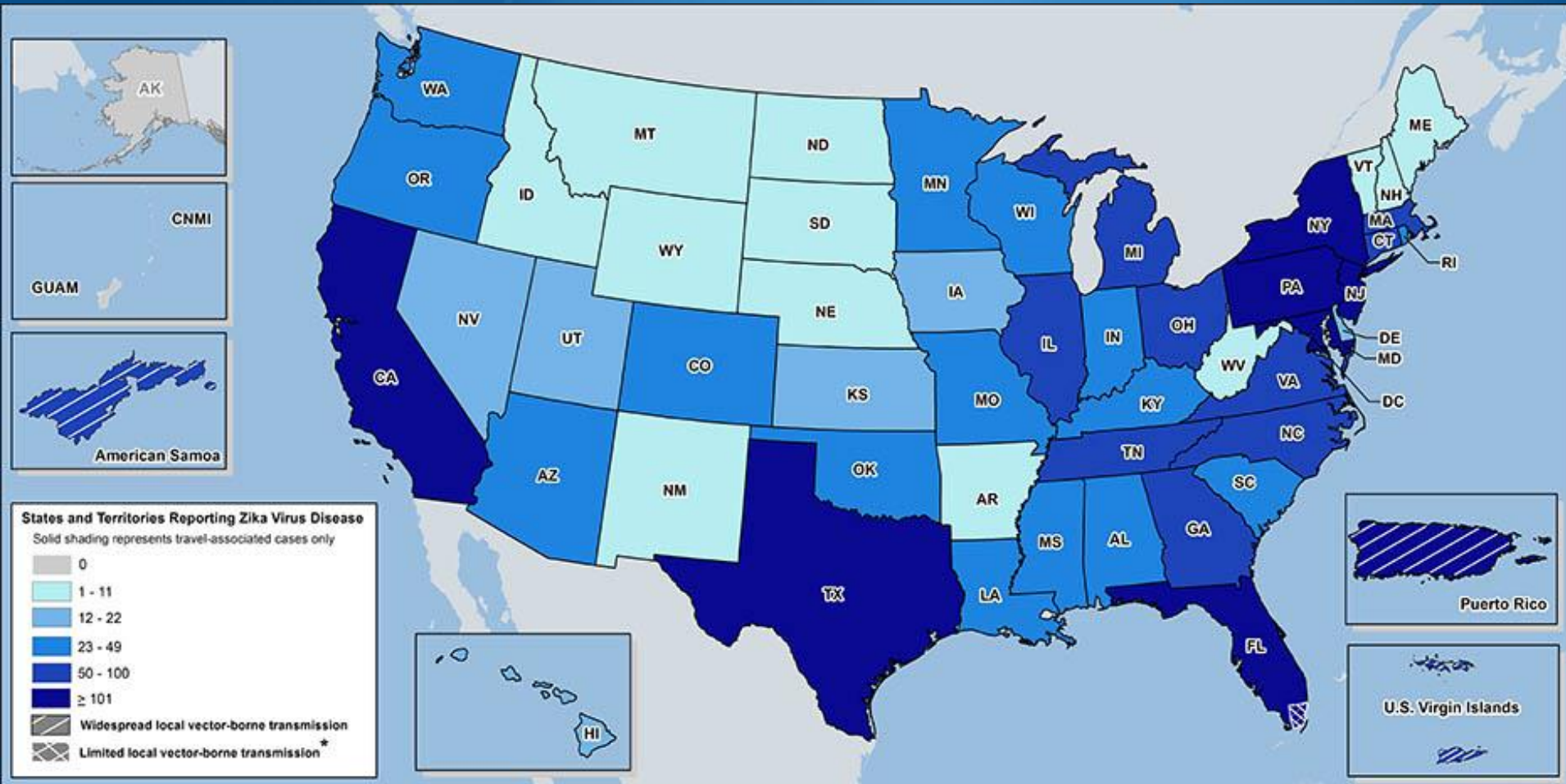
- New York City: 811 (23%)
- Florida: 672 (19%)
- California: 267 (7%)
- Texas: 204 (6%)
- New Jersey: 133 (4%)
- Pennsylvania: 129 (4%)

Case Counts: U.S. Territories

- Locally acquired cases reported: 21,988 (98% in Puerto Rico)
- Travel-associated cases reported: 81
- Total: 22,069*
 - Guillain-Barré syndrome: 39

*Sexually transmitted cases are not reported for US territories

Zika Cases in the United States

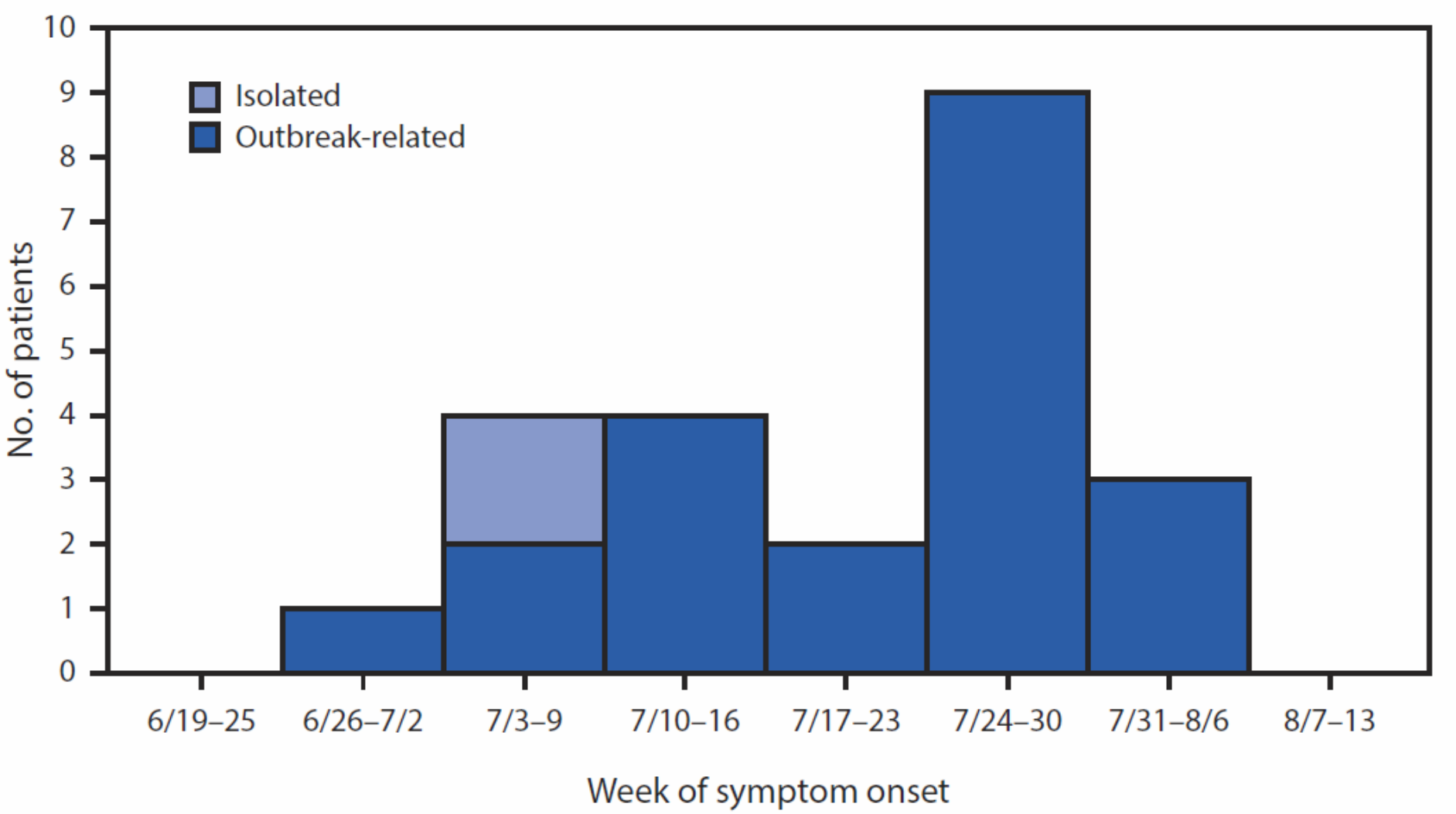


Wynwood Neighborhood, Miami, FL

- 2 cases identified in early July
- Cases worked within 120 meters of each other
- Tested both workplaces:
 - Workplace A: 1 additional case
 - Workplace B: 5 additional cases
- Community Uro-survey (150 meter radius):
 - 52 urine specimens from 28 households collected
 - 6 asymptomatic cases identified
- August 1st: CDC issued a travel advisory

- 3 surveys at locations bordering the 1-square mile area:
 - 289 specimens collected from 150 households
 - One travel-associated case
 - No cases of local transmission
- FQHC clinic within 1-square mile neighborhood
 - 77 urine samples collected
 - 3 additional cases
- Additional cases have since been identified in the Wynwood area
- Total associated case count: 29

FIGURE 2. Number of patients (n = 23) with symptomatic cases of locally transmitted Zika virus infection, by week of symptom onset and outbreak status — Miami-Dade and Broward counties, Florida, June–August 2016



CDC Recommendations on Florida

- Pregnant women should avoid travel to a 4.5-square mile area of Miami Beach
 - Exposure risk period: July 14th – present
- No longer recommends against travel for pregnant women to Wynwood
 - Exposure risk period: June 15 – Sept 18
- Pregnant women and partners of pregnant women concerned about potential Zika-virus exposure may consider postponing non-essential travel to all parts of Miami-Dade County

Transmission of Zika

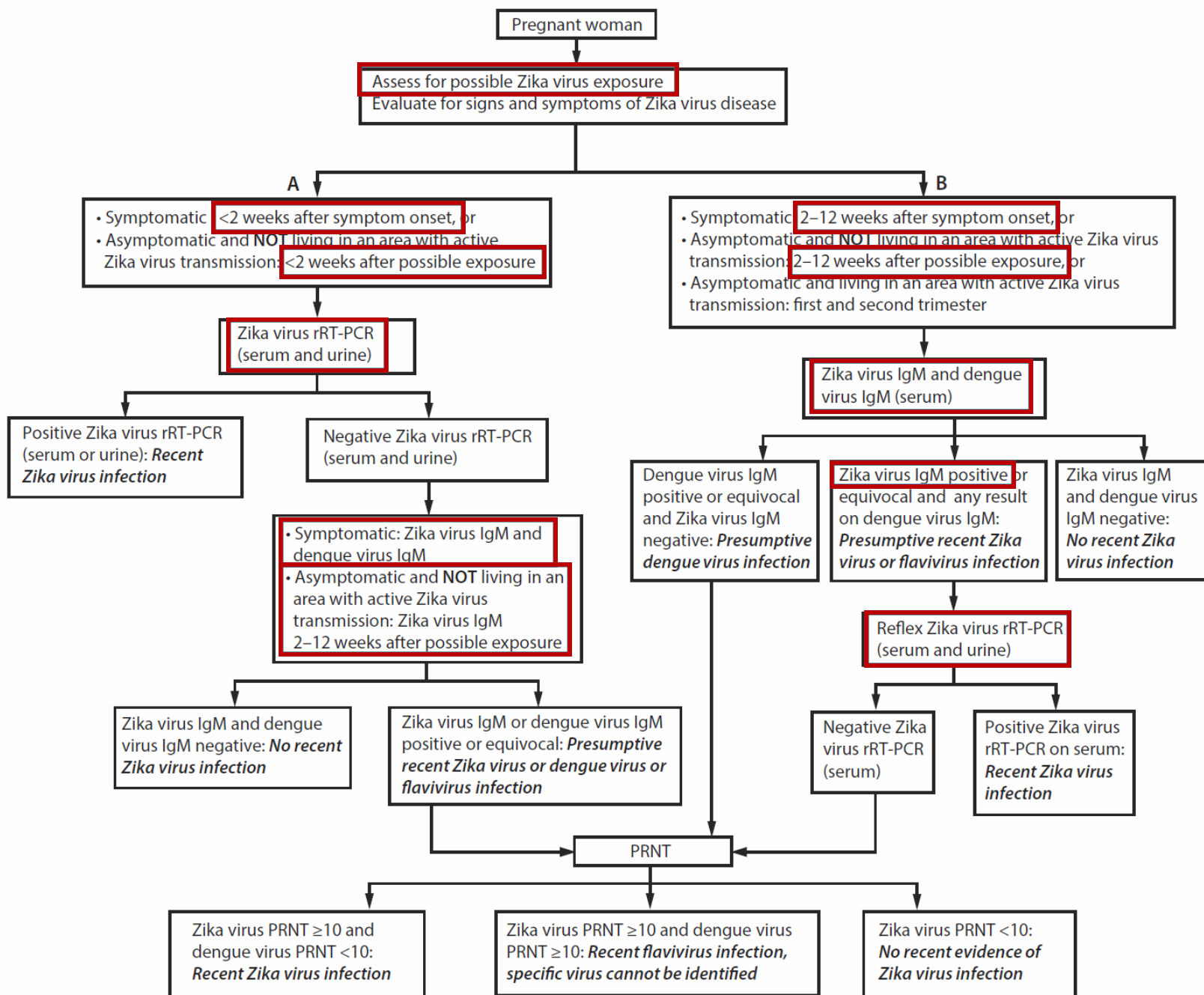
- Main modes of transmission:
 - Travel to an area with active transmission (mosquito bite)
 - Sexual contact with someone who has traveled
- Main concern is:
 - Pregnant women and their developing fetuses
 - AND
 - Those trying to conceive (intentionally or unintentionally)

General Recommendations Re: Travel to an Area with Active Zika Transmission

- Pregnant women should NOT travel
- Pregnant women who must travel:
 - Strictly follow steps to avoid mosquito bites
- Pregnant women who have traveled:
 - Talk to healthcare provider about testing
- Pregnant women who had sex with a traveler:
 - Talk to healthcare provider about testing
- Sexual partners of pregnant women who traveled:
 - Abstain from sex or consistently & correctly use condoms for the duration of pregnancy

CDC Guidelines for Caring for Pregnant Women with Possible Zika Exposure

<http://www.cdc.gov/zika/hc-providers/pregnant-woman.html>



What about someone who presents more than 12 weeks after exposure?

- Pregnant women with possible Zika virus exposure who seek care >12 weeks after symptom onset or possible exposure, IgM antibody testing might be considered.
- A negative IgM or PCR result >12 weeks after symptom onset or possible exposure does not rule out recent Zika virus infection.
- Serial fetal ultrasounds should be considered.

Healthcare Providers should call DPHS for Assistance with Testing

- 603-271-4496
- Patients should NOT call for testing

CDC Guidelines for Evaluation and Management of Infants with Possible Congenital Zika Virus Infection

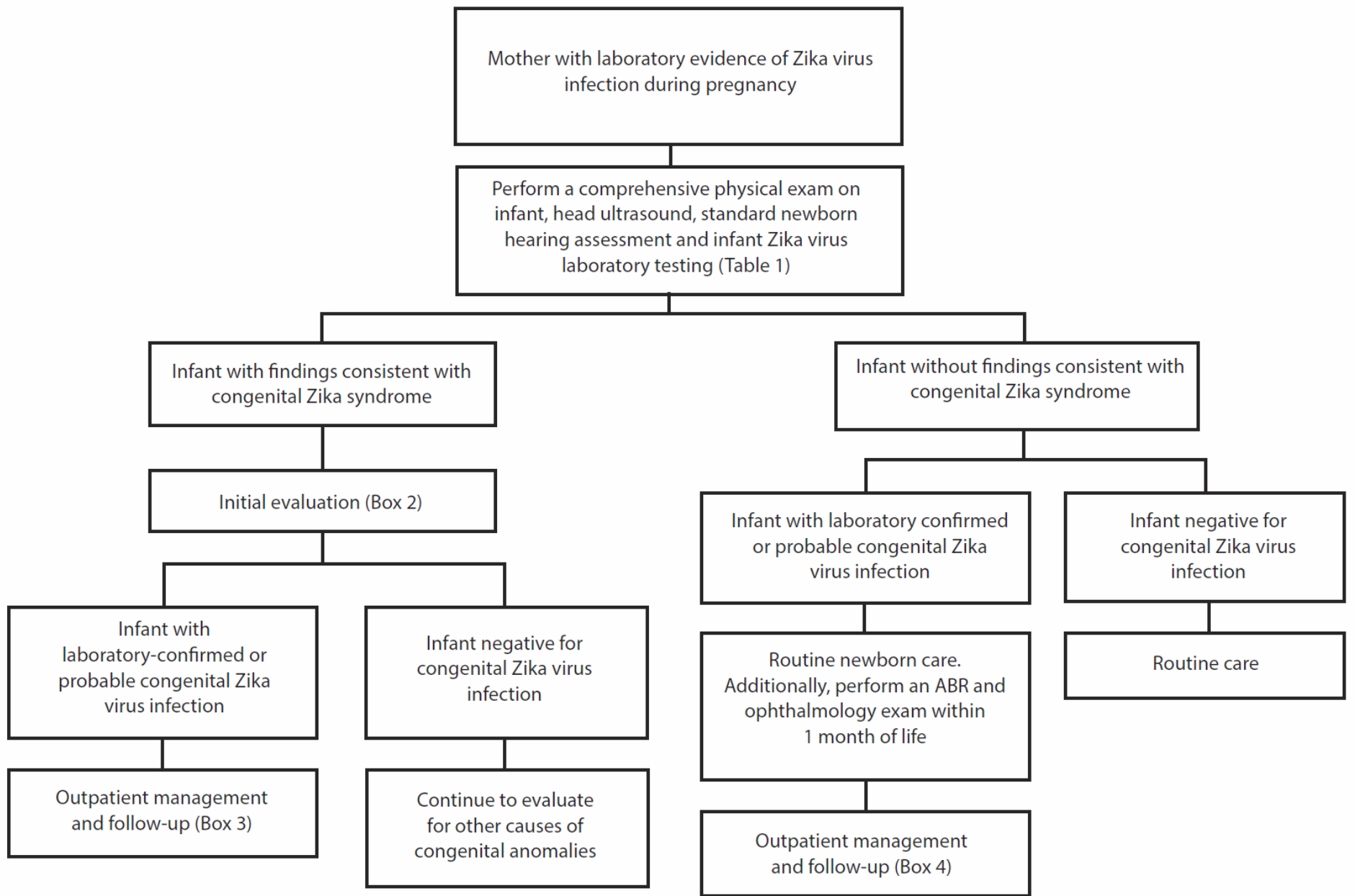
<http://www.cdc.gov/zika/hc-providers/infants-children.html>

Infant Diagnostic Testing For:

- Infants born to mothers with lab evidence of Zika infection

OR

- Infants with findings of congenital Zika syndrome AND whose mothers had a possible epidemiologic exposure
- *Infant testing includes: Urine and Serum PCR, Serum IgM, +/- CSF testing (if available) for PCR and IgM*



Should Non-Pregnant Patients be Tested for Zika?

- Testing to assess risk of sexual transmission is **not recommended**.
- Testing to assess risk to couple who are trying to conceive (and risk to potential fetus) is **not recommended**.
- Testing is available for people who may have been exposed to Zika through sex and who have symptoms.
- Testing is available for individuals who may have been exposed AND are symptomatic, if the healthcare provider thinks it will affect clinical management.

Reproductive Planning

- Healthcare providers should discuss reproductive/family planning with patients
- Those not wanting to conceive should be made aware of the risks of Zika and given access to effective contraception
- Semen testing is not available and not recommended to assess for sexual transmission risk

CDC Guidance For Those Trying to Conceive (*Updated by CDC 9/30/16*)

- Women (whether symptomatic or asymptomatic):
 - Wait **8 weeks** after symptoms first appeared, or exposure occurred, before attempting conception
- Men (whether symptomatic or asymptomatic):
 - Wait **6 months** after symptoms first appeared, or exposure occurred, before attempting conception
- Men and women trying to conceive should consider avoiding travel to areas of active transmission

Questions?