



## Zika Update: Summer 2016 Key Information for Clinicians

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# Objectives

- 1. Understand the scope of the current Zika Virus outbreak
- Recognize the clinical presentation of Zika Virus infection in adults, including pregnant women, children and infants
- Be familiar with suggested evaluation and testing of potentially infected individuals, particularly pregnant women and infants born to infected women
- 4. Be aware of the CNHS Congenital Zika Program and available resources for referral of patients.



### Case Presentation

- 33 yo G1Po Washington, DC resident vacationed for one week in Belize, Guatemala and Cancun at 11 weeks gestation
- 2 days after return to US, developed illness lasting 5 days:
  - Low grade fever
  - Erythematous maculopapular rash
  - Myalgia
  - Mild photophobia
  - No joint symptoms
  - -Husband (also on trip) developed identical symptoms within same time frame





### Case presentation (continued)

- Obstetrical Evaluation:
  - 13 weeks gestation (1 week post-symptoms):
    - Fetal ultrasound normal
  - 16 and 17 weeks gestation (4 and 5 weeks post-symptoms)
    - Repeat fetal ultrasounds normal
    - Serum Zika IgM and IgG positive, Zika RT-PCR positive
  - 19 weeks gestation (7 weeks post-symptoms):
    - Repeat fetal ultrasound abnormal
    - Referred to CNHS Fetal Medicine Institute for multidisciplinary evaluation
    - Fetal MRI: Multiple CNS abnormalities detected
    - Amniotic Fluid Zika RT-PCR positive



#### The NEW ENGLAND JOURNAL of MEDICINE

#### BRIEF REPORT

# Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities

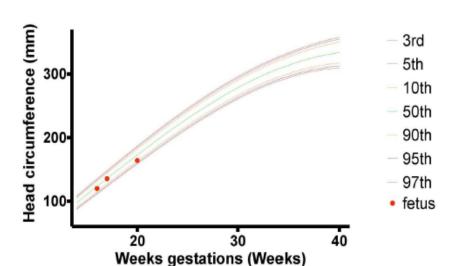
R.W. Driggers, C.-Y. Ho, E.M. Korhonen, S. Kuivanen, A.J. Jääskeläinen, T. Smura, A. Rosenberg, D.A. Hill, R.L. DeBiasi, G. Vezina, J. Timofeev, F.J. Rodriguez, L. Levanov, J. Razak, P. Iyengar, A. Hennenfent, R. Kennedy, R. Lanciotti, A. du Plessis, and O. Vapalahti

Epub ahead of print : Mar 30, 2016



### Fetal Ultrasound – 19 weeks

- No calcifications
- No "microcephaly"
- However, reduction in fetal head circumference from 47th to 24<sup>th</sup> percentile between 16 to 20weeks gestation
- Thin cerebral cortex
- Increased extra-axial spaces
- Dilated third ventricle
- Enlargement of frontal horns
- Absent cavum septum pellucidum

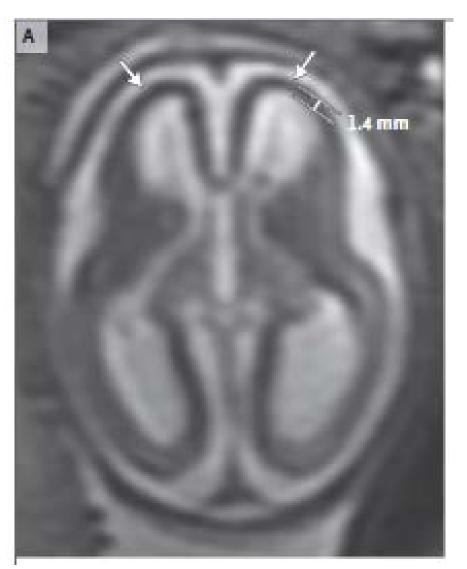


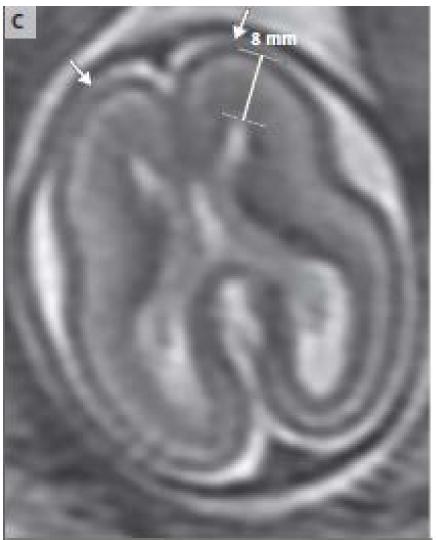






### Fetal MRI at 20 weeks gestation: Severe atrophy of cortical mantle





- Normal lamination pattern absent
- Subplate zone largely undetectable



### Fetal MRI at 20 weeks: Small Corpus Callosum

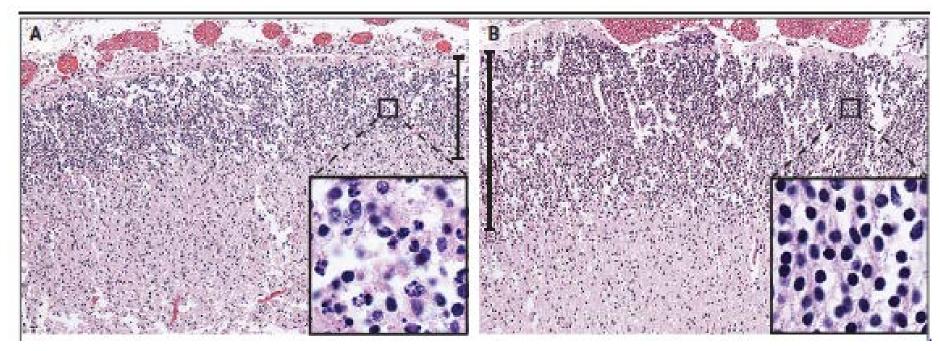




- No focal destructive lesions in cortex or white matter
- Cerebellum normal in size and appearance



### Neuropathologic Analysis of Fetal Zika Virus Infection



**Parietal Cortex** 

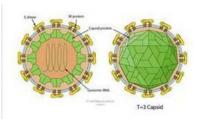
**Occipital Cortex** 

Children's National ...

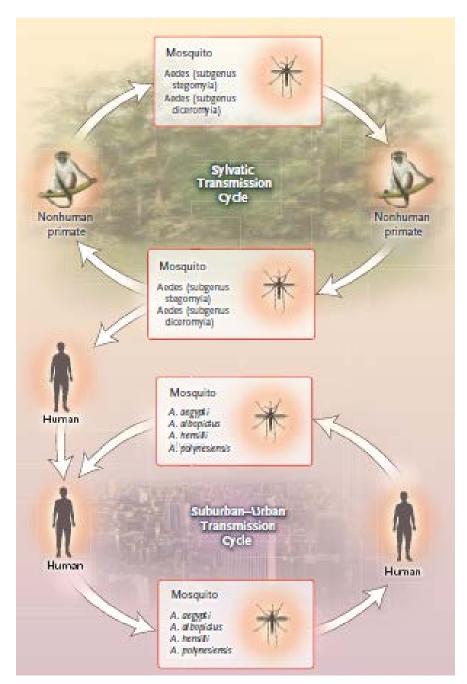
 Apoptosis of intermediately differentiated post-migratory neurons in neocortex Objective 1: Understand Scope of Current Zika Outbreak



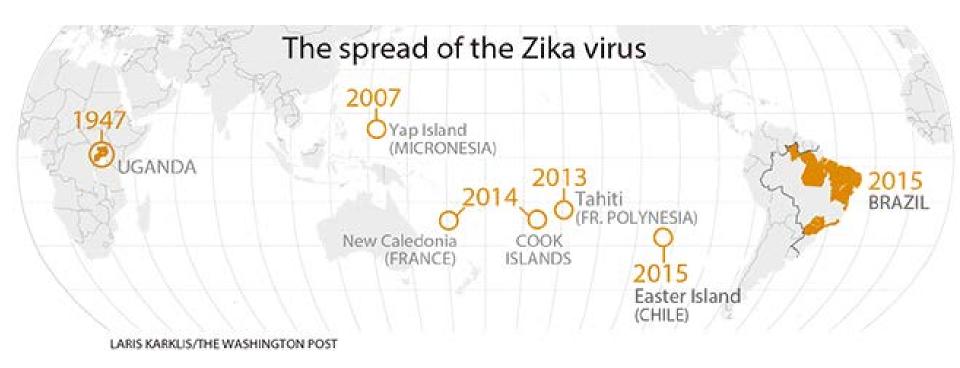
# Zika - What is it? - Virology



- Single-stranded RNA virus
- *Flaviviridae* family, genus *Flavivirus*.
  - Related to Dengue,
     Yellow Fever and West
     Nile viruses
- Non-human and human primates likely main reservoirs
- Mosquitos are vectors
- Anthroponotic (human-tovector-to-human) transmission occurs during outbreaks



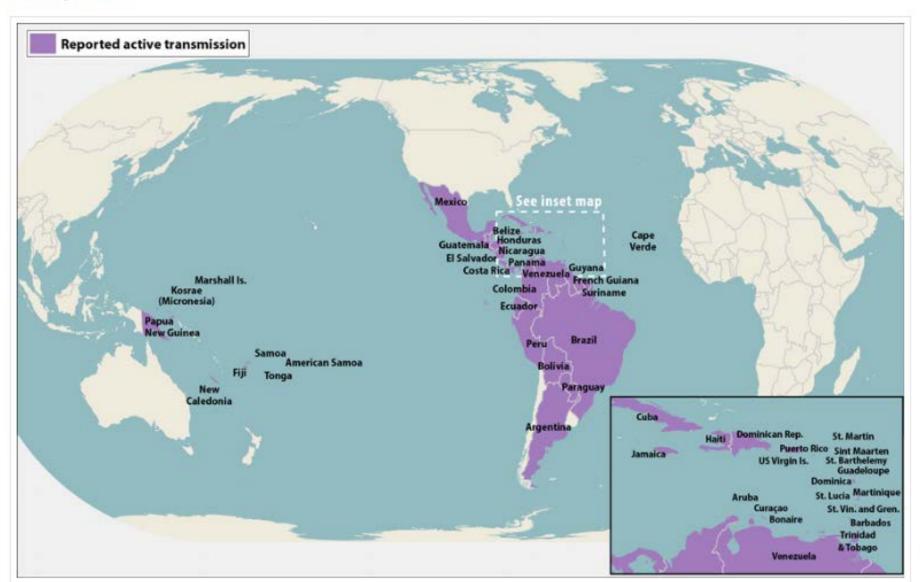
# Zika – Epidemiology and Emergence in Americas





# Where Local Transmission of Zika Virus has Occurred as of May 26, 2016

As of May 26, 2016



### Zika – How Concerned Should We Be in the US?

- Feb 1 WHO announces Zika as Global Emergency
- Feb 8 CDC activated to Level 1 Response (Highest)
- Spreading explosively in the Americas
- To date, local transmission of Zika virus <u>has not</u> been identified in the continental United States.
- U.S. travelers who visit countries where Zika is found have become infected
- U.S. mainland does have Aedes species mosquitos that can become infected with and spread Zika virus
- Limited local transmission may occur in mainland US but widespread transmission unlikely
  - Projections based on experience with recent chikungunya and dengue outbreaks in the US (same mosquito vector)
  - Suggests Zika outbreaks in US mainland will be small/focal



# Current US and US Territory Case Counts (As of June 2-8, 2016)

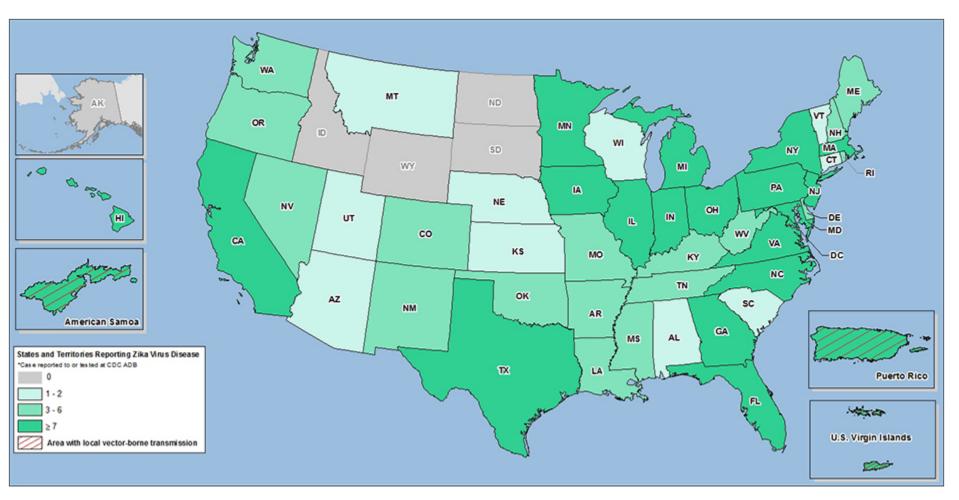
#### **US States**

- Total 691
  - Travel associated: 691
  - Locally acquired vector-borne cases: o
  - ■Pregnancy (with lab evidence): 206
  - ■Sexually Transmitted: 11
  - ■Guillan-Barre syndrome: 2

#### **US Territories**

- Total 1305
  - Travel associated : 4
  - Locally acquired: 1301
  - Pregnancy (with lab evidence): 106
  - ■Guillan-Barre syndrome: 7





Laboratory-confirmed Zika virus disease cases reported to ArboNET by state or territory — United States, 2015–2016 (as of June 08, 2016)

VA: 20

MD: 21

**DC:** 6

**WV: 7** 

16



### A. aegypti



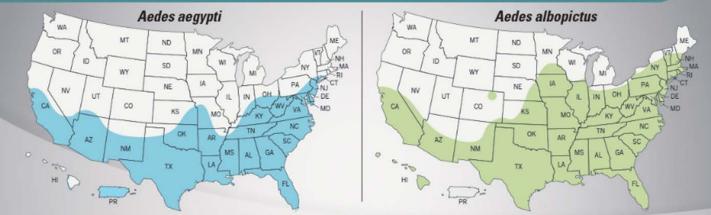
Originated in sub-Saharan Africa, spread throughout the tropics centuries ago

### A. albopictus



Originated in Asia, spread to the Americas, Africa and Europe beginning in 1985

#### Estimated range of Aedes aegypti and Aedes albopictus in the United States, 2016\*



Aedes aegypti mosquitoes are more likely to spread viruses like Zika, dengue, chikungunya than other types of mosquitoes such as Aedes albopictus mosquitoes.

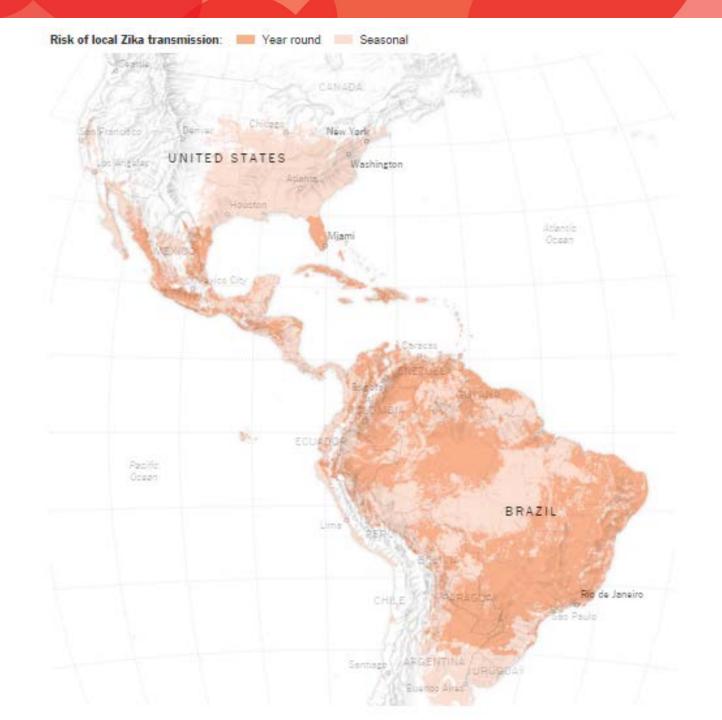
- These maps show CDC's best estimate of the potential range of Aedes aegypti and Aedes albopictus in the United States.
- These maps include areas where mosquitoes are or have been previously found.
- Shaded areas on the maps do not necessarily mean that there are infected mosquitoes in that area.

\*Maps have been updated from a variety of sources. These maps represent CDC's best estimate of the potential range of Aedes aegypti and Aedes albopictus in the United

States. Maps are not meant to represent risk for spread of disease.

SOURCE: Zika: Vector Surveillance and Control, www.cdc.gov/zika/vector/index.html





## Future spread in US?





### Objective 2:

Recognize the clinical presentation of Zika Virus infection in adults, children, and infants born to infected women



### **Zika – Clinical Features**

- Relatively mild problem for adults
  - 80% completely asymptomatic
  - 20% symptomatic:
    - 2 to 7 days after being bitten:
      - Fever, rash, arthralgia, and/or conjunctivitis
      - Also common: Myalagia, headaches
    - Symptoms last 5-7 days
  - Severe disease requiring hospitalization uncommon;
     case fatality is low
- Major risk for the developing fetus
  - Microcephaly and other birth defects
- Guillain-Barré syndrome reported following Zika



## Rash







### FIGURE 1

Conjunctivitis in a case of imported Zika virus infection from French Polynesia, Japan, January 2014



Although the patient was afebrile upon examination, both bulbar conjunctivas appeared congested.



### Joint Involvement



### Guillain-Barre Syndrome (GBS) Association

- Acute, inflammatory polyradiculoneuropathy with resultant weakness, decreased reflexes, and sometimes paralysis
- Rare disorder where a person's own immune system damages the nerve cells
- Symptoms can last a few weeks or several months.
- Most people fully recover from GBS, some people have permanent damage and in rare cases, people have died.
- Although there is an association, we do not yet know if Zika virus infection causes GBS
  - 4-8 fold increases in baseline incidence in countries with circulating Zika
- Studies in progress









# Congenital Microcephaly due to Zika





Baby with Microcephaly

Baby with Typical Head Size



- ■Brazil Ministry of Health reported marked increase in the number of babies born with microcephaly.
  - Identification of >4000 cases of microcephaly, some severe and fatal, between October 2015 and January 2016.
  - Prior baseline was about 150 cases per year
- 10% (around 400) of suspected cases have been confirmed microcephaly
  - <10% of the confirmed microcephaly are lab-confirmed as Zika</p>
- Large Case Control Study in progress (CDC)









### Zika Virus Infection in Pregnant Women in Rio de Janeiro — Preliminary Report

Patrícia Brasil, M.D., Jose P. Pereira, Jr., M.D., Claudia Raja Gabaglia, M.D., Luana Damasceno, M.S., Mayumi Wakimoto, Ph.D., Rita M. Ribeiro Nogueira, M.D., Patrícia Carvalho de Sequeira, Ph.D., André Machado Siqueira, M.D., Liege M. Abreu de Carvalho, M.D., Denise Cotrim da Cunha, M.D., Guilherme A. Calvet, M.D., Elizabeth S. Neves, M.D., Maria E. Moreira, M.D., Ana E. Rodrigues Baião, M.D., Paulo R. Nassar de Carvalho, M.D., Carla Janzen, M.D., Stephanie G. Valderramos, M.D., James D. Cherry, M.D., Ana M. Bispo de Filippis, Ph.D., and Karin Nielsen-Saines, M.D. March 4, 2016 | DOI: 10.1056/NEJMoa1602412

NEJM March 4, 2016

- Enrolled 88 pregnant women in whom a rash had developed within the previous 5 days and tested blood and urine specimens for ZIKV by PCR
  - 72% positive; timing of acute ZIKV infection 5 to 38 weeks of gestation.
  - Fetal ultrasonography in 42 ZIKV-positive women (58%) and in all ZIKV-negative
    - Fetal abnormalities detected by ultrasound in in 12 of the 42 (29%) PCR
       + women
    - Adverse findings included:
      - Fetal deaths at 36 and 38 weeks of gestation (2 fetuses)
      - In utero growth restriction with or without microcephaly (5 fetuses)
      - Ventricular calcifications or other central nervous system (CNS) lesions (7 fetuses)
      - Abnormal amniotic fluid volume or cerebral or umbilical artery flow (7 fetuses).

Children's National ...



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### **Zika - Potential Modes of Transmission**

- Bite from Vector Vast Majority
- Mother to Fetus/Infant:
  - In Utero
  - Perinatal
- Sexual Transmission
- Transfusion Related
- Other body fluids: Saliva/Urine/Breastmilk
  - Virus detectable, but transmission not documented



### **Sexual Transmission**

Update: Interim Guidance for Prevention of Sexual Transmission of Zika Virus — United States, 2016

Weekly/ April 1, 2016 / 65(12);323-325

- Feb 2, 2016: First Zika virus transmission within US: Dallas, Texas
  - Sexual contact with partner who traveled to Venezuela
- Duration of shedding in sperm may be up to 2 months
- No female to male transmission documented.
- New Recs:
  - Pregnant Partner: Abstain for duration of pregnancy
  - Nonpregnant Partner:
    - Symptomatic Male
      - Abstain/Condoms for > 6 months after symptoms
    - Asymptomatic Male with Travel Exposure:
      - Abstain/Condoms for <u>></u> 8 weeks after return

Objective 3
Be familiar with suggested evaluation and testing of potentially infected individuals



#### **Laboratory Diagnosis**



- RT-PCR
  - Blood: Indicated up to 7 days after symptom onset
  - Urine: Indicated up to 14-21 days after symptom onset
- Serology
  - Serum specimens collected >4 days after the symptom onset should be tested for Zika IgM and neutralizing antibody
  - Distinguishing Zika IgM from other flavivirus (e.g. Yellow Fever, Dengue) infections may be difficult (cross-reactive) - requires plaque reduction neutralization assay
  - CDC/DOH perform all testing (submitted via State Health Dept)
  - CDC Specimen Submission Forms
  - ■Commercial Testing:
    - FDA Emergency Authorization for Quest/Focus Labs PCR
    - No commercial IgM available yet



Update: Interim Guidance for Health Care Providers Caring for Women of Reproductive Age with Possible Zika Virus Exposure — United States, 2016

Weekly / April 1, 2016 / 65(12):315-322 CDC's Response to Zika **Updated Interim Guidance:** Testing Algorithm for a Pregnant Woman with Possible Exposure to Zika Virus<sup>1,2</sup>, Not Residing in an Area with Active Zika Virus Transmission<sup>3</sup> Pregnant woman with possible exposure to Zika virus IgM testing 2-12 weeks after Test for 7ika virus infection return if asymptomatic Positive or inconclusive for Zika virus infection Negative for Zika virus infection Fetal ultrasound to detect abnormalities Consider serial fetal ultrasounds consistent with Zika virus disease4 Fetal abnormalities Fetal abnormalities consistent with Zika virus consistent with Zika virus Possible exposure to Zika virus includes travel to an area with active transmission of Zika virus disease present disease **not** present (http://wwwnc.cdc.gov/travel/notices/), or sex without a condom with a man who traveled to. or resided in, an area with ongoing transmission of Zika virus. \*Testing is not currently recommended for pregnant women with possible sexual exposure to Zika virus if both partners are asymptomatic. Routine prenatal care Petersen EE, Polen K, Meaney-Delman D, et al. Update: Interim Guidance for Health Care Providers Retest pregnant woman

for Zika virus infection

\*Fetal abnormalities consistent with Zika virus disease include microcephaly, intracranial calcifications, and brain and eye abnormalities. Fetal ultrasounds might not detect abnormalities until late second or early third trimester of pregnancy.

Caring for Women of Reproductive Age with Possible Zika Virus Exposure-- United States, 2016.

MMWR, 25 March 2016.

#### CDC's Response to Zika

#### **Updated Interim Guidance:**

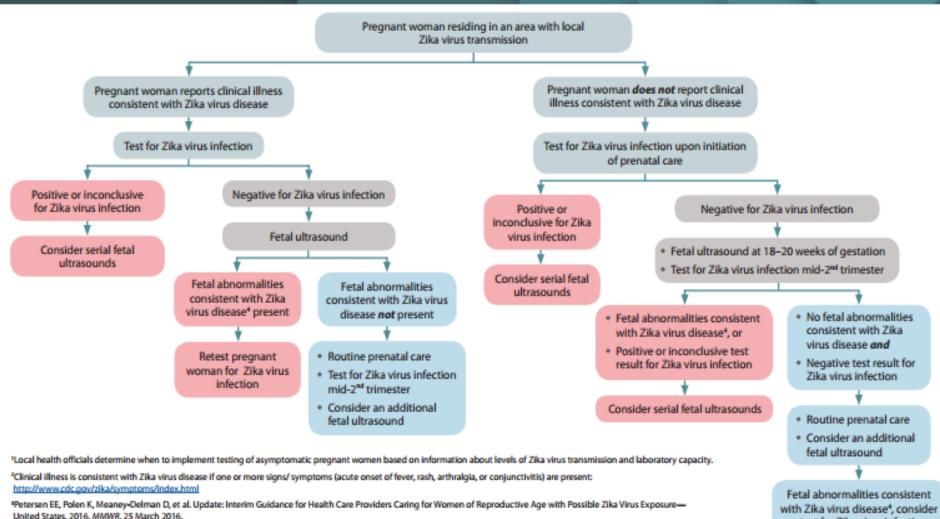
abnormalities until late second or early third trimester of pregnancy.

Testing Algorithm for a Pregnant Woman Residing in an Area with Active Zika Virus Transmission<sup>1</sup>, with or without Clinical Illness<sup>2</sup> Consistent with Zika Virus Disease<sup>3</sup>

Fetal abnormalities consistent with Zika virus disease include microcephaly, intracranial calcifications, and brain and eye abnormalities. Fetal ultrasounds might not detect

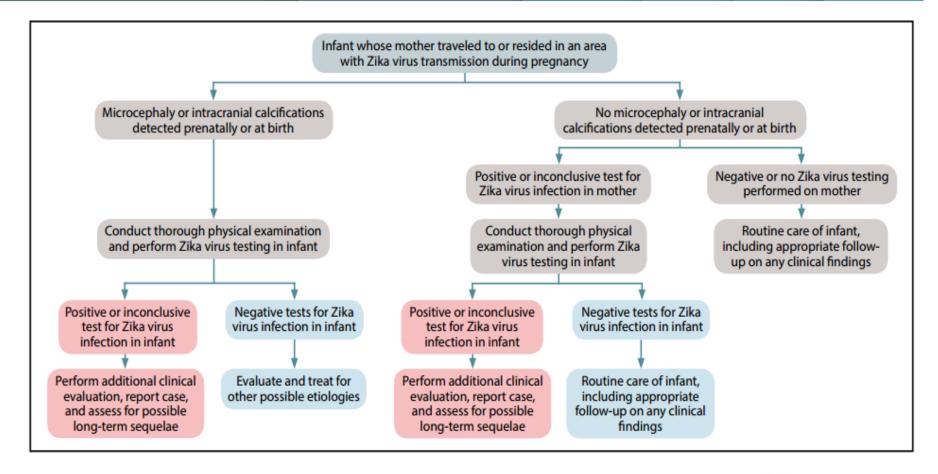


retest for Zika virus infection



## Interim guidelines for the evaluation and testing of infants whose mothers traveled to or resided in an area with ongoing Zika virus transmission\* during pregnancy<sup>†§</sup>







#### Laboratory Diagnosis for Infants When Indicated

- Which Infants Need Testing?
  - Infants with microcephaly, calcifications or other CNS abnormality born to woman who traveled to or resided in affected area during pregnancy
  - Asymptomatic infants born to mom with positive or inconclusive Zika testing
- What Should Be Tested?
  - Infant serum (cord blood or blood within 2 days of life):
    - Zika PCR; Zika and Dengue IgM and neutralizing Abs
  - If CSF obtained for other studies
    - Zika PCR; Zika and Dengue IgM and neutralizing Abs
  - Placenta and umbilical cord
    - Histopathologic examination
    - Immunohistochemical staining on fixed tissue
    - Zika PCR on frozen tissue

#### CDC's Response to Zika

#### Recommended evaluation and long-term follow up for infants with possible congenital Zika virus infection\*



#### Evaluation for all infants with positive or inconclusive Zika virus test results

- \* Thorough physical examination, including careful measurement of head circumference, length, weight, and assessment of gestational age
- \* Evaluation for neurologic abnormalities, dysmorphic features, enlarged liver or spleen, and rash/other skin lesions (including photographs of any rash, skin lesions, or dysmorphic features)†
- Cranial ultrasound (unless performed in the third trimester and clearly showed no brain abnormalities)
- Ophthalmologic evaluation (including retina) before hospital discharge or within 1 month after birth
- \* Evaluation of hearing by evoked otoacoustic emissions testing or auditory brainstem response testing before hospital discharge or within 1 month after birth
- Consultation with appropriate specialist for any abnormal findings

#### Additional evaluation for infants with positive or inconclusive Zika virus test results who have microcephaly or other findings consistent with congenital Zika virus infection

- Consultation with clinical geneticist or dysmorphologist
- Consultation with pediatric neurologist
- Testing for other congenital infections (such as cytomegalovirus, toxoplasmosis, and rubella); consider consultation with pediatric infectious disease specialist
- Complete blood count, platelet count, and liver function and enzyme tests
- Genetic or other teratogenic causes should be considered if additional anomalies are identified through history, clinical examination, or imaging studies

#### Long-term follow-up for infants with positive or inconclusive Zika virus test results

- Additional hearing screen at 6 months of age and audiology follow up of abnormal newborn hearing screening
- Continued evaluation of developmental characteristics and milestones, as well as head circumference, through first year of life
- Consultation with appropriate medical specialists (e.g., pediatric neurology, developmental and behavioral pediatrics, physical and speech therapy) if any abnormalities are noted and as concerns arise
- \*Refers to infants with positive or inconclusive Zika virus test results
- † Informed consent may be required per institutional policy



#### BOX 2. Recommended clinical evaluation and laboratory testing for infants with possible congenital Zika virus infection

- Comprehensive Physical Examination:
  - Head circumference, growth parameters, gest age
  - Attention to neurologic abnormalities, dysmorphic features, HSM, Rash, Skin Lesions
- Cranial Ultrasound
- Hearing evaluation
  - Evoked OAE or BAER before discharge or within one
    - month
- Ophthalmologic evaluation



#### Additional Evaluation For Infant with CNS Abnormalities

- Consult with geneticist or dysmorphologist
  - Consideration of other teratogenic or genetic causes based on other detected congenital abnormalities on physical exam or imaging
- Consult with pediatric neurologist
  - Determine imaging with U/S, MRI, CT, EEG
  - -Consult with Pediatric Infectious Diseases
    - Testing for other Congenital Infectoins
    - CMV, HSV, Toxoplasma, Lymphocytic Choriomeningitis Virus, Syphilis, Rubella
  - -Lab testing:
    - CBC, Liver enzymes and Liver function testing



#### Potential Long Term - Associated issues with Microcephaly

- Seizures
- Developmental delay
  - Speech
  - Motor milestones (sitting, standing, walking)
     Intellectual disability
- Problems with movement and balance
- Feeding problems, such as difficulty swallowing
- Hearing loss
- Vision problems



#### Pregnant Women Q and A

## If a woman has traveled to an area with Zika virus transmission, should she wait to get pregnant?

- Zika virus usually remains in the blood of an infected person for only a few days to a week.
  - However, prolonged viremia possible in pregnant women
- The virus will not cause infection in an infant that is conceived after the virus is cleared from the blood.
- There is currently no evidence that Zika virus infection poses a risk of birth defects in future pregnancies.
- A women considering or already pregnant, who has recently travelled (or whose partner has travelled) to an area with local Zika transmission, should consult her healthcare provider after returning.

## CDC Recommendations for Women With Possible Zika Exposure: Suggested Timeframes to wait before trying to get pregnant

Suggested timeframe to wait before trying to get pregnant		
Possible exposure via recent travel or sex without a condom with a man infected with Zika		
	Women	Men
Zika <u>symptoms</u>	Wait at least 8 weeks after symptoms start	Wait at least 6 months after symptoms start
No Zika symptoms	Wait at least 8 weeks after exposure	Wait at least 8 weeks after exposure.  Talk with your healthcare provider
People living in areas with Zika		
	Women	Men
Zika symptoms	Wait at least 8 weeks after symptoms start	Wait at least 6 months after symptoms start
No Zika symptoms	Talk with doctor or healthcare provider	Talk with doctor or healthcare provider



#### **Considerations for Travelers**

- January 15: CDC issues Level 2 travel alert for <u>pregnant</u> <u>women in any trimester</u> who may be traveling to South/Central American or Carribbean countries /territories where Zika is spreading
- No current recommendations/restrictions made for other populations including immunocompromised or children



Objective 4
Be aware of the CNHS Congenital Zika Program and available resources for referral





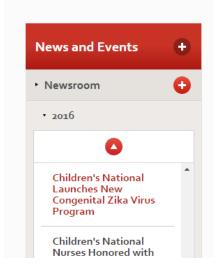




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### Children's National Launches New Congenital Zika Virus Program

May 16, 2016

Washington, DC — Each week, as temperatures rise, the likelihood increases that the United States will experience domestic Zika virus transmission. Indeed, such domestic Zika transmission already is occurring in Puerto Rico and the U.S. Virgin Islands. The Children's National Health System Fetal Medicine Institute and Division of Pediatric Infectious Disease announced today the formation of a Congenital Zika Virus Program to serve as a dedicated resource for referring clinicians and for pregnant women to receive counseling and science-driven answers about the impact of the Zika virus on their pregnancies.







#### The Congenital Zika Virus Program at Children's National

#### LOCATED IN THE FETAL MEDICINE INSTITUTE

- Multidisciplinary Program
- Adre du Plessis, MBChB (Fetal/Neonatal Neurology)
- Roberta DeBiasi, MD, MS (Pediatric Infectious Diseases)
- Dorothy Bulas, MD (Fetal Imaging)
- Gilbert Vezina MD (Neuroradiology)
- Taeun Chang MD (Fetal/Neonatal Neurology)
- Sarah Mulkey MD, PhD (Fetal/Neonatal Neurology)
- Lindsay Pesacreta MS, FNP-BC (Nurse Practitioner)

#### **CONTACT INFORMATION**

- Phone number: 202 476-7409
- Email: <u>fetalmedicine@childrensnational.org</u>
- www.childrensnational.org/zika



#### **CNHS Congenital Zika Program**

- Single visit coordinated multidisciplinary care
- Counseling and up to date guidance regarding Zika exposure and infection
- Streamlined Coordination of Testing with all State Health Departments
- Advanced Fetal Imaging
  - Fetal US (Standard screening technique)
    - Not sensitive for <u>early</u> detection of fetal microcephaly and calcifications in pregnant women with ZIKV infection
  - Fetal MRI (Standard neurodiagnostic technique)
    - Superior brain parenchymal definition
    - Capable of detecting more subtle and earlier changes of impaired fetal brain growth and development
    - Large normative database for fetal brain development between 18 and 38 weeks gestation
- Coordination with Obstetricians, MFM, Pediatrician for subsequent monitoring and multidisciplinary care (ID, neurology, genetics, neurodevelopmental)

#### Children's National Congenital Zika Virus Program

#### Guidelines for referring clinicians

If you suspect that your patient has been exposed to the Zika virus, please refer to the guidelines below to determine whether to refer to the Congenital Zika Virus Program at Children's National Health System. Program staff will streamline and coordinate all testing and schedule all follow-up tests, as needed. Please call 202-476-7409 to refer a patient who fits one or more of the following criteria:

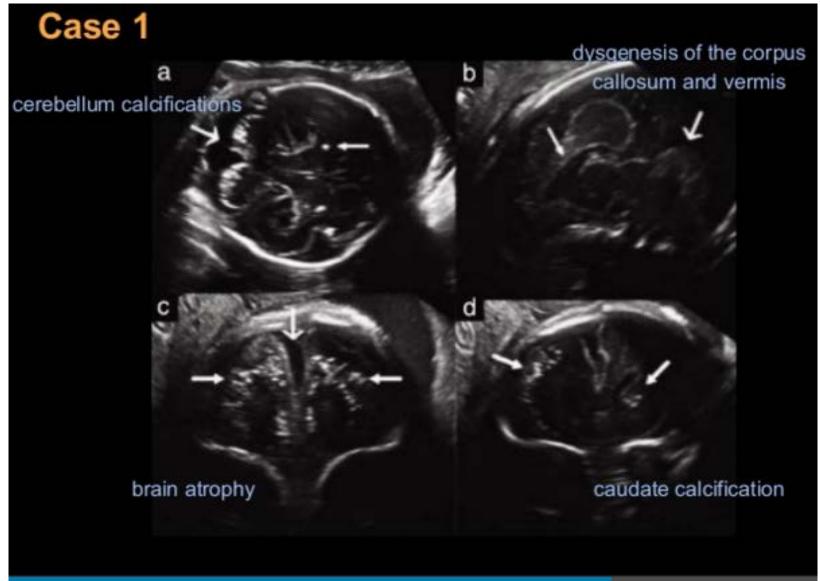
#### Pregnant women who:

- have traveled to or live in an area<sup>3</sup> with active Zika virus transmission—with or without symptoms<sup>3</sup>
- have had unprotected sex with a symptomatic or asymptomatic partner who
  - has confirmed Zika infection
  - or has traveled to or lives in an area\* with active Zika virus transmission
- have a history of mosquito bite(s) and have symptoms consistent with Zika<sup>2</sup>
- have ultrasound images that show a fetal head circumference that is not increasing as expected for gestational age,
   microcephaly, or intracranial calcifications

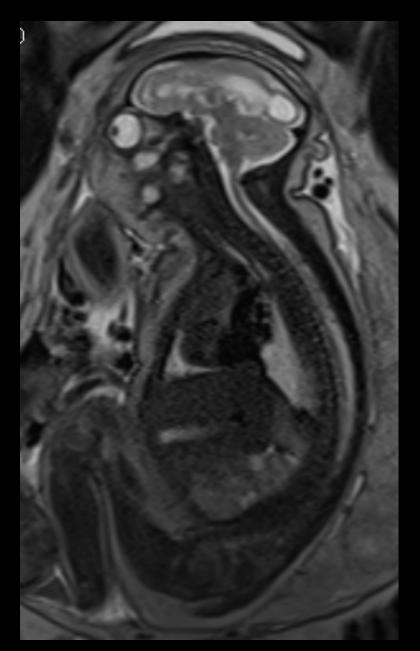
#### Infants who:

- were born to a mother who had a positive or inconclusive test result for Zika virus infection
- have microcephaly or intracranial calcifications—diagnosed prenatally or after birth
- have symptoms of Zika<sup>3</sup> in the first two weeks of life not explained by another etiology





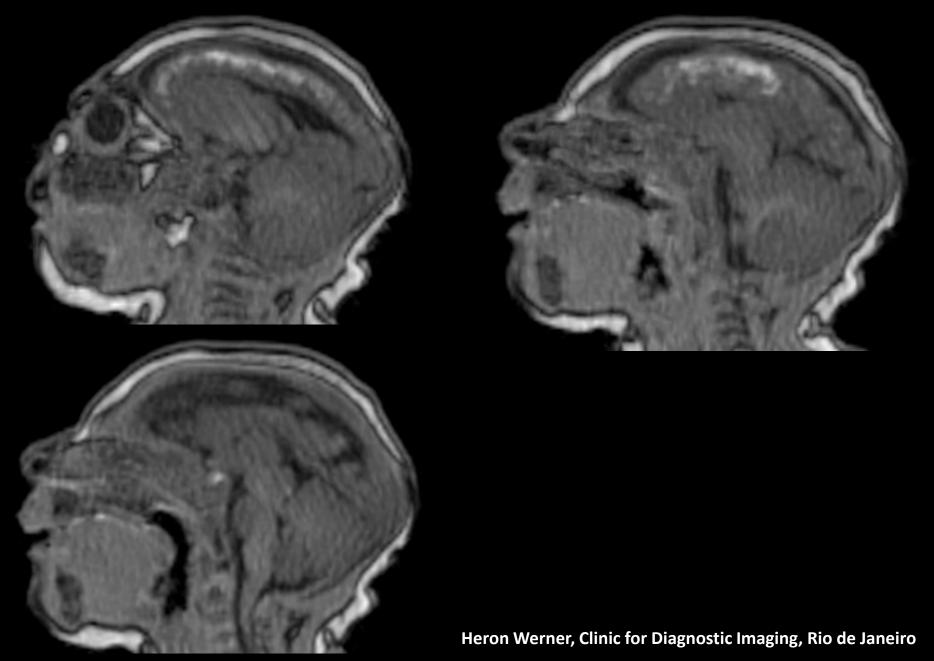
#### Fetal ZIKV Encephalopathy





Heron Werner, Clinic for Diagnostic Imaging, Rio de Janeiro

#### **Cerebral calcifications in ZIKV Encephalopathy**



## Questions Without Clear Answers Yet: Active Areas of Research

- What is the risk to a fetus/infant if a woman is infected with Zika virus while she is pregnant?
  - Is the fetus at higher risk of infection and /or neurologic injury during certain windows of pregnancy?
- What is the mechanism of damage to fetus:
  - Developmental arrest, direct brain injury or both?
  - What cell types are targeted?
  - What are the factors determining breach of the placental barrier and the blood/brain barrier that allows virus to reach the fetal brain?

#### Active Areas of Research - 2

- Risk Factors and Biomarkers for Fetal Infection:
  - Is duration or amount of viremia predictive of likelihood of injury to the fetus?
  - Early fetal MRI findings
  - Are specific demographic groups at higher risk for infection or severe sequelae?
  - Does co-infection or prior infection with other flaviviruses or other factors play a role in the severity of Zika infection?
- What is the natural history and long-term neurodevelopmental and neuropsychological outcome of survivors (both symptomatic and asymptomatic)?
  - Are there more subtle, prevalent effects of ZIKV on the developing brain?

## Mosquito Bite Prevention (United States)



Not all mosquitoes are the same. Different mosquitoes spread different viruses and bite at different times of the day.

Type of Mosquito

Viruses spread

Biting habits



Aedes aegypti, Aedes albopictus Chikungunya, Dengue, Zika

Daytime



Culex species

West Nile

Dusk (evening) to dawn (morning)



#### Protect yourself and your family from mosquito bites

#### Use insect repellent

Use an Environmental Protection Agency (EPA)-registered insect repellent with one of the following active ingredients. All EPA-registered insect repellents are evaluated for safety and effectiveness.

# Higher percentages of active ingredient provide longer protection DEET Off!, Cutter, Sawyer, Ultrathon Cutter Advanced, Skin So Soft Bug Guard Plus, Autan (outside the United States) Oil of lemon eucalyptus (OLE) or para-menthane-diol (PMD) IR3535 Some brand name examples\* Off!, Cutter, Sawyer, Ultrathon Cutter Advanced, Skin So Soft Bug Guard Plus, Autan (outside the United States) Repel Skin So Soft Bug Guard Plus Expedition, SkinSmart



 Insect repellent brand names are provided for your information only. The Centers for Disease Control and Prevention and the U.S. Department of Health and Human Services cannot recommend or endorse any name brand products.



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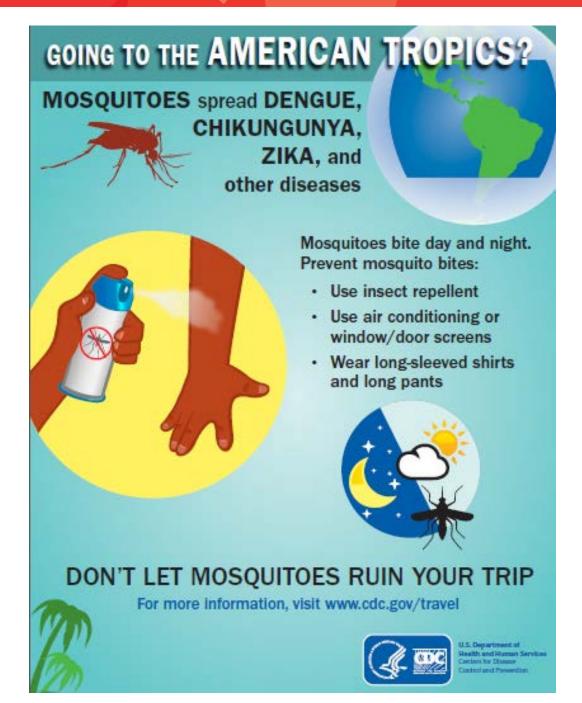
January 12, 2016

- Apply insect repellent after sunscreen
- Reapply every couple of hours
- Permethrin-treated clothing and gear

#### Natural insect repellents (repellents not registered with EPA)

- · EPA has not evaluated natural insect repellents for effectiveness.
  - » Examples of ingredients used in unregistered insect repellents include: citronella oil, cedar oil, geranium oil, peppermint oil, or soybean oil.







## The Congenital Zika Virus Center at Children's National

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