Zika Virus in the Americas

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21st Annual Chicago
Infection Control Conference
May 20, 2016

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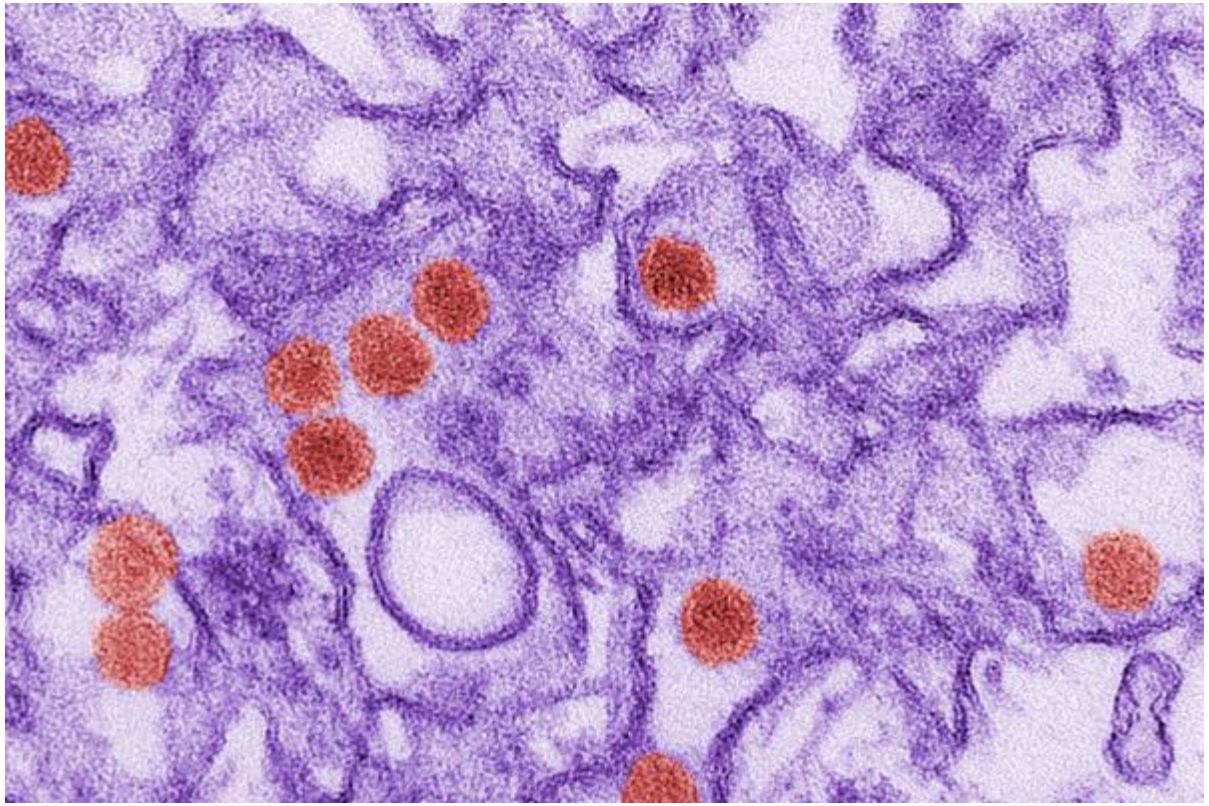
What is Zika Virus?

- Genus *Flavivirus*, Family *Flaviviridae*
- Closely related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses
- Single stranded RNA virus
- Transmitted to people by *Aedes aegypti* and *Aedes albopictus* mosquitoes



Transmission

- *Aedes aegypti* is the primary vector
  - Aggressive daytime biters, prefer to bite people, live indoors and outdoors, also bite at night
  - Also transmit dengue and chikungunya viruses
  - Lay eggs in domestic water-holding containers
  - Live in and around households
- Other modes of transmission
  - Maternal-fetal (intrauterine and perinatal), sexual transmission from infected males, laboratory exposure
  - Theoretical: blood transfusion, organ or tissue transplantation, breastmilk.

***Aedes aegypti* mosquito**

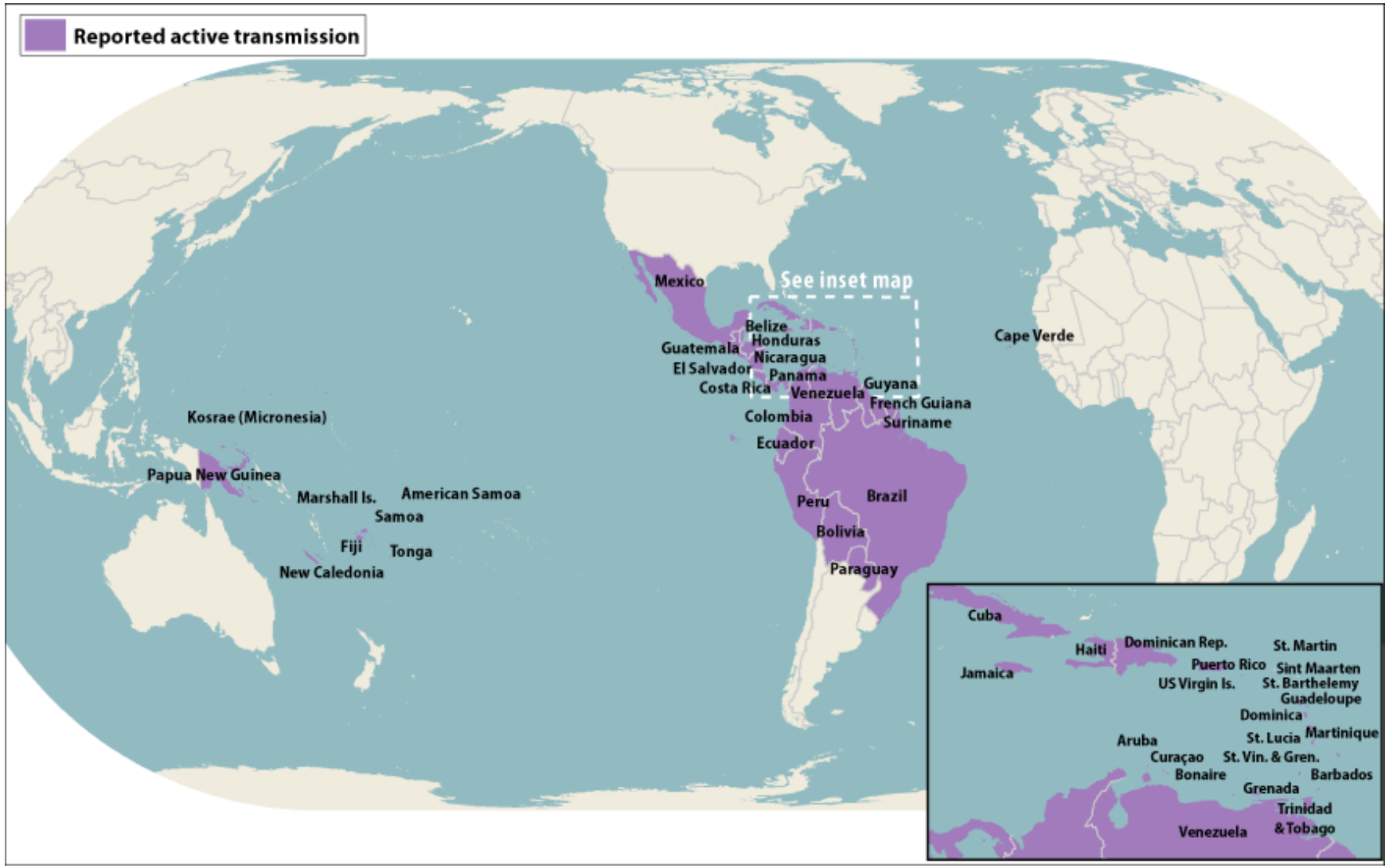
***Aedes albopictus* mosquito**

Zika Virus Epidemiology

- First isolated from a monkey in Uganda in 1947
- Prior to 2007, only sporadic human disease cases reported from Africa and Southeast Asia
- In 2007, first outbreak reported on Yap Island, Federated States of Micronesia
- In 2013–2014, an estimated 32,000 suspected cases reported from French Polynesia*
- In May 2015, the first locally-acquired cases in the Americas were reported in Brazil

*http://ecdc.europa.eu/en/publications/Publications/Zika-virus-French-Polynesia-rapid-risk-assessment.pdf

Where is Zika now?



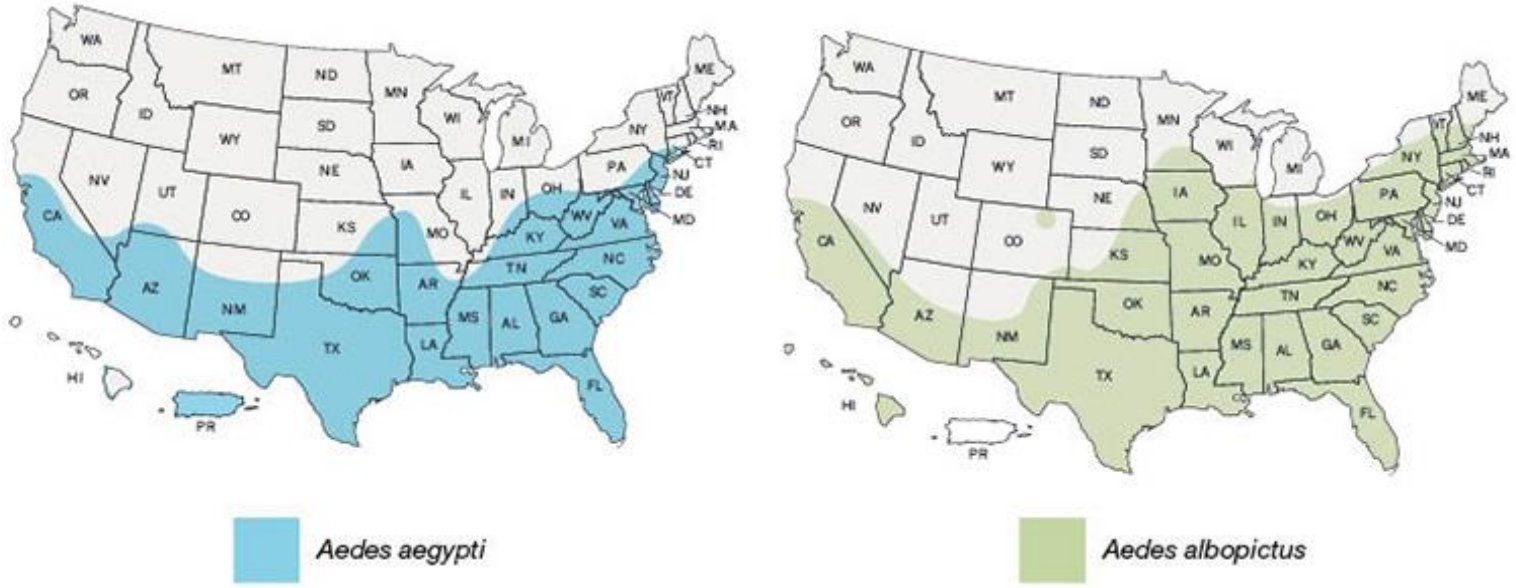
47 countries and territories worldwide reporting active Zika virus transmission

(As of May 12, 2016)

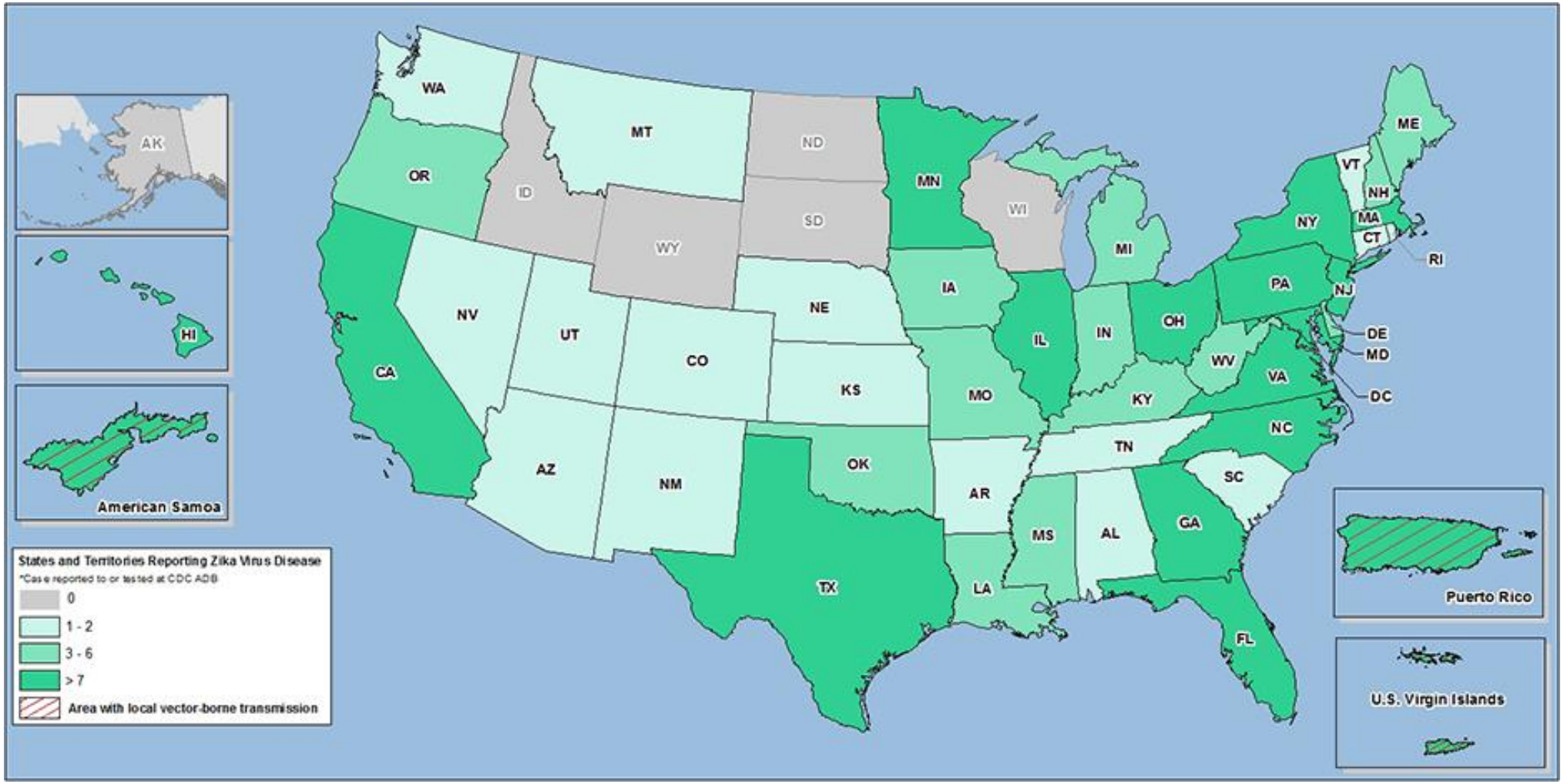
http://www.cdc.gov/zika/geo/active-countries.html

Zika Virus in the United States

- Local vector-borne transmission of Zika virus has not been reported in the continental United States
- With current outbreak in the Americas, cases among US travelers will likely increase
- Imported cases may result in virus introduction and local transmission in some areas of US



Laboratory-confirmed Zika Virus Disease Cases Reported to ArboNET by State or Territory — United States, 2015–2016 (as of May 18, 2016)



http://www.cdc.gov/zika/geo/united-states.html

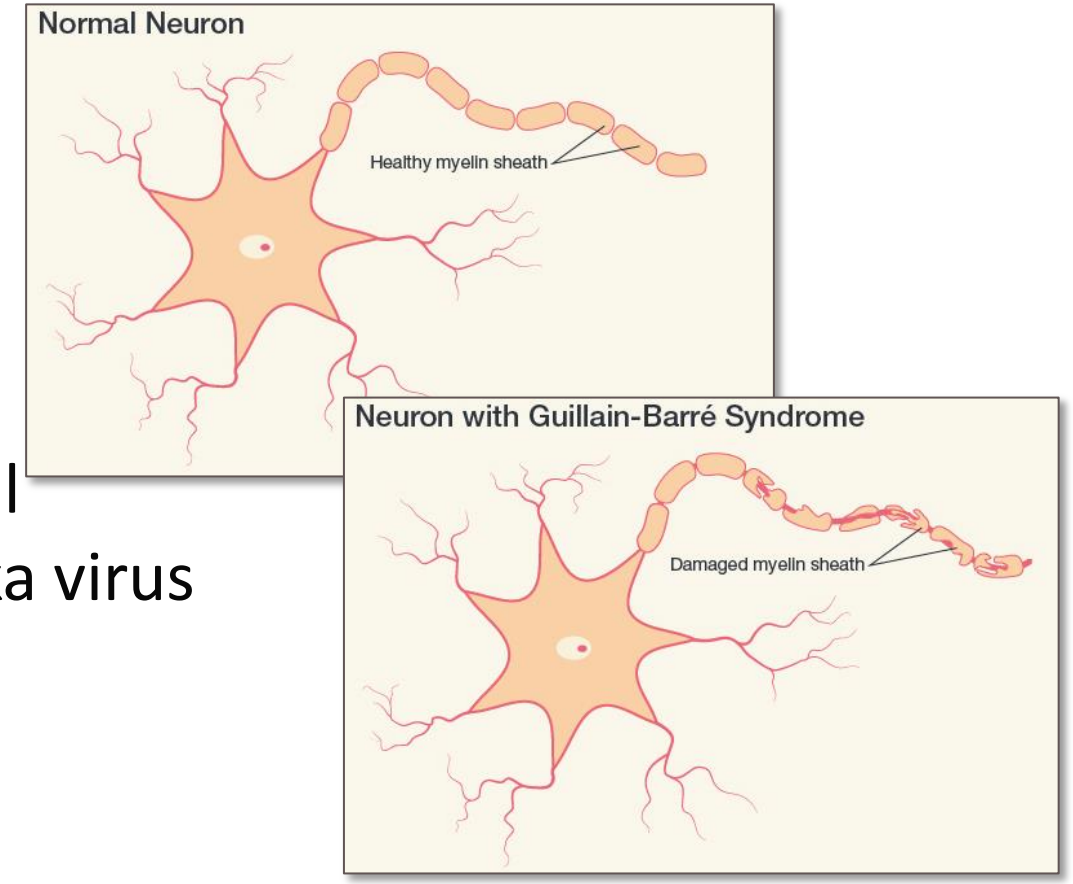
Clinical Features of Zika Virus Disease

- Most common symptoms include:
  - Fever
  - Rash — pruritic and macular or maculopapular
  - Joint pain
  - Conjunctivitis (red eyes)
- Other symptoms include:
  - Muscle pain
  - Headache

Brasil P et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1602412

Zika Virus Clinical Disease Course and Outcomes: Adults and Children

- Clinical illness usually mild
- Symptoms last several days to a week
- Severe disease requiring hospitalization uncommon
- Fatalities are rare
- Guillain-Barré syndrome reported in a small number of patients following suspected Zika virus infection



The 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,"
–Dr. Tom Frieden, Director, CDC, April 13, 2016

"…the last time an infectious pathogen (rubella virus) caused an epidemic of congenital defects was more than 50 years ago…"
–NEJM. April 13, 2016

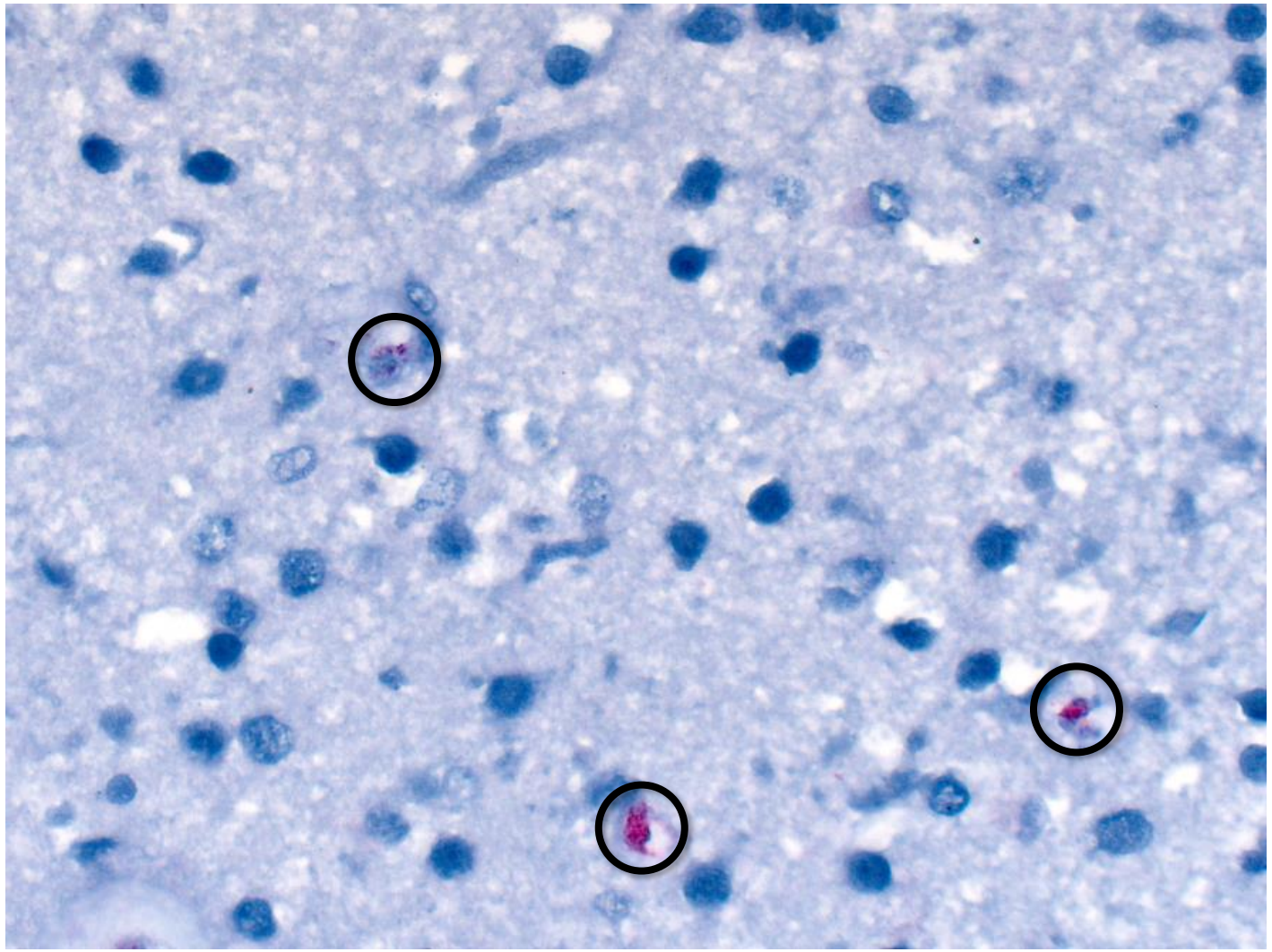
"[Zika] became the first major infectious disease linked to human birth defects to be discovered in more than half a century and created such global alarm that the World Health Organization (WHO) would declare a Public Health Emergency of International Concern."
– Petersen et al. March 30, 2016

Zika Virus Infection in Pregnant Women

- Pregnant women can be infected
  - Through a mosquito bite
  - Through sex with an infected male partner
- If infected around conception
  - Zika might present risk to fetus
- If infected during pregnancy
  - Zika can be passed to the fetus during pregnancy or around the time of birth

CDC Lab Confirms Zika In Fetal Tissues

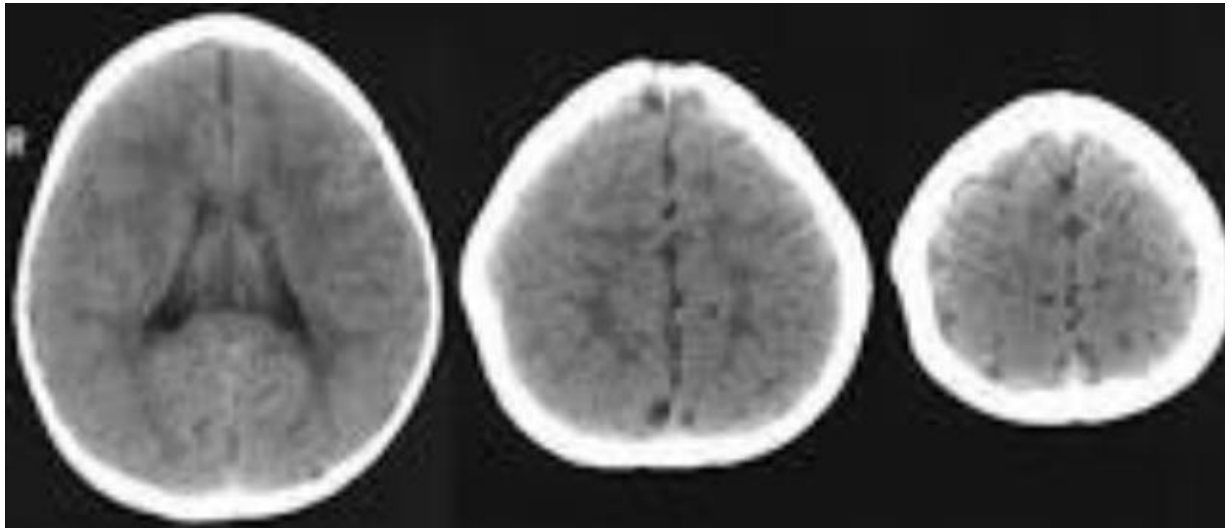
- Zika virus RNA and/or antigen has been identified in:
  - Amniotic fluid
  - Placenta
  - Brain
  - Products of conception



Infants with Microcephaly

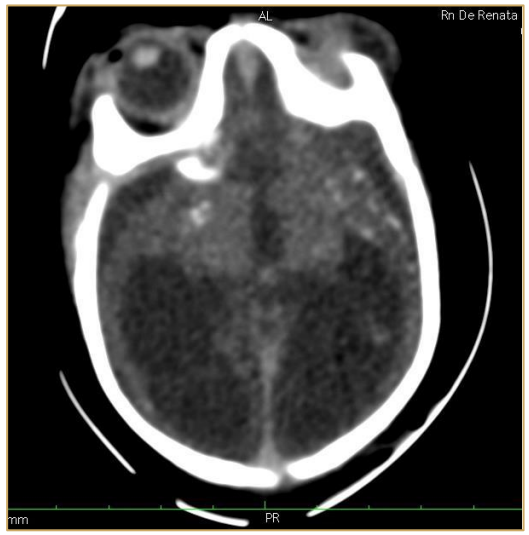
Baby with
Severe Microcephaly

Baby with Typical Head Size



Note scattered intracranial calcifications

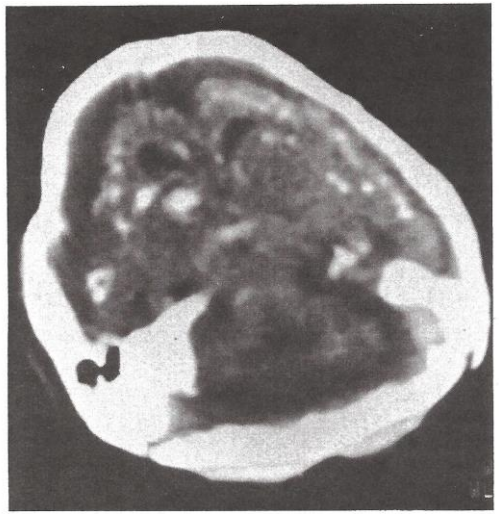
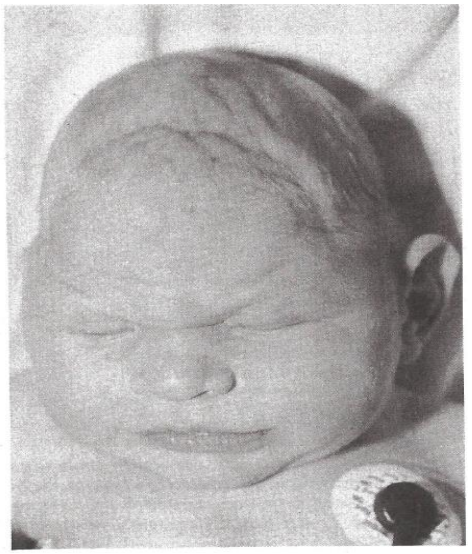
Note large ventricles and volume loss



CT scan images courtesy of Dr. Erin Staples

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


*Moore, et al. J Pediatr 1990;116:383-386.

Brain Abnormalities Associated with Congenital Zika Virus Infection (Other than Microcephaly)

- Intracranial calcifications
- Hydrocephalus ex-vacuo
- Hydranencephaly
- Pachygyria, lissencephaly
- Agyria
- Brain atrophy and asymmetry
- Enlargement of posterior fossa
- Ventriculomegaly
- Restricted middle cerebral artery flow
- Abnormally formed or absent structures
  - Corpus callosum
  - Thalami
  - Cerebellar vermis
  - Brainstem

Karwowski MP, Nelson JM, Staples JE, et al. Zika Virus Disease: A CDC Update for Pediatric Health Care Providers. Pediatrics. 2016;137(5):e20160621

Zika Virus – Brain Abnormalities in Fetuses and Infants

- Brazil study: 42 women with laboratory-confirmed Zika virus infection with prenatal ultrasound
  - 12 (29%) abnormalities detected, including 2 intrauterine fetal deaths
  - 7 (17%) structural brain anomalies (microcephaly, calcifications, cerebellar atrophy, ventriculomegaly)
- 2013-14 outbreak in French Polynesia
  - 8 cases of microcephaly identified
  - Modeling estimated infection with Zika during 1st trimester of pregnancy resulted in microcephaly risk of ≈1%

Brasil P, Pereira JP Jr, Raja Gabaglia C, et al. Zika virus infection in pregnant women in Rio de Janeiro—preliminary report. N Engl J Med 2016. Published online March 4, 2016. http://dx.doi.org/10.1056/NEJMoa1602412
Cauchemez S, Besnard M, Bomopard P, et al. Association between Zika virus and microcephaly in French Polynesia, 2013-15: a retrospective study. Lancet 2016. Published online March 15, 2016. http://dx.doi.org/10.1016/S0140-6736(16)00651-6

Brain Abnormalities in Fetus Born to Traveler and Prolonged Viremia

Case report

- Pregnant women traveled during 11th week of gestation to Mexico, Guatemala, and Belize; symptom onset at 12 weeks gestation
- Prenatal ultrasound
  - Decrease in head circumference from 47th at 16 weeks to 24th percentile at 20 weeks
  - Abnormal intracranial anatomy at 19 weeks
  - Fetal MRI at 20 weeks: brain abnormalities, including diffuse cerebral atrophy
- Postmortem evaluation following pregnancy termination at 21 weeks
  - Diffuse cerebral cortical thinning
  - High levels of Zika virus RNA; virus was cultured from brain tissue

Driggers RW, Ho C-Y, Korhonen EM, et al. Zika virus infection with prolonged maternal viremia ad fetal brain abnormalities. NEJM 2016 Mar 30. DOI: 10.1056/NEJMoa1601824

Reviewing the Evidence for Causality

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Zika Virus and Birth Defects — Reviewing the Evidence for Causality

Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H.,
Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.

SUMMARY

The Zika virus has spread rapidly in the Americas since its first identification in Brazil in early 2015. Prenatal Zika virus infection has been linked to adverse pregnancy and birth outcomes, most notably microcephaly and other serious brain anomalies. To determine whether Zika virus infection

POTENTIAL RELATIONSHIP BETWEEN ZIKA VIRUS INFECTION AND BIRTH DEFECTS

Since the identification of the Zika virus in Brazil in early 2015, the virus has spread rapidly throughout the Americas (www.cdc.gov/zika/geo/active-countries.html). An increase in the

Adverse Outcomes and Zika Virus

- A range of problems related to CNS injury have been detected among fetuses and infants with known or suspected congenital Zika virus infection
  - Eye abnormalities
  - Hearing impairment
  - Seizures
  - Swallowing impairment
  - Hypertonicity and posturing
  - Contractures including club foot and arthrogryposis
  - Severe irritability
  - Developmental delay
  - Growth abnormalities include IUGR and disproportionate growth (head size alone affected)

Karwowski MP, Nelson JM, Staples JE, et al. Zika Virus Disease: A CDC Update for Pediatric Health Care Providers. Pediatrics. 2016;137(5):e20160621

Pregnancy Outcomes and Zika Virus

- Zika virus has been linked to spontaneous abortion and fetal demise, but evidence is insufficient at this point in time
- Researchers are collecting data to better understand the clinical spectrum of congenital Zika virus disease

Many Questions Remain

- What is the level of risk from Zika virus infection during pregnancy?
- What is the level of risk when a woman has symptoms of Zika as compared to when she does not have symptoms?
- When during pregnancy Zika virus infection poses the highest risk to the fetus?
- What is the full range of potential health problems that Zika virus infection may cause?
- What are other factors (e.g., co-occurring infection) that might affect the risk for birth defects?

What CDC is Doing to Learn More

- Established US Zika Pregnancy Registry
- Established Zika Active Pregnancy Surveillance System (Puerto Rico)
- Collaborating with Colombia to monitor pregnancy outcomes in women with Zika virus disease
- Collaborating with Brazil to study the link with microcephaly
- Studying how long the virus stays in body fluids

US Zika Pregnancy Registry

- **Purpose of registry:** To monitor pregnancy and infant outcomes following Zika virus infection during pregnancy and to inform clinical guidance and public health response

- **Importance of state participation:** Collaboration with state, tribal, local, and territorial health departments is critical to guide and inform the response. The data collected will be used to update recommendations for testing and clinical care, plan for services, and improve prevention.

US Zika Pregnancy Registry

- **How it works:** The registry is a supplemental surveillance effort coordinated by CDC and dependent on the voluntary collaboration of the state, tribal, local, and territorial health departments

- **Who is included**: Pregnant women with laboratory evidence of Zika virus infection and exposed infants born to these women; infants with laboratory evidence of congenital Zika virus infection and their mothers

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 65
February 19, 2016

Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection — United States, February 2016

Katherine E. Fleming-Dutra, MD[1]; Jennifer M. Nelson, MD[2,3]; Marc Fischer, MD[4]; J. Erin Staples, MD, PhD[4]; Mateusz P. Karwowski, MD[2,5]; Paul Mead, MD[4]; Julie Villanueva, PhD[6]; Christina M. Renquist, MPH[7]; Anna A. Minta, MD[2,8]; Denise J. Jamieson, MD[9]; Margaret A. Honein, PhD[7]; Cynthia A. Moore, MD, PhD[7]; Sonja A. Rasmussen, MD[10]

CDC has updated its interim guidelines for U.S. health care providers caring for infants born to mothers who traveled to or resided in areas with Zika virus transmission during pregnancy and expanded guidelines to include infants and children with

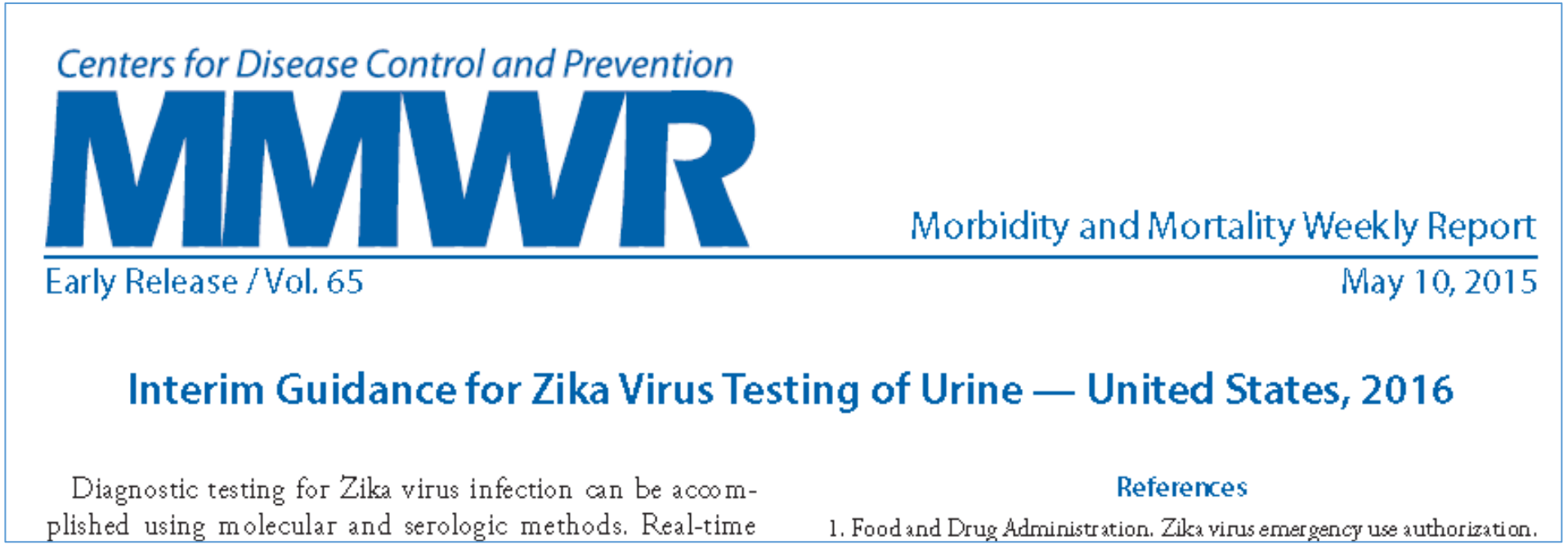
Americas as of February 17, 2016 (http://www.cdc.gov/zika/geo/active-countries.html). In October 2015, a marked increase in the number of infants with microcephaly was reported in Brazil (5). Because of the temporal and geographic occurrence of Zika

CDC Recommendations: Diagnostic Testing

- Real-time Reverse Transcription-Polymerase Chain Reaction (rRT-PCR) for viral RNA in serum collected ≤7 days after illness onset

- Serology for Immunoglobulin M (IgM) in serum collected ≥4 days after illness onset
  - Cross-reactivity can occur among related flaviviruses
  - Plaque Reduction Neutralization Test (PRNT) can be performed to measure virus-specific neutralizing antibodies

Interim Guidance for Zika Virus Testing of Urine



Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Early Release / Vol. 65

May 10, 2015

Interim Guidance for Zika Virus Testing of Urine — United States, 2016

Diagnostic testing for Zika virus infection can be accomplished using molecular and serologic methods. Real-time

References

1. Food and Drug Administration. Zika virus emergency use authorization.

- CDC recommends that Zika virus rRT-PCR be performed on urine collected <14 days after symptom onset in patients with suspected Zika virus disease
- Zika virus rRT-PCR testing of urine should be performed in conjunction with serum testing

Zika Virus Infection and Pregnancy: Clinical Management

- Positive or inconclusive Zika virus testing results
  - Antepartum
    - Consider serial ultrasounds every 3–4 weeks
    - Referral to maternal-fetal medicine specialist is recommended
  - Postpartum
    - Histopathologic examination of the placenta and umbilical cord
    - Testing of frozen placental tissue and cord tissue for Zika virus RNA
    - Testing of cord serum for Zika and dengue virus IgM and neutralizing antibodies

Prenatal Diagnosis of Brain Anomalies

- Microcephaly and intracranial calcification typically detected late 2nd or early 3rd trimester
- Might be detected at 18-20 weeks
- Prenatal microcephaly (head circumference 3 standard deviations or more below mean) has false positive rate of 43%
- Fetal MRI is not a screening tool
  - Interpretation requires specialized expertise
  - Limited availability

Gabis L, Gelman-Kohan Z, Mogilner M. Microcephaly due to fetal brain disruption sequence. Case report. J Perinat Med. 1997;25(2):213-5.
Meaney-Delman D, Rasmussen SA, Staples JE, et al. Zika virus and pregnancy. What obstetric health care providers need to know. Obstet Gynecol. 2016 Apr;127(4):642-8.
CDC.
Leibovitz Z, Daniel-Spiegel E, Malinger G, et al. Microcephaly at birth-the accuracy of three references for fetal head circumference. How can we improve prediction?. Ultrasound in Obstet Gynecol. 2015 Oct.

Reporting Zika Virus Disease Cases

- Zika virus disease is a nationally notifiable disease
  - Healthcare providers are encouraged to report cases with laboratory evidence of Zika infection to their state, tribal, local, or territorial health department
- Health departments are requested to notify CDC of cases with laboratory evidence of Zika infection
- Timely reporting allows health departments to assess and reduce the risk of local transmission or mitigate further spread

Initial Assessment and Treatment

- No specific antiviral therapy
- Treatment is supportive (i.e., rest, fluids, analgesics, antipyretics)
- Suspected Zika virus infections should be evaluated and managed for possible dengue or chikungunya virus infections
- Aspirin and other NSAIDs should be avoided until dengue can be ruled out to reduce the risk of hemorrhage and, in children, Reye's syndrome

Zika Virus Preventive Measures

- No vaccine or medication to prevent or treat infection or disease
- Primary prevention measure is to reduce mosquito exposure
  - Long sleeves, long pants, EPA-registered mosquito repellents, permethrin-treated clothing
  - Stay in places with air conditioning or with window/door screens
  - Sleep under a mosquito bed net if air conditioned or screened rooms are not available
  - Eliminate standing water in and around homes
- Pregnant women should not travel to areas with ongoing Zika virus outbreaks
- For men who live in or traveled to an area with Zika virus
  - The couple should either use condoms every time they have sex or not have sex during the pregnancy. To be effective, condoms must be used correctly, from start to finish, every time they have vaginal, anal, or oral sex.
- People infected with Zika virus should take steps to prevent mosquito bites during the first week of illness to prevent further transmission.

Pregnancy Planning and Access to Contraception

- Primary strategy to reduce Zika-related pregnancy complications is to prevent pregnancy in women who want to delay or avoid pregnancy.
- If couples decide to wait to conceive, healthcare providers should discuss
  - Strategies to prevent unintended pregnancy
  - Use of the most effective contraceptive methods that can be used correctly and consistently
  - Role of correct and consistent use of condoms in reducing the risk for sexually transmitted infections, including Zika

Progress on Zika Vaccine

- NIH/NIAID is actively working on vaccine candidates to prevent Zika virus infection – scientists had already created vaccine platforms for other flaviviruses that can be used as a starting point for a Zika vaccine
- NIH/NIAID is pursuing several vaccine approaches
  - DNA-based vaccine: uses strategy similar to an investigational vaccine for West Nile virus infection
  - Live-attenuated investigational Zika vaccine: similar to vaccine approach used for dengue virus
  - Investigational Zika vaccine that uses a genetically engineered version of vesicular stomatitis virus: approach was successfully used in an investigational Ebola vaccine tested by NIAID

https://www.niaid.nih.gov/topics/Zika/ResearchApproach/Pages/vaccineResearch.aspx

CDC's Response to Zika Virus

- Monitoring spread of Zika virus through public health surveillance
- Increasing laboratory capacity for testing to identify Zika infection
- Assisting with the development of tests that can improve detection of previous infection with Zika
- Working with partners to improve mosquito control efforts
- Providing recommendations for prevention
- Promoting effective health communication strategies
- Focusing on supporting state, local, tribal, and territorial response efforts

Thanks to our many collaborators and partners!

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For U.S. Zika Pregnancy Registry questions, please contact

ZikaPregnancy@cdc.gov

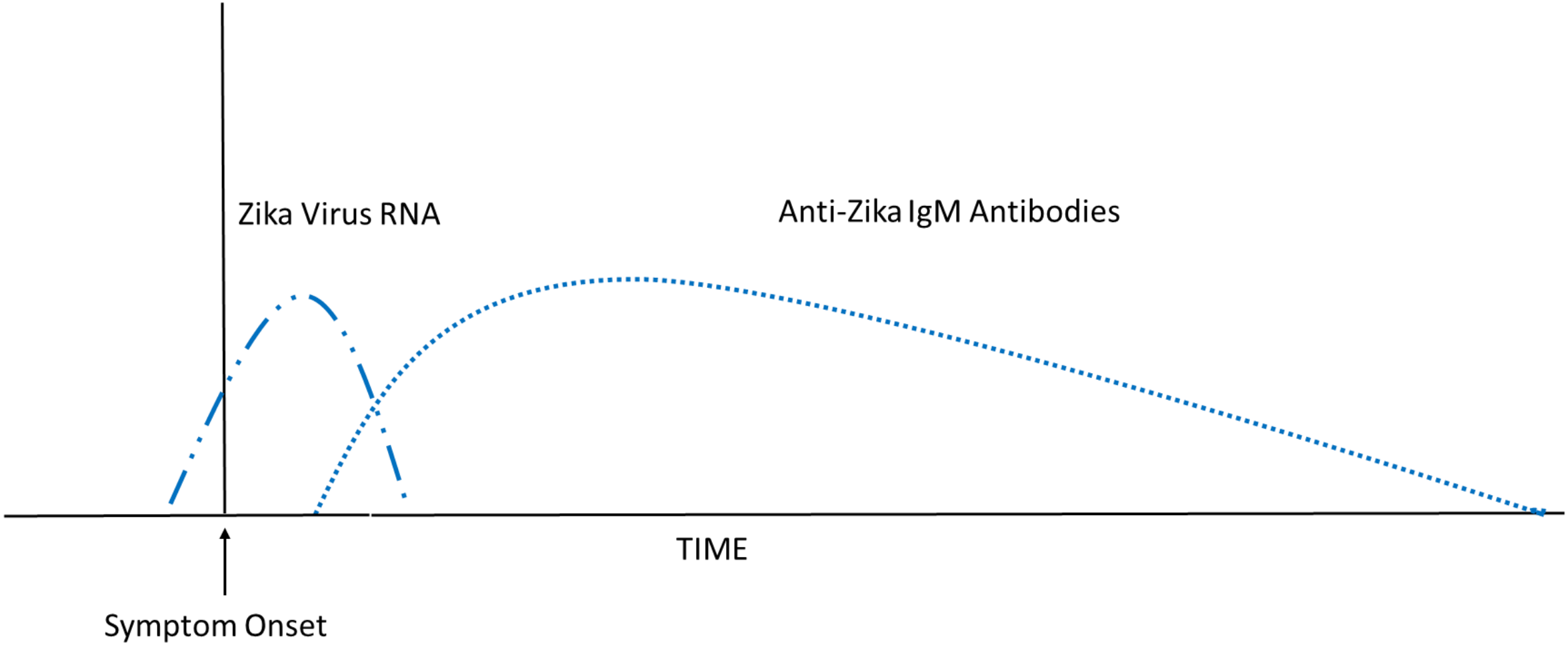
For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Extra

More Information about Zika

- More information is available on the US Zika Pregnancy Registry website at http://www.cdc.gov/zika/hc-providers/registry.html
- To contact CDC Registry staff, call 770-488-7100 and ask for the Zika Pregnancy Hotline or email ZIKApregnancy@cdc.gov
- More information on caring for pregnant women, infants, or children with Zika virus infection is available at http://www.cdc.gov/zika/

Detecting Zika Virus RNA and Antibodies



Evaluation and Testing for Infants with Possible Congenital Zika Virus Infection

- Thorough physical examination, including careful measurement of the head circumference, length, weight, and assessment of gestational age*
- Cranial ultrasound, unless prenatal ultrasound results from third trimester demonstrated no abnormalities of the brain
- Further evaluation
  - Neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly, and rash or other skin lesions*
  - Hearing by evoked otoacoustic emissions testing or auditory brainstem response testing, either before discharge from the hospital or within 1 month after birth*
  - Eye exam to include visualization of the retina, optic nerve, and macula either before discharge from the hospital or within 1 month after birth*
- Other evaluations specific to the infant's clinical presentation

*If any abnormalities are noted, consultation with the appropriate specialist is recommended.

Fleming-Dutra KE, Nelson JM, Fischer M, et al. Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection — United States, February 2016. MMWR Morb Mortal Wkly Rep 2016;65:182–187.

Recommended Testing of Infants for Congenital Zika Virus Infection

- Recommended tests
  - Zika virus RNA (rRT-PCR), IgM, and neutralizing antibodies
  - Dengue virus IgM and neutralizing antibodies
- Clinical specimens
  - Serum (umbilical cord or direct, within 2 days of birth if possible)
  - Cerebrospinal fluid, if obtained for other studies
- Consider histopathologic evaluation (placenta and umbilical cord)
  - Zika virus immunohistochemical staining (fixed tissue)
  - Zika virus rRT-PCR (fixed and frozen tissue)
- If not already performed, test mother's serum
  - Zika virus IgM and neutralizing antibodies
  - Dengue virus IgM and neutralizing antibodies

Fleming-Dutra KE, Nelson JM, Fischer M, et al. Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection — United States, February 2016. MMWR Morb Mortal Wkly Rep 2016;65:182–187.

Zika Virus Laboratory Testing of Infants whose Mothers Have Possible Zika Virus Infection

- Recommended for
  - Infants with any abnormality associated with Zika virus with no other clear etiology

    AND

  - Infants born to mothers with positive or inconclusive test results for Zika virus infection
- Not recommended for
  - Infants without abnormalities associated with Zika virus and the mother has negative or no Zika virus testing

Additional Evaluation for Infants with Microcephaly or Intracranial Calcifications or Other Brain and Eye Abnormalities

- For infants with microcephaly, consultations are recommended with
  - A clinical geneticist or dysmorphologist
  - A pediatric neurologist to determine appropriate brain imaging and additional evaluation (e.g., US, CT scan, MRI, and/or EEG)
  - A pediatric infectious disease specialist should be considered after testing for other congenital infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus, lymphocytic choriomeningitis virus, and herpes simplex viruses
- Further testing includes
  - Complete blood count, platelet count, and liver function tests including alanine aminotransferase, aspartate aminotransferase, and bilirubin
- Genetic and other teratogenic causes based on additional congenital anomalies that are identified through clinical examination and imaging studies should be considered

Fleming-Dutra KE, Nelson JM, Fischer M, et al. Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection — United States, February 2016. MMWR Morb Mortal Wkly Rep 2016;65:182–187.

Perinatal Transmission of Zika Virus

- Evidence of perinatal infection (near time of delivery)
  - Zika virus outbreak in French Polynesia 2013–2014
    - Two pregnant women with signs and symptoms consistent with Zika virus infection around the time of delivery
    - Zika virus RNA detected by RT-PCR in both mothers
    - Zika virus infection was confirmed in the neonates, 1–3 days after delivery
    - Unlikely that neonates were exposed to mosquitoes
    - Babies recovered but long-term follow up not reported

Besnard, M., et al. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. Euro Surveill, 2014. 19(14): p. 1-5.

Guidelines for Breastfeeding for Mothers with Zika Virus Infection and Living in Areas with Zika Virus

- Zika virus RNA has been identified in breastmilk
- Zika virus has been cultured from breastmilk
- No cases of Zika transmission associated with breastfeeding have been reported
- Mothers are encouraged to breastfeed their infants
- Current evidence: benefits of breastfeeding outweigh theoretical risks

Recommended Long-term Follow-up of Infants with Possible Congenital Zika Virus Infection

- Report case to state, territorial, or local health department and monitor for additional guidance as it released
- Consider conducting additional hearing screen at age 6 months, plus any appropriate follow-up of hearing abnormalities detected through newborn hearing screening
- Carefully evaluate head circumference and developmental characteristics and milestones throughout the first year of life
  - Consult medical specialists (e.g., pediatric neurology, developmental and behavioral pediatrics, physical and speech therapy) as appropriate