ZIP Study: Understanding the Impact of Zika Virus on Pregnancy and Child Outcomes

Catherine Y. Spong, M.D.
Acting Director, NICHD
Brazil Zika Outbreak

- May 2015: First infection in Brazil
- October 2015: Increase in microcephaly

Microcephaly cases in Brazil 2010-14: suspected/confirmed cases 2015-2016

- 2010: 153 cases
- 2011: 139 cases
- 2012: 175 cases
- 2013: 167 cases
- 2014: 147 cases
- 2015-2016: 4,568 cases

1,551 confirmed (224 confirmed Zika+ by PCR)

suspected* (3,017)

*does not include 3,262 cases investigated and discarded

Source: Brazilian MOH; data as of 6/4/2016.
Zika Associated Pregnancy Outcomes

- Fetal loss/miscarriage, stillbirth
- Fetal growth abnormalities
- Fetal brain anomalies
  - Microcephaly
  - Ventriculomegaly
  - Intracranial calcifications
- Eye abnormalities
- Neurologic
  - Hypertonia
  - Arthrogryposis
  - Seizures
  - Neurobehavioral anomalies

Miranda-Filho et al, AJPH April 2016, Vol 106 No. 4
Zika Virus Infection in Pregnant Women in Rio de Janeiro — Preliminary Report

- 88 women with rash
  - 82% Zika positive
- 58% (n=44) Zika+ followed with ultrasound
- 29% with fetal abnormalities
- 17% with microcephaly, atrophy, calcifications

Brasil et al, NEJM online 3/4/16
Fetal Brain Anomalies

• Microcephaly
• Hydrocephalus/hydranencephaly
• Absent structures: (CC, pons, cerebellar vermis)
• Neuronal migration disorders (lissencephaly)
• Fetal brain disruption sequence
• Cerebral calcifications
• Brain asymmetry
CT Scans Reveal Extensive Abnormalities

23 infants with microcephaly in Pernambuco, Brazil

- Intracranial calcifications
- Global cortical hypogryration
- Ventriculomegaly
- Global cerebellar hypoplasia

Hazin et al, NEJM April 6, 2017
29 infants with microcephaly
  - 79% with suspected Zika
    - 18 in first trimester
  - 29% with ocular findings
    - Bilateral macular and perimacular lesions
    - Optic nerve abnormalities
Asymptomatic Zika Infection

- Case report from Brazil
- Upper and lower limb spasms
- CT: cerebral calcifications, ventriculomegaly, lissencephaly
- Ocular exam: chorioretinal scar
Long Term Outcomes: Unknown

• Long term function: motor and sensory abnormalities
• Anticipate a spectrum of outcomes:
  • Developmental delay
  • Intellectual impairments
  • Mental disorders – autism, schizophrenia, etc
  • Motor abnormalities
Zika and Timing of Infection
First trimester                       Second trimester                     Third trimester

Blastocyst

Week 0

25 days

13

100 days

20

5 months

30

6 months

40

8 months

9 months

Kolb and Fantie, adapted from Cowan, Scientific American 1979
Risk not limited to 1st trimester

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

Figure 2. Week of Gestation at the Time of ZIKV Infection and Abnormal Ultrasonographic and Doppler Findings. Twelve of 42 women (29%) in whom fetal ultrasonography was performed had abnormal findings.

Brasil et al, NEJM online 3/4/16
Zika Research Gaps: Pregnancy and Pregnancy Outcomes

- Risk of infection in pregnancy
  - Modeling estimates microcephaly risk of 1-13% from 1st trimester infection. *NEJM Johansson 6/8/16*
- Outcome from asymptomatic infection
- Sequelae of Zika exposed and infected infants without microcephaly
- Long-term reservoirs for Zika
- Evaluation, management, treatment for children exposed to Zika in utero
Modes of Transmission
Modes of Transmission

- Vector born
- Sexual
- Mother to infant
- Blood donation/transfusion
- Organ transplant donors
Could increased incidence of ZIKV in women be caused by sexual transmission?

Zika incidence in men and women by age class, excludes pregnant women

90% more cases per 100,000 women in sexually active group (15-65 years)

Sexual Transmission: What We Don’t Know

- Transmission for asymptomatic infection
- For how long after the infection semen can infect a sexual partner
  - *Lancet* 6/7/16: transmission 34-41 d after infection
- If a woman with Zika can pass the virus to her sex partners
- If Zika can be transmitted through saliva
Zika and Viremia
Pregnancy: Prolonged Viremia

Figure 1. Timeline of Symptoms and Radiographic and Laboratory Studies.
This timeline highlights the symptoms of Zika virus (ZIKV) infection in the mother (bottom row) and the corresponding radiographic and laboratory findings in the fetus (top row). The inset photograph shows the mother’s rash at the time of the onset of the acute illness. DENV denotes dengue virus, MRI magnetic resonance imaging, PBMC peripheral-blood mononuclear cells, and PRNT plaque-reduction neutralization test.

Viremia persisted for 10 weeks

Driggers RW et al, NEJM March 30, 2016
Pregnancy: Prolonged Viremia

Virus is likely from fetus

1) Virus in plasma, not urine, suggesting the maternal immune system was able to contain virus replication

2) Viral variants detected near the end of the "typical" viremia (d7) are distinct from those in "prolonged" viremia (d21). This would be seen if the fetus was infected with a small number of transmitted/founder viruses from the mother during the initial burst of virus replication

Prepared by: Blue Brain Project

Preliminary Data courtesy of David O’Connor at University of Wisconsin.
How Might Zika Virus Affect the Fetus?
Proposed Mechanism

• ZIKV directly infects human cortical neural progenitor cells with high efficiency, resulting in stunted growth, transcriptional dysregulation and cell death

Garcez et al, Science 4/14/16
Tang et al, Cell Stem Cell 4/4/16

Human neurospheres infected with the Brazilian Zika virus after 96 hours. Compared to mock-infected controls, the neurospheres show dramatic cell death with arrested growth, resulting in significantly reduced size. Credit: UC San Diego Health
Impact on Fetal Brain: Congenital CMV

4 rhesus macaques infected in second trimester
Direct virus-mediated damage to the developing CNS
• Loss of neural progenitor cells (early gestation infection>damage)
• Loss of supporting vasculature in the CNS

Tarantal, et.al., J Infec Dis, 1998
What Are We Doing to Address This Public Health Emergency?
Guidance Documents

- Travel
- Pregnancy
- Reproductive planning
PAR-16-106 - Rapid Assessment of Zika Virus (ZIKV) Complications (R21)

- Open March 20, 2016 and expires on March 1, 2019
- Applications accepted on a rolling basis, beginning on April 20, 2016

Provides an expedited (rapid) funding mechanism for research on Zika virus (ZIKV) and its complications given the urgent need to determine whether ZIKV infection causes microcephaly and other congenital abnormalities in babies and the potential rapid spread of ZIKV to the United States.
Zika in Infants and Pregnancy (ZIP) Cohort Study

- Multi-site, multi-country prospective observational cohort study
- To determine the risks of Zika infection during pregnancy on maternal and fetal outcomes while controlling for potential confounders
- 10,000 women planned
- 4 current sites, additional sites planned
- Standardized protocol, data collection
- Supported by NICHD, NIAID, NIEHS and Fundacao Oswaldo Cruz-Fiocruz
Initial ZIP Study Sites

- Data Coordinating Center, USA, North Carolina
- NIEHS-Puerto Rico, Northern Karst site
- NIAID-Colombia, Medellin site
- NIAID-Brazil, Salvador site
- NICHD-Brazil, Sao Paolo site
ZIP Cohort Study

• Recruitment through prenatal clinics and community outreach
• Enrollment early in pregnancy with monthly assessments during pregnancy
• Clinical information and biospecimens will be collected
• Infants will be evaluated within 48 hours of birth and at 3, 6, and 12 months
Zika Cohort Study

Followed through pregnancy

- Zika infection - symptomatic
- Zika infection - asymptomatic
- No Zika infection

Cofactors:
- environmental exposures
- co/prior infections
- toxins

All children followed: those with and without anomalies

<13 wks gestation
Offered enrollment into cohort study
Zika Cohort Study Template: Pregnancy

- **Enroll**
  - 13 wks

- **Second trimester**
  - Physical exam
  - US

- **Third trimester**
  - Blood & urine
  - Health questions
  - US
  - PE

- **Delivery**
  - PE

- **6 wk visit**
  - PE
Zika Cohort Study Template: Infant

**Birth**
- Plasma, saliva & urine
- Head US & CT data *if obtained*
- Ophthalmologic exam
- Audiology assessment
- Otoacoustic emissions
- History & Physical

**3 months**
- Plasma, saliva & urine
- Head US & CT data *if obtained*
- Ophthalmologic exam
- Audiology assessment
- Otoacoustic emissions
- History & Physical

**6 months**
- Plasma, saliva & urine
- Head US & CT data *if obtained*
- Ophthalmologic exam
- Audiology assessment
- Otoacoustic emissions
- History & Physical

**12 months**
- Plasma, saliva & urine
- Head US & CT data *if obtained*
- Ophthalmologic exam
- Audiology assessment
- Otoacoustic emissions
- History & Physical
Workshop Focused on the Children

• September 2016 in Bethesda, Maryland
• Define the evidence to understand how prenatal Zika virus infection affects child development and to identify strategies for evaluation, management, and treatment

*Photo attribution: Agência Brasil*
Questions?