Zika Virus: The Evolving Epidemic

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Zika Virus

- First discovered in 1947 in Zika forest in Uganda isolated from febrile Rhesus Macaques
- Arbovirus of the genus Flavivirus
- 1952: first human cases detected
- Sporadic infections reported in tropical Africa, Southeast Asia, and the Pacific Islands
Brazil Zika And Congenital Malformations

• May 2015: First infection in Brazil
• ~500,000 to 1.5 million Zika virus cases by December 2015
• September 2015: increase in microcephaly in north-east region
Number Of Microcephaly Cases By Year, Brazil, 2000 -2016

Source: Ministério da Saúde eandSecretarias Estaduais de Saúde ( update in 20/02/2016)

Presented at PAHO meeting 03/01/2016 by
Giovanini Evelin Coelho
Ministry of Health - Brazil

Source: Ministério da Saúde eandSecretarias Estaduais de Saúde ( update in 20/02/2016)
Caribbean and South America

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<th>American Samoa</th>
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Estimated Range Aedes aegypti and Aedes albopictus in the United States, 2016

These maps show CDC’s best estimate of the potential range of Aedes aegypti and Aedes albopictus in the United States.
Microcephaly: Causes and Risk Factors

• U.S. prevalence: 2-12/10,000 livebirths
• Unknown
• Genetic mutations
• Exposures during pregnancy:
  • Infections, such as toxoplasmosis, rubella, or cytomegalovirus (“TORCHS”)
  • Severe malnutrition
  • Exposures to alcohol, certain drugs, or toxic chemicals
• Interruption of the blood supply to the baby’s brain during development
MMWR: Notes from the Field: Evidence of Zika Virus Infection in Brain and Placental Tissues from Two Congenitally Infected Newborns and Two Fetal Losses — Brazil, 2015

Weekly / February 19, 2016 / 65(06);159–160

- Zika virus confirmed in postmortem brain, amniotic fluid or placental tissue in infants with microcephaly

- Detection and Sequencing of Zika Virus from Amniotic Fluid of Fetuses with Microcephaly in Brazil: a Case Study
  G Calvet, AM de Filippis, et al.

- Zika Genome detected in amniotic fluid of two pregnant women from Paraiba State in NE Brazil whose fetus had been diagnosed with microcephaly

- Complete Zika virus genome from one sample and genome fragments from the second
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)

Pregnant?

- Do not travel to areas where Zika virus is spreading.
- If you must travel to these areas, talk to your doctor first.
- Strictly follow steps to prevent mosquito bites during your trip.
- If you have a male partner who lives in or has traveled to an area with Zika, either use condoms the right way every time you have vaginal, oral, or anal sex, or do not have sex during the pregnancy.

Trying to become pregnant?

- Before you travel, talk to your doctor about your plans to become pregnant and the risk of getting Zika.
- Strictly follow steps to prevent mosquito bites during your trip.

Before you travel, check the CDC travel website frequently for the most up-to-date recommendations. http://wwwnc.cdc.gov/Travel
Zika Associated Adverse Outcomes
Range of adverse outcomes

- Fetal loss/miscarriage
- Stillbirth
- Fetal brain anomalies
- Eye abnormalities
Spectrum Of Teratogenic Effects Of Zika

- IUGR
- Miscarriage/stillbirth
- Eyes: cataracts, chorioretinitis
- Brain:
  - Microcephaly
  - Hydrocephalus/hydranencephaly
  - Absent structures: (CC, pons, cerebellar vermis, etc)
  - Neuronal migration disorders (lissencephaly)
  - Fetal brain disruption sequence
  - Cerebral calcifications
  - Brain asymmetry

- Neurologic: hypertonia, swallowing problems, arthrogryposis (joint contractures), seizures
- Neurodevelopment?
Affected Fetus With Documented Zika Infection

Driggers et al, NEJM

Figure 2. Fetal Ultrasonography at 19 Weeks of Gestation.

Figure 3. Magnetic Resonance Imaging of the Fetal Brain at 19 Weeks of Gestation.
Adverse Fetal Outcomes Not Limited To Microcephaly

- JAMA Ophthalmology BP Freitas, R Belfort et al.
  - February 2016
  - Ocular findings Congenital Infection in Salvador Brazil

Fundus Photographs of a 20-Day-Old Infant
Zika Virus: First Cohort Study

• Study of 42 Zika+ pregnant women in Brazil followed with serial ultrasound:

29% with fetal anomalies
17% with microcephaly, atrophy, or calcifications

Brasil et al, NEJM
Risk May Not Be 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
WHO Update: New Findings

• Unpublished data from Colombia and Panama suggest other systems affected
  • Cardiac
  • Digestive
  • Genitourinary

http://www.who.int/bulletin/volumes/94/6/16-176990
Diagnostic Challenge
Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities
Rita W. Driggers, M.D., Cheng-Ying Ho, M.D., Ph.D
March 30, 2016

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.
Potential Mechanisms
Zika Kills Developing Human Brain Cells

- Zika Virus infects Human Cortical Neural Progenitor cells
- Attenuates their Growth more efficiently compared to mature cortical neurons
- Causing dysregulation and cell Death
- Zika Virus also Impairs Growth in Human Neurospheres and Brain Organoids

Garcez et al, Science
H Tang, G Ming et al., Cell
Mouse Model Zika In Utero Transmission

Zika Virus Infection during Pregnancy in Mice Causes Placental Damage and Fetal Demise


null, Volume 165, Issue 5, 2016, 1081–1091
Mouse Model Zika In Utero Transmission


null, Volume 165, Issue 5, 2016, 1081–1091

http://dx.doi.org/10.1016/j.cell.2016.05.008
The Brazilian Zika Virus strain causes birth defects in experimental models:
- ZIKV crosses the placenta
- Targets cortical progenitor cells
- Induces cell death by apoptosis and autophagy

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
Zika and the Placenta
Primary Human Trophoblasts

Type III Interferons Produced by Human Placental Trophoblasts Confer Protection against Zika Virus Infection

Avraham Bayer, Nicholas J. Lennemann, Yingshi Ouyang, John C. Bramley, Stefanie Morosky, Ernesto Torres De Azeved Marques Jr., Sara Cherry, Yoel Sadowsky, Carolyn B. Coyne

null, Volume 19, Issue 5, 2016, 705–712
http://dx.doi.org/10.1016/j.chom.2016.03.008
Zika virus PR type replicates in primary human placental macrophages, Hofbauer cells and lesser extent cytotrophoblasts, suggesting that Zika virus gains access to the fetal compartment by directly infecting placental cells and disrupting the placental barrier.

Quicke et al. May 2016
Three hypotheses as to why Zika virus causes new clinical syndromes

- Zika virus has evolved at the sequence level

- Different host populations: unique human genetics

- Pre-existing immunity to a related flavivirus predisposes to more severe Zika virus infection
Zika: Research Gaps Related to Pregnancy and Pregnancy Outcomes

- Risk of infection in pregnancy
- Sequelae of Zika exposed and infected infants without microcephaly
- Diagnostics
- Long-term reservoirs for Zika
- Treatment
- Vaccine
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
Zika cohort study

Followed through pregnancy

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

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

<13 wks gestation
Offered enrollment into cohort study

All children followed: those with and without anomalies
Acknowledgments

- Cathy Spong
- Bill Britt
- Mike Diamond
- Melissa Parisi
- Christine Rogers
Questions?