Fetal Zika Virus Encephalopathy: 
An Accelerated Learning Curve

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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-to-vector-to-human) transmission occurs during outbreaks
Zika – Epidemiology and Emergence in Americas

The spread of the Zika virus

1947
UGANDA

2007
Yap Island (MICRONESIA)

2014
New Caledonia (FRANCE)

2013
Tahiti (FR. POLYNESIA)

2015
Easter Island (CHILE)

2015
BRAZIL

LARIS KARKLIS/ THE WASHINGTON POST
Where Local Transmission of Zika Virus has Occurred as of August 31st, 2016
Zika Virus Outbreak 2015

Lanciotti et al., EID 2016:
http://wwwnc.cdc.gov/eid/article/22/5/16-0065_article
Wynwood: June 15th  
Miami Beach: July 14th
Zika – How Concerned Should We Be in the US?

- January 15, 2016: CDC issues Level 2 travel alert for pregnant women in any trimester who may be traveling to South/Central American or Caribbean countries where Zika is spreading.
- Feb 1, 2016 – WHO announces Zika as Global Emergency.
- Feb 8 – CDC activated to Level 1 Response (Highest).
- Feb – July 2016: Explosive spread in the Americas:
  - U.S. travelers who visit countries where Zika circulating infected.
  - U.S. mainland has Aedes species mosquitoes that can become infected with and spread Zika virus.
- July 29, 2016: First reports of local transmission of Zika virus in the continental United States occur in Miami, Florida.
  - Limited local transmission may occur in mainland US but widespread transmission unlikely.
Current US and US Territory Zika Case Counts (As of Sept 14, 2016)

**US States**
- **Total 3176**
  - Travel associated: 3132
  - Locally acquired vector-borne cases: 43 (Florida)
  - Lab acquired: 1
  - Sexually Transmitted: 26
  - Guillan-Barre syndrome: 8
- **Pregnant (with lab evidence): 713**
  - 18 liveborn with birth defects; 5 pregnancy loss with birth defects

**US Territories (Puerto Rico, US Virgin Islands, American Samoa)**
- **Total 17,694**
  - Travel associated: 65
  - Locally acquired: 17,629
  - Guillane-Barre syndrome: 34
- **Pregnant (with lab evidence): 1156**
US Cases as of September 14, 2016

- VA: 81 (3%)
- MD: 95 (3%)
- PA: 102 (3%)
- DC: 17 (1%)
- WV: 11 (<1%)

Reflects about 10% of US cases
Aedes aegypti
Originated in sub-Saharan Africa, spread throughout the tropics centuries ago

Aedes 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 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.


International Symposium on the FETAL BRAIN
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: Myalgia, 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
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.
Zika Virus and the Guillain–Barré Syndrome — Case Series from Seven Countries

- Association of Zika virus infection to GBS
  - 2 to 10 fold rate ratio (increase over baseline) in countries with circulating Zika

DOI: 10.1056/NEJMc1609015
Detecting Zika RNA and Antibody

- Distinguishing Zika IgM from other flavivirus (e.g. Yellow Fever, Dengue) infections may be difficult (cross-reactive)
- Requires plaque reduction neutralization assay
Congenital Brain Abnormalities and Zika Virus: What the Radiologist Can Expect to See Prenatally and Postnatally¹

Soares de Oliveira-Szejnfeld, et al
Radiology 2016; 281: 10-16
Fetal ultrasound in 42 lab-confirmed women infected at 5 to 39 weeks gestation

Fetal abnormalities detected by ultrasound in 12/42 (29%) PCR + women

- Fetal deaths at 36 and 38 weeks of gestation (2 fetuses)
- In utero growth restriction with or without microcephaly (5)
- Ventricular calcifications or other central nervous system (CNS) lesions (7)
- Abnormal amniotic fluid volume or cerebral or umbilical artery flow (7).
June 15, 2016

12,000 Zika-infected pregnant women (1500 lab confirmed)

Report on 1850 infected in third trimester; 90% had given birth

- None of the infants had structural abnormalities of the brain
- First and second trimester infections still being followed, and longer term follow-up of the third trimester infected infants ongoing.
Pregnancy Outcomes in Setting of Zika Infection

- CDC: US Pregnancy and Infant Registry:
  - 17 liveborn infants with birth defects
  - 5 pregnancy losses with birth defects
    - Microcephaly
    - Calcium deposits in the brain
    - Excess fluid in the brain cavities and surrounding the brain
    - Absent or poorly formed brain structures
    - Abnormal eye development
    - Clubfoot or inflexible joints
    - Hearing loss
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
Questions Without Clear Answers Yet:
Active Areas of Research

- Can we predict 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 fetal brain:
  - 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/genotypic 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?
    - Does mode of acquisition affect risk of transmission to fetus?

- What are the long-term neurodevelopmental and neuropsychological outcome of survivors (both symptomatic and asymptomatic)?
  - Are there more subtle, prevalent effects of ZIKV on the developing brain?
Colombia Congenital Zika Project
Children’s National Congenital Zika Virus Program

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