Bench to Bedside in Real Time: Rapid Progress Against Zika Virus

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Outline and Disclosures

• Biology of Zika Virus
• Current Zika Virus Disease Epidemic
  – Onset
  – Clinical features
  – Mortality events
• Surveillance, Diagnosis, Risk Assessment
• Future Disease Management

Nothing to disclose
Zika CME Learning Objectives

• Discuss the origins of the current outbreak

• Describe the clinical features of Zika virus disease in different patient populations

• Describe the current options for diagnosis and vaccination

• Advise patients on relative risk and best practices for prevention
Zika Virus Disease

- Historical view of ZIKV disease
Zika Virus Biology

• Arbo Flavivirus
  – RNA
  – Latency?
  – Antivirals?

• Features of Flaviviruses
  – Transmission
  – Prevention
  – Diversity

Flavivirus Family Tree

Farfan-Ale et al, 2009
Zika Virus Disease in the Americas

Zika virus, a cause of fever in Central Java, Indonesia.

Abstract

In 1977 and 1978 selected in-patients at the Tegalwadi Hospital, Kotlin, Indonesia who had recent onsets of acute fever were serologically studied for evidence for alphavirus and flavivirus infections. A brief clinical history was taken and a check list of signs and symptoms was completed on admission. Acute and convalescent phase sera from 30 patients who showed evidence that a flavivirus had caused their illnesses were tested for neutralizing antibodies to several flaviruses which occur in South-east Asia. Paired sera from seven patients demonstrated a fourfold rise in antibody titre from acute to convalescent phase. The most common clinical manifestations observed in this series of patients included high fever, malaise, stomach ache, dizziness and anorexia. None of the seven patients had headache or rash despite the fact that headache and rash had been associated with two of the three previously studied. The onsets of illness clustered toward the end of the rainy season when populations of Aedes aegypti, a probable vector in Malaysia, were most abundant.
Diversity of Zika Virus

- 33 Assembled Genomes
  - Collection site, time, location varied substantially
Zika Virus Sequence Alignment

- Aligned all 33 genomes
  - ClustalΩ

- SNP-level diversity

70 OF 10,000+ BASES
Zika Diversity by Gene

Changes/100 Residues

PrM | E | NS3 | NS5

May and Relich 2016
Clinical Relevance?

• Diagnostics, vaccines (more on this later!)

• Outbreak history
  – How did Zika arrive in the Western hemisphere?
Clinical Relevance?

- Diagnostics, vaccines (more on this later!)
- Outbreak history
  - How did Zika arrive in the Western hemisphere?
Clinical Relevance?

• Diagnostic

• Outbreak
  – How did Zika arrive in the Western hemisphere?

Lednicky et al., 2016
Zika Introduction into the Western Hemisphere in Summation

2007
Clinical Presentation* of Zika Virus Disease

• Classic
  – Mild, febrile illness with malaise
  – Conjunctivitis
  – *Itchy* rash

Maculopapular rash
Zika Emergence and Microcephaly Spike

• Zika confirmed May 2015

• Microcephaly spike October 2015
  – Contemporary, but causal?

Congenital Zika Syndrome

- Microcephaly
  - Diagnosing [<2 SD vs. <3 SD vs. 3%ile]

- Brain Abnormalities
  - Cerebral calcification
  - Atrophy, abnormalities

Broxmeyer et al. 2016
Congenital Zika Syndrome

• Non-microcephalic infants?

Blindness, deafness, ataxia, swallowing difficulties, seizures, hyperirritability.... in infants. Children/adults?

Melo et al., JAMA Neurol. October 03, 2016
Neuropathies in Children and Adults

- Guillain-Barré syndrome
  - Zika confirmed in May 2015
  - Spike June 2015

- Presentation
  - Ascending paresis, tetraparesis

- Treatment
  - IV IgG, plasmaphoresis

H&E in peripheral nerve during GBS

Emerging Neurotropism?

• Was this always part of Zika’s clinical picture?
Mortality

• 10 total case reports
• Encephalitis
  – 47 yo female, hx unremarkable
• Zika fever w/ thrombocytopenic pupura
  – 70 yo male, hx unremarkable
• Zika fever
  – 15 yo female, hx includes sickle cell disease
• Zika “shock syndrome”
  – 73 yo male, hx includes sero+ Dengue
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Transmission and Risk in the U.S.

- Vectorborne

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.*

Clinical Laboratory Features

- Biosafety level [2?3? Complicated...]
- Virus isolation [Vero cells]
  - DPH vs. contract labs
- NAATs
  - DPH vs. contract labs

ZIKV-infected Vero cells
Image: R. Relich IU Med

Shameless Plug for
Infectious Agent Isolation
NAATs

• Specimens
  – Blood, urine*, CSF, amniotic fluid

• Numerous have received FDA EUA
  – CDC uses Trioplex (Zika/Chikungunya/Dengue)
  – xMAP (Luminex)
    • 6 different RNA targets (minimize false negs)
Positive Zika Diagnosis...Now What?

• Report to the state

• Most Patients
  – Fever control, supportive care
  – Advise on sexual transmission
  – Advise on mosquito repellant
  – Monitor for GBS 2-3 weeks
Management of Obstetric Patients

• General
  – Travel advisories!!!!!!!!!!!!!!!!!!!!!
  – Insect repellant; sexual transmission

• Suspect
  – Time to confirmed diagnosis
  – Imaging

• Confirmed
  – CVS for virus detection, path in patients >12wks
Management of Infants with Prenatal Zika Exposure

• Aggressive monitoring
  – Cognitive, behavior, sensory, etc.
  – Not just microcephalic

• Early intervention
  – Demonstrated benefit

• Refer to social work colleagues for support services
Zika Vaccine Trials

• Target population
  – Greatest risk (XX, CBA)
  – Rubella vax model

• NIH/NIAID trial
  – safety stage
  – DNA vaccine; E protein
    • Previous Flavivirus vaccines
Zika Vaccine Trials...Complications?

- Envelope Protein as a vaccine antigen
  - $E$ is under sig ($P<0.05$) diversifying selection in Zika
  - NOT SO for WNV, DENV

- Vaccine escape?

May and Relich PLoS One 2016
Summary

• Zika virus is a rapidly developing situation

• Majority of patients are subclinical or recover fully

• Congenital syndrome is concerning

• EUA has been issued for diagnostics, vaccines
Additional Resources

- CDC Clinical Guidance for Zika

- WHO Guidelines for Infants and Neonates with Zika Exposure
  - [http://apps.who.int/iris/bitstream/10665/204475/1/WHO_ZIKV_MOC_16.3_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/204475/1/WHO_ZIKV_MOC_16.3_eng.pdf?ua=1)

- CDC Guidance for Infants with possible congenital Zika
  - [http://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm](http://www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm)

- Zika and insect repellants during pregnancy

- Zika Diagnostic tests: FDA EUA list
  - [http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika](http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika)

- NIH Considerations for Zika Vaccine Design
  - [https://respond.niaid.nih.gov/conferences/Zika/Presentations/Julie%20E.%20Ledgerwood.pdf](https://respond.niaid.nih.gov/conferences/Zika/Presentations/Julie%20E.%20Ledgerwood.pdf)