UPDATE: CONGENITAL ZIKA VIRUS SYNDROME

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Dr. Byrne has no conflict of interest, financial or otherwise, related to the content of this presentation.
What is Zika?
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1947</td>
<td>Zika virus identified in macaque in Uganda (Zika Forest): fortuitous discovery during a yellow fever study</td>
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<td>1953</td>
<td>Zika virus recognized as cause of human illness in Nigeria</td>
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<td>1953-2007</td>
<td>Sporadic cases of mild febrile illness attributed to Zika in Africa and Asia</td>
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<td>2007</td>
<td>Large outbreak of Zika virus illness in the State of Yap, Federated States of Micronesia: 5000 infections occurred in a total population of 6700; Spectrum of Zika illness defined</td>
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<td>2013-2014</td>
<td>Large outbreak of Zika virus infection in French Polynesia with 32,000 cases</td>
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<td>Mar 2015</td>
<td>Zika virus first identified in the Americas in Brazil</td>
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Zika virus timeline

- Sept 2015  Increased number of infants born with microcephaly noted in Brazil
- Early 2016  Increase in microcephaly retrospectively noted in French Polynesia following the 2013-2014 outbreak
- Jan 2016  CDC issues interim travel guidance for pregnant women for areas with ongoing Zika virus transmission
- Feb 2016  WHO declared Public Health Emergency of International Concern
- Nov 2016  Public health emergency status downgraded
What is Zika Virus?

- Single stranded RNA Virus
- Genus Flavivirus
- Closely related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses
- Primarily transmitted by two Aedes species mosquitoes – Aedes aegypti and Aedes albopictus
What is Zika Virus?

- *Aedes* species mosquitoes are aggressive daytime biters.
- Live in and around households; lay eggs in domestic water holding containers.
- Can also transmit dengue and chikungunya viruses.
Additional modes of transmission

- Intrauterine transmission
- Intrapartum transmission from viremic mother
- Sexual transmission
- Blood transfusion
- Laboratory exposure
Zika virus infection

- Intrauterine viral infections may affect the fetal brain (neurotropic)
- TORCH infections (toxoplasmosis, rubella, CMV, herpes)
- West Nile encephalitis- rare cases of fetal brain abnormalities
- Zika goes a step further
Zika virus infection

- Infection is generally associated with a mild disease (fever, arthralgias, erythema, conjunctivitis)
- Often asymptomatic (80%)
- Cases of Guillain-Barré syndrome also reported, although rare
What happened in Brazil?

- Cluster of severe microcephaly cases in Brazil corresponding with outbreak of Zika virus in May 2015; incidence of microcephaly 20 times the baseline rate

- Case definition difficulties
  - Revised case definition in June 2016
Why no fetal cases until 2015?

- First identified in Uganda in 1947
- Underreporting of cases?
- Acquisition of immunity in endemic areas?
- Disease rare until recently?
- Genomic changes → more virulent strains?
- Possibly the severe cases represent the “tip of the iceberg” and that less severe cases are not recognized at birth → underreporting of cases....
Ultrasound findings suggestive of Zika virus infection

- Microcephaly
  - Onset often ~24-28 wk gestation
- Intracranial calcifications
  - Frequently subcortical rather than more common periventricular
- Ventriculomegaly
  - Often severe, asymmetric
- Brain destruction is significant and affects posterior fossa (cerebellum), brainstem, thalami
- Arthrogryposis- often atypical joint deformations
Zika virus infection at 13 wk gestation

Courtesy of NOVA Diagnóstico por Imagem
Zika Virus in Pregnancy

- Incidence of Zika virus infection in pregnant women is not known
- Infection can occur in any trimester
- No evidence of more severe disease compared with non-pregnant women
- No evidence of increased susceptibility during pregnancy
Possible adverse reproductive outcomes due to Zika infection

- Fetal death - early and late pregnancy loss
- Infant with microcephaly and serious brain anomalies **
- Infant with other birth defects
- Infant with less severe brain anomalies and developmental disabilities
- Infant with developmental disabilities alone
- Other adverse pregnancy outcomes such as preterm birth

** causal relationship established
Consider Zika virus disease in patient with compatible clinical S/Sx and who traveled to or resides in areas with ongoing Zika transmission

History of sex without condom with someone who traveled to or resides in areas with ongoing Zika transmission

All pregnant women should be assessed for possible Zika virus exposure at each prenatal visit
  - Offer testing to those with symptoms or asymptomatic with risk factors
Risk stratification

- Offer testing to asymptomatic pregnant women who:
  - Traveled to or live in an area with active Zika virus transmission
  - Had sex without a condom with someone who traveled to or resides in an area with active Zika virus transmission
Many unanswered questions:

- How often does maternal infection result in fetal infection?
- What proportion of positive amniotic fluid tests will result in infected fetus/infants?
- What proportion of infected fetus/infants will be severely affected?
- What proportion of asymptomatic infants will have sequelae?
- What are those potential long-term sequelae?
Confirmed maternal infection

- Refer to maternal-fetal medicine
- Counsel about reproductive options
- Consider invasive testing (amniocentesis)
  - Zika virus RT-PCR can be performed on amniotic fluid, however it is not known how sensitive or specific this is for congenital infection
- Serial ultrasounds for growth, evaluation of the CNS
- Consider other imaging modalities (e.g. MRI)
  - MRI is *NOT* for screening
- Postnatal evaluation of neonate, placenta- coordinate with health department
Prenatal Zika virus infection →
Congenital Zika Syndrome

Destruction of existing CNS tissue & Disruption of future developmental processes

Brain volume loss

- Severe microcephaly
- Misshapen skull with overlapping sutures
- Redundant scalp

Neurologic dysfunction

- Hearing, vision, swallowing problems
- Global developmental impairment
- Limb contractures
- Hypertonia, epilepsy, extreme irritability

Recognizable pattern: Congenital Zika syndrome
Congenital Zika Syndrome: Unique Pattern of Malformations

- Severe microcephaly with partial skull collapse
- Intracranial calcifications in the subcortical region
- Macular scarring and focal pigmentary retinal mottling
- Congenital contractures
- Neurologic abnormalities both pyramidal and extrapyramidal
Features

- Severe microcephaly (most more than 3 SD below the mean)
- Partial collapse of the skull with overlapping sutures
- Occipital bone prominence
- Small or absent anterior fontanel
- Scalp rugae

Consistent with fetal brain disruption sequence (FBDS)

Not all with severe microcephaly have FBDS phenotype

FBDS is rare but not unique to congenital Zika syndrome
Newborn with microcephaly

CT reconstruction

Cortesia Maisa Wanderley
Congenital Zika Syndrome - Ocular findings

Normal fundus

Fundus of presumed Zika infection
Ventura, et.al. 2016
Congenital Zika Syndrome-Arthrogryposis
Imaging in Congenital Zika Syndrome
29 wk gestation

Zika affected

Normal

Adriana Melo-IPESQ
29 wk gestation

Zika affected  Normal

Adriana Melo-
IPESQ
30 wk gestation

Zika affected

Normal

Adriana Melo-IPESQ
Calcifications - transvaginal ultrasound
Scope of the problem in the US

- US Zika Pregnancy Registry (CDC)
  - Preliminary data by Honein et.al. (JAMA 2017)
  - 442 completed pregnancies with +lab evidence Zika
  - Zika related birth defects found in 6% of infants of symptomatic women; 6% of infants of asymptomatic women
  - Primarily microcephaly and brain abnormalities
  - With exclusive first trimester exposure, birth defects in 11% of infants
Lab confirmed symptomatic Zika cases
U.S. and territories 2015-2018
Total positive moms to date: 21

All travel related:
- Mexico 47.62%
- Marshall Islands 14.29%
- Venezuela 14.29%
- Honduras 9.52%
- Guatemala 4.76%
- Dominican Repub. 4.76%
- El Salvador 4.76%

* Data from Utah Birth Defect Network/ Utah Public Health Laboratory
Utah experience as of 5/2018

- Total positive moms to date: 21
- Infants born to positive moms who then tested positive: 0
- 2 SABs tested positive for Zika - both 1st trimester
- Infants born to positive moms with microcephaly or “typical” Zika related birth defects: 0
- 1 infant not meeting milestones at 18 months
Utah experience as of 5/2018

- No major updates with testing
- Utah Public Health Laboratory
  - Symptomatic persons and exposed pregnant women tested free of charge
- Many commercial labs also conduct Zika testing for a fee
Zika Travel Information
Areas with Risk of Zika Transmission

- Africa
- Asia
- The Caribbean
- North America
- Pacific Islands
- South America

Visit CDC’s Zika website:  http://www.cdc.gov/zika
Page last reviewed 5/24/18
Pregnant women or those trying/capable of becoming pregnant should be counseled against travel to endemic areas.

If travel unavoidable, extreme caution to avoid exposure:

- Insect repellent (DEET, picaridin, IR3535, oil of lemon eucalyptus, para-menthane-diol, 2-undecanone)
- Long sleeves, long pants
- Screens on windows
- Air conditioning
“We’re going to Puerto Rico for a wedding- is that ok?”

- Sexual transmission is well documented
- If pregnant, recommendation is for avoidance of unprotected intercourse for up to 6 months (or for duration of pregnancy) after travel to an endemic area
“I was in a place with risk of Zika recently (I went to a wedding in Puerto Rico). How long do I need to wait after returning to get pregnant?”

- **Women**: Women who have traveled to a place with a CDC travel notice should wait at least 8 weeks after travel (or 8 weeks after symptoms started if they get sick) before trying to conceive.
Men: Men who have traveled to a place with a CDC travel notice should wait at least 6 months after travel (or 6 months after symptoms started if they get sick) before trying to conceive with their partner.

The waiting period is longer for men because Zika stays in semen longer than in other body fluids.
Longer term sequelae reported to date include the following:

- Motor and cognitive disabilities (French Polynesia)
- Hydrocephaly – some requiring a VP shunt
- Worsening epilepsy
- Feeding problems and severe reflux – some requiring a G-tube
- Respiratory problems – diaphragmatic paralysis
- Glaucoma
- Potential cerebral palsy
- Potential endocrine abnormalities
- Microcephaly onset after birth
Many questions remain....

- What is the full range of potential reproductive health problems that Zika virus infection may cause?
- How long does the virus persist in various tissues after infection?
- What are other factors (e.g., co-occurring infection, nutrition, presence of symptoms) that might affect the risk for birth defects?
- Is there a way to predict who is at risk for long term sequelae?
Thanks to my CDC friends

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  - Editor-in-chief, *Morbidity and Mortality Weekly Report*
Questions?