Travel to a Zika Endemic Region – Should My Patient Worry?

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DISCLOSURES

• Michael Libman: no disclosures
• Margaret Honein: no disclosures
• Bram Goorhuis: no disclosures

Zika Virus

• Single stranded RNA virus of Flavivirus genus
• Closely related to dengue, West Nile, yellow fever, and Japanese encephalitis viruses
• Arbovirus: arthropod-borne virus
• Primary vector - Ae. aegypti but several other Aedes spp. and Culex spp. capable of transmission (in laboratory)
  – Strain dependent

Two Distinct Zika Lineages – Only One Serotype

• African
• Asian
  • All strains have identical surface antigens
  • Antibodies elicited after infection with Asian lineage potently inhibit both lineages in vitro
  • Sequence homology 90% (primer problems)
  • Oddly, African strain seems more pathogenic
    • Liu, Z Nat Rev Microbiol 17, 131–139 (2019)
Travel-Associated Zika Virus Disease Acquired in the Americas Through February 2016

A Geospatial Analysis

Figure 1. Clinical symptoms and signs among 93 patients diagnosed with Zika virus disease acquired in the Americas.

*46 persons reported a total of 71 additional symptoms and signs in the form of comments in this category. Those observed in ≥3 patients: gastrointestinal (17%, post-feeding parathesia (9%), abdominal pain (9%), vomiting (6%), headache (6%), and macular rash (5%).

Data were not collected systematically.
Zika rash
Photo courtesy of Marc Shaw, Auckland, NZ

Less Common Signs
- Joint swelling
- GI: diarrhea, nausea, vomiting
- Paraesthesias
- Retro-orbital pain
- Pharyngitis
- Dysgeusia
- Subcutaneous hematomas
- Epididymitis

Substantial Clinical Overlap Among Common Arboviruses

<table>
<thead>
<tr>
<th>Feature</th>
<th>Zika</th>
<th>Dengue</th>
<th>Chikungunya</th>
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<td>Rare</td>
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<td>Shock</td>
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Zika Neurological Complications
- Congenital Zika syndrome
  - Fetal brain disruption sequence
  - In vitro: Asian strain only
    - ZIKVAF – monkey adapted
      - Cugia, Nature 2016
- Guillain-Barré syndrome (GBS)
- Meningoencephalitis
- Acute myelitis
- Hearing loss
- Posterior uveitis

Sexual transmission

Numbers of Zika Cases
Scenario 1:
Woman who is pregnant wants to travel to country X, and wants to know if it is “safe”.

Current CDC Guidance
• CDC now recommends pregnant women and couples trying to become pregnant within the next three months talk to their healthcare providers before traveling to areas that report past or current spread of Zika but no current outbreak.
• CDC’s recommendation that pregnant women not travel to areas where a Zika outbreak is occurring has not changed.

What have we learned?
Among pregnancies with lab evidence of Zika:
~5-10% of infants had Zika-related birth defects of the brain or eye
~9% had neurodevelopmental disabilities potentially related to Zika

Zika-associated birth defects
• Microcephaly at birth
• Selected congenital brain anomalies
• Selected congenital eye anomalies

Neurodevelopmental Disabilities Possibly Associated with Zika
• Hearing abnormalities
• Congenital contractures
• Seizures
• Body tone abnormalities
• Movement abnormalities
• Swallowing abnormalities
• Possible developmental delay based on standardized screening or evaluation
• Possible visual impairment
• Postnatal-onset microcephaly
Case Scenario:
What factors should be considered?

- Level of risk unknown
- Potential delays in identifying an outbreak
- Type and length of exposure
  - Accommodation type
  - Repellent/clothing
  - Risk of sexual transmission

Case Scenario 1:
Important to Discuss Risks

- Pregnant women considering travel to an area with potential risk for Zika should talk with their healthcare provider
- Level of risk of infection likely low for most countries with endemic Zika
- Important to consider severity of adverse outcomes and long term implications
Usual clinical practice...

Simon's hobby: neglecting rare birds

Zika conference Tallinn 2018

- Duncan Smith, Mahidol University, Thailand
- Talk on Friday June 15th
- Unpublished data from Thailand
- 135 healthy Thai volunteers
- Zika nABS in 70% (PRNT50≥10)


Where is the epidemic going?

- Risk in Latin America markedly reduced and comparable to Africa and Asia
- Insufficient reason to advise against travel for pregnant women
- Risk assessment should be made per individual pregnant traveler
- Other (more important) risks for pregnant travelers!
Next topic: sexual transmission

Scenario 2: Man goes on a trip to country X, wants to conceive with his partner without delay when he returns from the trip

Risks for Sexual Partners of Infected Travelers

- **CDC recommends** that men with possible Zika virus exposure who are planning to conceive with their partner wait for at least 3 months after possible exposure before engaging in unprotected sex

- Zika virus can persist in semen, and the period during which infection can be transmitted to sexual partners is unclear
  - Unlikely to identify sexual transmission in those with asymptomatic infections
  - Published studies report a range of RNA positivity extending as long as 370 days post-symptom onset

Updated WHO Guidance

For the new recommended duration for correct and consistent use of condoms or abstinence to prevent sexual transmission of Zika virus, a distinction is made between men and women, and the recommended duration has been reduced from 6 to 3 months for men, 2 months for women.

https://apps.who.int/iris/bitstream/handle/10665/311028/WHO-RHR-19.4-eng.pdf?ua=1
Dutch advice

• Based on the same literature
• Women: postpone post travel pregnancy until 1 month after return
• Men: postpone conception attempts until 2 months after return

Taking into account the decline of circulating Zika virus combined with the observation that the duration of semen infectivity over 2 months is exceptional, it seems rational to update recommendations for the prevention of the sexual transmission of Zika virus and to limit the recommendation to postpone pregnancy attempts to **2 months** after the last possible exposure for both men and women.

Are the Dutch crazy?

Scenario 3: woman travels to country X and has some non-specific symptoms, and recognizes that she is ~5 weeks pregnant shortly after returning from travel

Available Testing

- **Nucleic Acid Amplification Tests**
  - Only when viremic
  - Maybe longer in urine, placenta

- **Serology**
  - Huge problems with cross-reactivity with other flaviviruses
  - Low a priori probability = low specificity
  - Remote infection = “false positive”
  - Kinetics of antibody appearance and decay not homogeneous

It's a simple stress test - I do your blood work, send it to the lab, and never get back to you with the results
Importance of Detecting Zika during Pregnancy

- Allows for coordination of care between maternal and pediatric providers
- Can inform decision to deliver near tertiary care center, and help families know what to expect
- Can provide a diagnosis to families and prevent expensive and invasive clinical diagnostic work up for other causes
- Important to get genetic counseling on risks for subsequent pregnancies

Occurrence of Congenital Zika Syndrome Before Outbreaks in the Region of the Americas

- Born in 2009 and 2011
- Mothers lived in Cambodia during pregnancy, with Zika-like symptoms in pregnancy
- Phenotype – Severe CZS
- Serologic testing
  - Mothers – consistent with prior Zika infection
  - Children – negative Zika testing

Role of other Testing

- Ultrasound, Amniocentesis
  - Unknown sensitivity and specificity
  - Negative test result on amniotic fluid cannot rule out congenital Zika virus infection
  - If amniocentesis is indicated as part of the evaluation for abnormal prenatal findings, NAT testing for Zika virus should be considered to assist with the diagnosis of fetal infection.

Congenital Zika Syndrome without Microcephaly at Birth

- Microcephaly from congenital infection can occur afterbirth
- The full spectrum of poor outcomes caused by Zika virus infection during pregnancy remains unknown


Monitoring and Care for Babies Born to Mothers with Zika during Pregnancy

- Birth should have a doctor’s visit at each three month interval and receive the indicated care. If problems are obtained at any point, babies may be referred to specialists as clinically indicated.
So – what’s our advice?

Risk assessment

- Risk of C\textsubscript{2}\textsubscript{2}\textsubscript{i}f infected (US\textsubscript{a}registry)
  - Approx 5% (51/1297 pregnancies)
  - 10% if lab confirmed (24/250),
  - 15% 1\textsuperscript{st} trimester (9/60)
  - 30x higher than baseline
  - 1/5 risk of 1\textsuperscript{st} trimester rubella
- Risk of GBS
  - About 1/4000 cases (cf. Campylobacter)
  - Maybe faster, milder
  - Acute motor axon type

Similarities with other Congenital Infections - Toxoplasma

- If newly infected with Toxoplasma during just before pregnancy, infection can be passed to the baby
- Pregnant women can be asymptomatic
- Most infected infants do not have clinical findings at birth but complications such as blindness or mental disability can be diagnosed later
- Occasionally, infected newborns have serious eye or brain damage at birth

Similarity of Recommendations: Malaria

- Malaria may be much more serious in pregnant than in non pregnant women and is associated with high risks of illness and death for both mother and child.
- Because no prophylactic regimen provides complete protection, pregnant women should avoid or delay travel to malaria-endemic areas.
- If travel is unavoidable, pregnant women should take precautions to avoid mosquito bites, and use of an effective prophylactic regimen is essential.