Zika Virus

Not your daddy’s arbovirus (hopefully)

Michael Libman MD
J.D. MacLean Centre for Tropical Diseases
McGill University
NO CONFLICT OF INTEREST TO DECLARE
(EXCEPT ON CATMAT GUIDELINES COMMITTEE)
U.S. officials: The more we know about Zika, the scarier it is

What Every Woman Needs to Know About Zika

Zika 'spreading explosively'
'Level of alarm is extremely high' about virus, WHO leader says

The New York Times
Zika Is Coming

By PETER J. HOTEZ  APRIL 8, 2016

HUFFPOST HEALTHY LIVING
An Illustrated Guide To The Zika Outbreak

The virus is suspected of causing birth defects and a rare autoimmune disorder.

Zika virus  Full coverage of the outbreak

Thanks: Ling Yuan Kong
Virus inoculated via mouse brain suspension to a 34 year old European male: fever, headache 3.5 days after inoculation
Outline

- Where is Zika?
- Transmission modes – what do we know
- Manifestations, Diagnosis – quick recap
- Risk assessment
- Recommendations - Guidelines
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 \textit{in vitro}
  - Sequence homology 90% (primer problems)

- Dowd K et al. Cell Reports 2016
Epidemiology

Discovered in Zika Forest, Uganda 1947
Epidemiology

- First human case diagnosed 1962-3 in Uganda
- Serosurveys – neutralizing antibodies in East and West Africa, India, and SE Asia
  - Late 1940s to late 1990s
- Outbreaks in Yap, Micronesia in 2007
  - First cases outside Asia/Africa, first outbreak
  - French Polynesia 2013, Easter Island 2014
- Brazil early 2015 then spread in the Americas
Two lineages: African Asian

Sero evidence of ZIKV multiple mammals viro only NHP

Human cases were mild

Yap, Fr Poly no NHP

Serologic evidence

Virus detection or confirmed human case
GeoSentinel Epi Curves

- Dengue
- Chik
- Zika
Why has Zika emerged now?

- Naïve populations in South Pacific amplified virus and facilitated spread via global mobility
- Abundance of competent vectors in the Americas
- Antibody-dependent enhancement in a heavily dengue-exposed population
- Mutational change (‘Asia strain’) - enhanced viral infectivity of Aedes vectors
- Mutational change – higher human viremia and improved transmission efficiency
Probable Sentinel Cases

- **2012: Indonesia (diagnosed in Australia)**
  - Kwong JC et al. AJTMH 2013

- **2014: the Philippines (dx in Germany)**
  - First case since 2012 for this country

- **2013: Thailand (dx in Canada)**
  - Serological data in Thailand from the 1950s
  - Fonseca C et al. AJTMH 2014

- **2015: Vietnam (dx in Israel)**
  - Serological data in Vietnam from the 1950s
Sentinel Cases

- **2010**: Cameroon (diagnosed retrospectively in Belgium)
  - Only reported case in Cameroon since 2010
- **2015**: Kirabati (dx in New Zealand)
  - First known report
- **April 2016**: East Timor (dx in Germany)
  - First known report although only probable
Figure 2. Map of Asian countries in which Zika virus circulation has been reported up to September 1, 2016.
Transmission – Other Modes

Proven:

- **Sexual**
  - Male to female; male to male; female to male

- **Blood products**
  - Documented in Brazil and French Polynesia

Theoretically possible, with serious implications:

- **Breast milk** *(Colt PLOS NTD April 2017)*
  - 3 cases, 1 culture pos (VL 850k/ml) day 4 postpartum
  - No clear transmission to child by milk

- **Saliva or tears**

- **Transplantation**
Transmission – Transfusion

- Martinique January to June 2016
  - Screened 4129 blood donations
  - 1.84% positive by nucleic acid testing
- Contacted donors to determine whether they were or became symptomatic
  - Mean log$_{10}$ RNA higher if symptomatic ($P = .0013$)
  - Symt:asympt 1:1

Gallian P et al. Blood 2017
Sexual Transmission

- Preliminary semen carriage studies:
  - Up to 188 days by PCR. Mean 34, CI 28-41
  - Unpublished intermittent shedding upto 1 yr (ECDC)
  - Replication competent Zika in semen for 69 days
    - But RNA virus: likely real
- High viral load in semen (and urine)
- Rarely hematospermia or microhematospermia
- Viral shedding in vaginal secretions to 14 days and in cervical mucus to day 11 post-symptom onset
- Time from sexual contact to symptom onset 8-21 days
  - Hamer DH et al. Curr Infect Dis Rep 2017
  - Paz-Bailey NEJM 2017
Clinical symptoms and signs in 93 patients with Zika virus disease acquired in the Americas

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>82</td>
</tr>
<tr>
<td>Fever/sweats</td>
<td>71</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>67</td>
</tr>
<tr>
<td>Headache</td>
<td>57</td>
</tr>
<tr>
<td>Myalgia</td>
<td>56</td>
</tr>
<tr>
<td>Other*</td>
<td>46</td>
</tr>
<tr>
<td>Fatigue</td>
<td>44</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>37</td>
</tr>
<tr>
<td>Pruritus</td>
<td>21</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>2</td>
</tr>
</tbody>
</table>

Maculopapular rash after travel to Haiti
Zika rash

Photo courtesy of Marc Shaw, Auckland, NZ

Maculopapular rash after travel to Haiti
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>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Rash</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Arthralgia/arthritis</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Myalgia</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Headache</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Rare</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Shock</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
### Co-infection Data for 346 Nicaragua Children

Waggoner JJ et al. CID 2016

<table>
<thead>
<tr>
<th>ZCD Assay Result</th>
<th>Number, n (% of all Samples)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive</strong></td>
<td></td>
</tr>
<tr>
<td>Mono-infections</td>
<td></td>
</tr>
<tr>
<td>ZIKV</td>
<td>47 (13.6)</td>
</tr>
<tr>
<td>CHIKV</td>
<td>91 (26.3)</td>
</tr>
<tr>
<td>DENV*</td>
<td>54 (15.6)</td>
</tr>
<tr>
<td><strong>Coinfections</strong></td>
<td></td>
</tr>
<tr>
<td>ZIKV-CHIKV</td>
<td>16 (4.6)</td>
</tr>
<tr>
<td>ZIKV-DENV*</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>CHIKV-DENV*</td>
<td>43 (12.4)</td>
</tr>
<tr>
<td>ZIKV-CHIKV-DENV*</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
<td>83 (24.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CHIKV, chikungunya virus; DENV, dengue virus; ZCD, multiplex real-time reverse-transcription polymerase chain reaction for the detection and differentiation of ZIKV, CHIKV, and DENV; ZIKV, Zika virus.

* Serotypes of 109 DENV-positive samples: DENV-2, 107; DENV-1, 1; DENV-4, 1.
Zika Neurological Complications

- Congenital Zika syndrome
  - Fetal brain disruption sequence
  - In vitro: Asian strain only
    - ZIKV^AF – monkey adapted
      - Cugola, Nature 2016

- Guillain-Barré syndrome (GBS)

- Meningoencephalitis

- Acute myelitis

- Hearing loss

- Posterior uveitis
So – what’s our advice?
Risk assessment

- Risk of CZS if infected (USA registry)
  - Approx 5% (51/1297 pregnancies)
    - 10% if lab confirmed (24/250),
    - 15% 1st trimester (9/60)
  - 30x higher than baseline
  - 1/5 risk of 1st trimester rubella

- Risk of GBS
  - About 1/4000 cases (cf Campylobacter)
  - Maybe faster, milder
  - Acute motor axon type

MMWR April 7 2017, Song BH, J neuroimmunol 2017
When is the risk?

1\textsuperscript{st} trimester – consistently shows highest risk
  – Peri-conception: theoretically low risk, but not supported by epi data
  – Placental persistence

All pregnancy
  – Interrupted brain development at any stage
  – May seem normal at delivery
  – Should be imaged

After delivery??
  – Low inoculum, more intact BBB
Risk assessment
Where are travelers getting Zika?

<table>
<thead>
<tr>
<th>Region of Travel</th>
<th>Canada (n=482)(^a)</th>
<th>Country visits from Canada over two years(^b)</th>
<th>United States (n=2,382)(^c)</th>
<th>England (n=295)(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caribbean</td>
<td>65% (313)</td>
<td>7,328,800</td>
<td>65% (1,545)</td>
<td>73% (215)</td>
</tr>
<tr>
<td>South America and Central America</td>
<td>19% (92)</td>
<td>2,921,800</td>
<td>27% (658)</td>
<td>23% (68)</td>
</tr>
<tr>
<td>N America</td>
<td>9%(^e) (43)</td>
<td>4,330,800(^g)</td>
<td>5% (111)</td>
<td>2% (6)</td>
</tr>
<tr>
<td>Cumulative % from the Americas</td>
<td>99.6%</td>
<td></td>
<td>99%</td>
<td>98.6%</td>
</tr>
<tr>
<td>Asia</td>
<td>0.4%(^f) (2)</td>
<td>5,395,800</td>
<td>&lt;1% (11)</td>
<td>1.7%(^i) (4)</td>
</tr>
<tr>
<td>Oceania</td>
<td>0% (0)</td>
<td>390,200(^h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>0% (0)</td>
<td>1,237,600</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
</tbody>
</table>

Many numbers are estimates extrapolated from multiple sources, not official
WHO Classifications of Zika Transmission

• Category 1:
  • Countries with a reported outbreak from 2015 onwards
  • e.g. Angola, Brazil, Maldives, USA

• Category 2:
  • Countries with evidence of transmission before 2015 and ongoing transmission
  • e.g. Haiti, Viet Nam
WHO/CDC Classifications of Zika Transmission

• Category 3:
  • Countries with evidence of local mosquito-borne Zika infections in or before 2015, but without documentation of cases since, or outbreak terminated (interrupted transmission) (potential future transmission?)
  • e.g. Easter Island, French Polynesia

• Category 4:
  • Established competent vector, no known transmission
  • e.g. most of Africa, Uruguay, various islands
CDC Recommendations for pregnant women

- Category 1 (plus Haiti, not USA): Travel health notice
  - do not travel

- Category 2, some cat 4
  - (38 countries, incl. most of Africa, Asia)
  - Should not travel
  - Includes most of the tropical world

- Sexual transmission precautions for all

- Based on uncertainty in risk

- Implications for insurance, personal ??
How can we estimate the risk?

Asia:
- 1 zika case / 2.5 million trips
- So really 1/250,000 (1/5 symptomatic-say 1/10)
- Risk of CZS 1/2,500,000 (6% - say 10%)
- Maybe 1/250,000 (10-fold under estimate)

S/C America, Caribbean = 100x higher

Compare:
- Risk of maternal death – 1/5000 live births
- Risk of death by MVA – 1/7000/year (x40 in Africa)
- Baseline risk of major malformation 1-3/100
- Baseline risk of “Zika-like” malformation 3/1000
Other types of pregnancy risk

Risk of congenital rubella syndrome:
- 65-85% in 1\textsuperscript{st} 2 months of gestation
- Major screening and vaccination programs

Congenital CMV syndrome:
- 50% of primary infections, 1/400 pregnancies
- No program

CATMAT: >1/10,000 = travel advisory during pregnancy
- So Category 1 + Haiti
Pregnancy
- Cat 1: avoid travel
- Cat 2: moderate risk, 3-4 low risk
- Cat 2-4: consider postponing, caution for malaria, discuss with couple, values/preference/risk tolerance

Sexual contact: Cat 1 = usual avoidance rec’s
- Cat 2-4: avoidance measures not routinely recommended, but discuss
Make modifications of WHO cat’s

- Subdivide cat 1 countries into regions when possible
- Cat 2+ = areas of cat 2 with “new documented intense transmission” (>10 cases/3 mo, or cases in >1 region)
  - Eg Vietnam, Philippines
- 4a: no transmission, but border cat 2

1, 2+ = high, 2=mod, 3, 4a=low, 4=very low
- No specific recommendations
Big questions

Why is Brazil CZS rate >> USA? (29% vs 6%)

- USA registry based
  - Maybe more severe entered registry
  - Maybe cases occurring outside of registry
- Outcomes detection systems/methods
  - Few infants PCR+, some IgM-, imaging erratic, multiple outcomes
- Demographic/genetic differences (age)
- Co-morbidities, exposure to cofactors (dengue?)
- Not viral strain
- USA rates higher than French Polynesia (1%)
Big questions

Is epidemic peaking?

– In South America, still waves of outbreaks, but less than 2016
  – Argentina this austral summer
– Central America: moving north through the summer
  – USA? Hawaii? Australia?
– Caribbean: Very slow in Martinique, Guadeloupe, St Martin, French Guiana
– French Polynesia: outbreak terminated at 50% seroprevalence
  – New Caledonia 12%
    – Aubry M EID 2017, Musso CMR 2016
What about late term or post partum exposure

- Subtle imaging changes?
- Subtle cognitive changes?
  - Cf toxoplasma
Where is the epidemic going?

De Oliveira WK NEJM 2017