Texas Society of Infection Control & Prevention
March 23, 2017

Zika
The Arbovirus du Jour

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University of Texas Southwestern Medical Center at Dallas
The Latest Numbers: 
Zika-Associated Congenital Syndrome*

Confirmed cases by Strict Case Definition, as of October 20, 2016

Brazil 2,033**
Rest of Central and S. America 113 (and counting)
U.S. 28 (and counting)
Canada 1 (and counting)

*Microcephaly, Ca++ deposits, enlarged ventricles, etc.
**reported >4,000

PAHO. Regional Zika Epidemiologic Update (Americas), October 20, 2016
## The Latest Numbers in the U.S.: Acute Zika Illness

**Cases reported to ArboNET, Jan 2015 – March 8, 2017**

<table>
<thead>
<tr>
<th>Category</th>
<th>U.S.</th>
<th>U.S. Territories*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel-associated</td>
<td>4,813</td>
<td>147</td>
</tr>
<tr>
<td>Locally mosquito-borne**</td>
<td>221†</td>
<td>37,952</td>
</tr>
<tr>
<td>Locally sexually transmitted</td>
<td>45</td>
<td>??</td>
</tr>
<tr>
<td>Guillain-Barre syndrome</td>
<td>14</td>
<td>40</td>
</tr>
<tr>
<td>Pregnancies with Zika lab evidence</td>
<td>1,534</td>
<td>3,225</td>
</tr>
<tr>
<td>Births with defects / completed pregnancies</td>
<td>52/1,143</td>
<td>??</td>
</tr>
</tbody>
</table>

*97% in Puerto Rico  **Brazil: 109,596 confirmed, 200,465 suspected  †Florida 215, Texas 6

“Here’s the plain truth: that Zika and other diseases spread by *Aedes aegypti* [mosquito species] are really not controllable with current technologies. So we will see this become endemic . . . . It will come back every year.”

Tom Frieden, MD  
Director, CDC  
Oct. 25, 2016  
Miami
Current Zika Spread in the U.S.

Brownsville, Texas (6 cases)

Miami, Dade Co., Florida (215 cases)
A Sudden Epidemic of Microcephaly in NE Brazil

“IN AUGUST 2015, something strange began happening in the maternity wards of Recife, a seaside city perched on the northeastern tip of Brazil where it juts out into the Atlantic.

‘Doctors, pediatricians, neurologists, they started finding this thing we had never seen,’ said Dr. Celina M. Turchi, an infectious diseases specialist at the Oswaldo Cruz Foundation, Brazil’s most famous scientific research institute. . . .”

The Microcephaly Epidemic in Brazil
Initial Epidemic Investigation of Microcephaly in Brazil

Brazil Ministry of Health, CDC, PAHO

Pernambuco State (capitol: Recife)

Microcephaly restrictive case definition:
- \( \geq 3 \) SD below mean for age & sex

![Map of Brazil with Pernambuco State highlighted]
First Estimation of Longitudinal Trend in Microcephaly, Brazil, Nov 2015

Number of cases (case definition: head circumference at birth <33 cm)

- Pernambuco
- Sergipe
- Piauí
- Tocantins
- Distrito Federal
- Paraíba
- Alagoas
- Ceará
- Rio de Janeiro
- Rio Grande do Norte
- Bahia
- Maranhão
- Goiás

Year reporting:
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015

Microcephaly

• “Small head” – head circumference is significantly (>2 or 3 SD) below age-sex norm for gestational age.
• Usually caused by failure of brain growth to expand the pliable skull or massive brain shrinkage and skull collapse.
• Maternal conditions during gestation causing microcephaly:
  – TORCH Syndrome: Toxoplasmosis, Other including Rubella, CMV, Herpes
  – Drug or alcohol abuse, fetal alcohol syndrome, fetal hydantoin syndrome
  – Untreated PKU
  – Toxic chemicals (e.g., mercury) or radiation
  – Severe malnutrition
  – Chikungunya* and dengue virus infections (probably not West Nile†)
• Fetal chromosomal abnormalities (e.g., Downs, Craniosynostosis)

Diagnosis of Microcephaly

- Head circumference on prenatal sonogram
  - Microcephaly suspected at >2 SD below mean for gestational age (not apparent before 22 weeks)
  - Confirmed by >5 SD or associated MRI findings
  - Restrictive case definition: ≥3 SD below normal
  - Average gestational age at diagnosis: 28 weeks

- MRI findings in Zika-related microcephaly*
  - Cerebral calcifications (cortex-WM junction)
  - Dilated ventricles
  - Flattened gyri (smooth brain surface)
  - Cerebellar or brainstem hypoplasia
  - Absent corpus callosum

\[ HC = (\text{BPD} + \text{OFD}) \pi/2 \]

*Aragao et al. BMJ 2016; 353: i1901
Computed Tomography in Eight Infants with Congenital Microcephaly.

- Linear Ca++
- Enlarged ventricles (ventriculomegally)
- Global cortical hypogyration
- Absent corpus callosum
- Cerebellar hypoplasia
- Punctate Ca++
- Ischemic stroke in region of the L MCA

"As the horrified doctors compared notes, one thing stood out: many of the mothers mentioned that, months earlier, they had had the doença misteriosa—Portuguese for the ‘mystery disease’—that had first appeared nine months earlier in Recife, Salvador, Natal, and Fortaleza, the cities of Brazil’s arid northeast.

“Back then, the disease had not seemed a big deal. Everyone appeared to have the symptoms: an itchy pink rash; fever and chills; bloodshot eyes; headaches and joint pains.”

Zika Virus Acute Illness

- Usually mild acute illness
- Incubation period prob. 4-7 d, max 14 d (?)
- lasts up to 7 days
- Illness characteristics
  - Itchy maculopapular rash (90%)
  - Fever—low grade and brief (65%)
  - Arthralgias or arthritis (65%)
  - Non-purulent conjunctivitis, keratitis and uveitis (55%)
  - Headache (45%)
  - Upper and lower extremity edema (19%)
  - Vomiting (10%)
  - Aphthous ulcers
  - Testicular pain and hematospermia (rare)
- But 80% have no symptoms.

Duffy et al. NEJM 2009; 360: 2536
Zika Skin Rash
Percentage of Symptomatic Zika Cases (A) Incubation Period, (B) Time to Viral Clearance, and (C) Time to IgM Detection
Based on 25 fully documented case reports

**Incubation period (days, N=25)**

<table>
<thead>
<tr>
<th>Percentile</th>
<th>5%</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>95%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>3.2</td>
<td>4.6</td>
<td>5.9</td>
<td>7.6</td>
<td>11.2</td>
<td>46</td>
</tr>
</tbody>
</table>

**Mean time to viral clearance (PCR neg, N=22)**

<table>
<thead>
<tr>
<th>Percentile</th>
<th>5%</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>2.4</td>
<td>5.8</td>
<td>9.9</td>
<td>12.7</td>
<td>18.9</td>
</tr>
</tbody>
</table>

**Mean time to seroconversion (IgM, N=22)**

<table>
<thead>
<tr>
<th>Percentile</th>
<th>5%</th>
<th>25%</th>
<th>50%</th>
<th>75%</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>4.4</td>
<td>7.1</td>
<td>9.1</td>
<td>10.1</td>
<td>13.7</td>
</tr>
</tbody>
</table>

Lessler et al. *Bull WHO* E-pub: 1 Apr 2016
Initial Epidemic Investigation of Microcephaly in Brazil

Brazil Ministry of Health, CDC, PAHO

(Restrictive case definition: head size $\geq 3$ SD below normal)

Rash illness began

Pernambuco State
(capitol: Recife)

1st trimester
(38-26 weeks earlier)


MMWR March 11, 2016 65(9): 242-247

Brasil et al. PLoS Negl Trop Dis 2016 (April); 10(4): e0004636
<table>
<thead>
<tr>
<th>States with lab-confirmed Zika</th>
<th>Microcephaly rate (per 10,000 births)</th>
<th>RR = 4.7</th>
<th>P &lt; 0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (15)</td>
<td>2.80 (1.86-4.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (4)</td>
<td>0.60 (0.22-1.31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Zika Virus

- A member of the *Flavividae* family along with dengue, yellow fever, Japanese encephalitis & West Nile.
- Named for the Ziika Forest in Uganda, where identified in 1947.
- Transmitted by *Aedes* mosquitoes: *mosquito* → *human* → *mosquito* cycle.
- Mostly by *Aedes aegypti* (the yellow fever mosquito), but maybe by *Aedes albopictus* (Asian Tiger mosquito).
- Also transmitted vertically, sexually and most likely by transfusion.
- A ssRNA virus, prone to mutating

On highway between Kampala and Entebbe airport
# Major Arthropod-Borne Viruses

<table>
<thead>
<tr>
<th>Flaviviridae</th>
<th>Togaviridae</th>
<th>Bunyaviridae</th>
<th>Reoviridae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow fever*</td>
<td>Chikungunya*</td>
<td>La Crosse*</td>
<td>Colorado tick fever¶</td>
</tr>
<tr>
<td>Dengue*</td>
<td>Western equine*</td>
<td>California*</td>
<td></td>
</tr>
<tr>
<td>Zika*</td>
<td>Eastern equine¶</td>
<td>Jamestown Canyon*†</td>
<td>Bluetongue¶</td>
</tr>
<tr>
<td>St. Louis†</td>
<td></td>
<td>Heartland virus¶</td>
<td></td>
</tr>
<tr>
<td>West Nile†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powassan¶</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Active in U.S.        |                        |                                     |                                   |
| Japanese†             | Venezuelan equine*†     | Crimean-Congo hemorrhagic fever¶    | Equine Encephalosis virus¶        |
| Murray Valley†        | Ross River*†           |                                    | Banna†                            |
| Spondweni*            | O’nyong’nyong¶         | Bunyamwera*                         | African Horse sickness¶           |
| Tick-borne encephalitis¶ |                      | Rift Valley fever†                  |                                   |
|                       |                        | Toscana¶                            |                                   |

| Not in U.S.           |                        |                                     |                                   |
|                       |                        |                                     |                                   |

| Main vector:          |                        |                                     |                                   |
| *Aedes                | †Culex                 | ¶Other (mosquitoes, ticks, sand flies, midges) |
Zika Virus Transmission Cycles

Petersen LR et al. NEJM  April 14, 2016 (advance online)
Zika Virus Transmission Cycles

Petersen LR et al. *NEJM* April 14, 2016 (advance online)
**Aedes vs Culex Mosquitoes**

**Aedes**
- Spreads yellow fever, dengue, chikungunya, Zika
- Mosquito → **human** → mosquito
- Sipper – must bite 3 or 4 times
- Human loving – lives near homes
- Day biter

**Culex**
- Spreads West Nile
- Mosquito → **bird** → mosquito → human
- Gulper – needs to bite only once
- Canopy dweller – lives in tree tops
- Dawn-to-dusk biter
Aedes aegypti vs Aedes albopictus

Yellow fever mosquito
Imported with slave trade in 1600s
Silvery lyre-shaped pattern
Urban: breeds/lives near humans
Loves man-made containers
Slips indoors, hides in closets
Sneaky biter (primarily humans)
Highly efficient transmitter

Asian tiger mosquito
Imported from Asia in used tires in 1980s
Single silvery stripe
Sylvan: breeds/lives in vegetation
Prefers tree holes and vegetation
Mostly outdoor, garden mosquito
Aggressive biter (animals & humans)
Inefficient transmitter (important??)
Zika Spreads Explosively in Favelas with Plastic Trash and Old Tires Plus Windows without Screens
Traditional Boundaries of Year-Round Survival of *Aedes aegypti* – a tropical pest
Traditional Geographical Distributions of *Aedes aegypti* and *Aedes albopictus*

Approximate distribution of *Aedes aegypti* in the United States*

Approximate distribution of *Aedes albopictus* in the United States*

*Maps were developed using currently available information. Mosquito populations may be detected in areas not shaded on this map, and may not be consistently found in all shaded areas.

http://www.cdc.gov
New Extended (2016) Geographical Distributions of *Aedes aegypti* and *Aedes albopictus*

The strongest determinant of distribution is temperature, followed by rainfall.

[http://www.cdc.gov](http://www.cdc.gov)
Climate change appears to be moving the jet streams poleward, possibly expanding the tropical zone and moving the limits of *Aedes* mosquitoes northward.

Also Hadley cell expansion

[Map of the United States showing approximate distribution of *Aedes aegypti* in the United States]

[Maps showing global climate change impacts and jet stream changes]
Approximate Ranges of *A. aegypti* and *A. albopictus* in the United States (as of March 2016).
Before 2007 only 14 cases of human disease had been reported.
In April and May 2007, physicians on Yap Island noted an outbreak of illness:
- Fever, rash, conjunctivitis, arthralgia and arthritis.

Sent acute and convalescent sera to CDC Arbovirus Reference Lab in Ft. Collins, CO

Zika confirmed by PCR, IgM, PRNT and dengue PRNT

*PRNT = Plaque reduction neutralization test

Duffy et al. *NEJM* 2009: 360: 2536
The 2007 Zika Epidemic on Yap Island

- CDC’s EIS conducted a sero-survey of 200 (16%) randomly selected households. 173 of 200 participated. Included 852 residents, and 557 provided a blood sample.

- Population estimates:
  - 73% had anti-ZIKV IgM.
  - 18% of the infected had a clinical illness.
  - The attack rate of clinical illness increased with age (like WNV), but the rate of serological infection did not.

- Later look-back found no microcephaly
  - In small population (7,391) would expect only 3 excess cases.

Duffy et al. *NEJM* 2009; 360: 2536
The 2007 Zika Epidemic on Yap
The Mosquito Investigation

- 148 of 170 (87%) surveyed houses had water containers infested with mosquito larvae.
- 587 of 1366 (43%) water-holding containers had mosquito larvae.
- 9 mosquito species were identified, but 83% of the infested containers had *Aedes hensilli*. No other species inhabited more than 3%.

73% infected under conditions like this.

Water-holding containers around a typical Yap dwelling. Water tanks hold thousands of larvae.

Duffy et al. *NEJM* 2009; 360: 2536
Ledermann et al. *PLOS Negl Trop Dis* 2014; 8: e3188.
Zika Epidemic in Tahiti/French Polynesia

- Population: 270,000
- Annual births: 4,182
- Mild rash illness, Oct 2013 to April 2014
- Serologic surveys: 66% of residents infected
Guillain-Barre Syndrome after Zika
Tahiti/French Polynesia, 2013-2014

- 42 cases of GBS
- 37 (88%) had prior illness typical of Zika
- Compared with pre-Zika incidence of 5/year, 42 in 7 mo. is a 21-fold increase.
- Typical GBS findings
  - Ascending paralysis, abn NCS
  - 16 in ICU, 12 on ventilator
    - None died
    - 24 improved by 3 mo.

Cao-Lormeau et al. Lancet 2016 (April); 387: 1532
Look-Back Study of Microcephaly
Tahiti/French Polynesia
2013-2014

- 8 microcephaly cases = 95/10,000 births
- Baseline microcephaly rate = 2/10,000 births
- RI* = 53 (CI 7-1061)
- Compared to RI in 4 N.E. Brazilian states of 42 to 77.
- Statistical modeling showed best fit of cases to 1st trimester (P = 0.0007).

*RI = relative increase over baseline

“Molecular clock” analysis suggests that Zika spread to Brazil from Tahiti in mid-2013.

Rodriguez Faria et al. Science 2016 (April); 352: 345.
Guillain-Barre Syndrome after Zika in the Americas

<table>
<thead>
<tr>
<th>Location</th>
<th>Cases</th>
<th>RI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahia State, Brazil</td>
<td>155</td>
<td>2.7</td>
</tr>
<tr>
<td>Colombia</td>
<td>320</td>
<td>3.1</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>45</td>
<td>2.5</td>
</tr>
<tr>
<td>El Salvador</td>
<td>184</td>
<td>2.0</td>
</tr>
<tr>
<td>Honduras</td>
<td>71</td>
<td>2.6</td>
</tr>
<tr>
<td>Suriname</td>
<td>15</td>
<td>5.0</td>
</tr>
<tr>
<td>Venezuela</td>
<td>684</td>
<td>9.8</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>30</td>
<td>--</td>
</tr>
<tr>
<td>U.S.</td>
<td>7</td>
<td>--</td>
</tr>
</tbody>
</table>

RI = Relative increase over baseline

### Duration of Zika Epidemics Seem Finite

<table>
<thead>
<tr>
<th>Location</th>
<th>Duration (wks)</th>
<th>Months</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yap State, Micronesia</td>
<td>16</td>
<td>Apr – Jul</td>
<td>2007</td>
</tr>
<tr>
<td>French Polynesia</td>
<td>28</td>
<td>Oct – Apr</td>
<td>2013</td>
</tr>
<tr>
<td>Bahia State, Brazil</td>
<td>52</td>
<td>Dec – Jan</td>
<td>2014-2016</td>
</tr>
<tr>
<td>Colombia</td>
<td>22</td>
<td>Oct – Apr(?)</td>
<td>2015-2016</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>13</td>
<td>Jan – May(?)</td>
<td>2015</td>
</tr>
<tr>
<td>El Salvador</td>
<td>28</td>
<td>Oct – Apr(?)</td>
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<tr>
<td>Honduras</td>
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<tr>
<td>Suriname</td>
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<td>2015-2016</td>
</tr>
<tr>
<td>Venezuela</td>
<td>17</td>
<td>Jan – May(?)</td>
<td>2015</td>
</tr>
</tbody>
</table>

Evidence That Zika Causes Microcephaly

- **Epidemiology**
  - The appearance of ZIKV infection was followed by a >20-fold increase in rates of microcephaly in French Polynesia, Brazil and Latin America.
  - Consistent association with 1st trimester Zika exposure (like Rubella)

- **Viral detection by Brazilian Ministry of Health**
  - ZIKV isolated from CSF of miscarried microcephalic fetuses.
  - ZIKV from brain, CSF, heart, lungs, liver, spleen, kidney of an infant dying after birth
  - Zika IgM in CSF of 12 children born with microcephaly. Testing negative for TORCH (Toxoplasma, Other agents, Rubella, CMV, Herpes) and dengue and chikungunya.
  - ZIKV isolated from amniotic fluid of 2 pregnant mothers with history of Zika infection and microcephalic fetus by ultrasound.
  - ZIKV found by PCR in placental cells from an 8-week miscarriage

- **U.S. confirmation**
  - CDC confirmed ZIKV in brain of 4 microcephalic infants and placentas
  - Mlakar et al. found PCR+ ZIKV RNA in brain and placenta of 29 week miscarriage

De Oliveira et al. *J Pediatria* (Brazil) 2016 (July); 92(2): 103
How Does Zika Virus Affect Fetal Brains?

- Tang et al. infected cell cultures of various neuronal precursor cells with Zika (Uganda 1947) virus.
  - Zika infects **neural progenitor cells** (hNPC) with high efficiency compared with human **embryonic stem cells** (hESC), human induced **pluripotent stem cells** (hiPSC) and immature **neurons**.
  - Causing cell death and dysregulation of the cell-cycle progression.

- Nowakowski et al. surveyed expression of candidate receptors for Zika entry.
  - Identified increased expression of **Axl** (Tam) receptors in Zika infection as possible determinant of cell tropism.

Western Zika Virus in Human Fetal Neural Progenitors Persists Long Term with Partial Cytopathic and Limited Immunogenic Effects

Natasha W. Hanners,1,2 Jennifer L. Eitson,1 Noriyo Usui,3 R. Blake Richardson,1 Eric M. Wexler,4 Genevieve Konopka,3 and John W. Schoggins1,*

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2Division of Infectious Disease, Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA
3Department of Neuroscience, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA
4Department of Psychiatry, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA 90095, USA
*Correspondence: john.schoggins@utsouthwestern.edu
http://dx.doi.org/10.1016/j.celrep.2016.05.075

SUMMARY

The recent Zika virus (ZIKV) outbreak in the Western hemisphere is associated with severe pathology in newborns, including microcephaly and brain damage. The mechanisms underlying these outcomes are under intense investigation. Here, we show that a 2015 ZIKV isolate replicates in multiple cell types, including cell cultures and animal models have begun to reveal mechanisms of ZIKV-induced pathology. Recent studies have reported that ZIKV infects stem-cell-derived human neural progenitors (hNPs), neurospheres, and organoids with growth-attenuating effects (Cugola et al., 2016; Dang et al., 2016; Garcez et al., 2016; Qian et al., 2016; Tang et al., 2016). African and Asian ZIKV infections do not infect full-term primary human placental trophoblasts due to type III interferon-mediated viral restriction.
Modes of Transmission of Zika Virus

1. Mosquito bite
2. Vertical transmission from mother to fetus
3. Subcutaneous injection of infected monkey brain (1)
4. Laboratory acquisition (2 reports)
5. Transfusion acquisition
   
   3% of donated blood Zika-positive in French Polynesia.
   Cases of transmission in Brazil being investigated.

6. Breast milk contains virus, but no cases.
7. Sexual transmission

Sexual Transmission of Zika Virus

• 2011 - An American scientist returned from Senegal, Africa, to northern CO.
  – Had vaginal intercourse on day of return; 9 days later, he developed Zika illness including perineal pain and bloody semen; 4 days after his onset wife became ill.
  – Zika was later established serologically by HAI and PRNT confirmation.

• 11 papers reporting sexual transmission
  – Male to female except one case between gay men and one suspected female to male.
  – Where known, intercourse occurred during illness or shortly before.
  – 5 studies confirmed Zika in seminal fluid of the sexual donor.
  – Zika RNA load was higher in semen than serum.
  – In 2 cases symptoms included testicular pain and hematospermia.
  – 3 semen samples showed replicating virus, indicating infectivity.
  – Sexual transmission is mostly from symptomatic men; one exception reported.
  – In 1 case Zika RNA was found in semen 62 days after illness onset.
  – 2 men found to have ZIKV RNA in semen 6 months after exposure, but not grown.

Foy et al. Emerg Infect Dis 2011; 17: 880
Grischott et al. ScienceDirect 2016 (July); 41: 313
Sexual Transmission in an Asymptomatic Couple Seeking Evaluation in a French IVF Clinic

Timelines showing key dates of possible Zika exposure and results of PCR testing of semen, urine and serum, France, March-April 2016.

She most likely got infected between D21 and D36. Both remained asymptomatic.

Fréour et al.  www.eurosurveillance.org  2016 (9 June); 21 (23): pii=30254
Suspected Sexual Transmission from Woman to Man

- Nonpregnant woman in her 20s had unprotected vaginal sex on the day (day 0) she returned from travel to an area of ongoing Zika transmission.
- The next day (day 1) she developed symptoms of Zika illness. PCR was positive for ZIKV in blood and urine.
- 7 days after intercourse (day 6), the male partner in his 20s developed typical Zika illness.
- On day 9 PCR was positive in urine but negative in blood.
- The man had not been outside the U.S., confirmed only vaginal sex, no penile lesions, no bleeding during intercourse, and no other recent sexual partners or mosquito bites.

Literature

- ZIKV found by PCR in a woman’s cervical mucous, genital swab and endocervical swab 3 days after onset of Zika illness.
- ZIKV found in vaginal secretions of 3 nonpregnant female primates up to 7 days after inoculation.

Davidson et al. MMWR 2016 (July 15); 65 (Early Release): 716
Complications of Zika Virus Illness

- **Complications**
  - Babies of mothers infected in 1\textsuperscript{st} & 2\textsuperscript{nd} trimesters (est. risk 1%, 29% and 8%)
    - Fetal death with miscarriage, stillbirth
    - Microcephaly, seizures, mental retardation
    - Chorioretinal atrophy, optic nerve hypoplasia, and blindness
    - Concern for more subtle brain damage in infants infected later in pregnancy, not after birth (ADHD, bipolar, schizophrenia)?
  - In adults
    - Guillain-Barré syndrome
    - Immune thrombocytic purpura (ITP)
    - Possible acute disseminated encephalomyelitis in adults

Will not be known for at least 6 years
Immune Thrombocytic Purpura (ITP) after Zika

- 11 cases reported in 4 papers
- Occurred in French Polynesia (4), Suriname (1), Columbia (3), Puerto Rico (2)
- 4 of 11 died of hemorrhagic complications
  - 1\textsuperscript{st} Zika-related death in Puerto Rico was due to brain hemorrhage from ITP

Ioos et al. *Med Mal Infect* 2014; 44: 302
Sarmiento-Ospina et al. *Lancet Inf Dis* 2016
Sharp et al. *Clin Infect Dis* (online Aug. 4, 2016)
Acute Disseminated Encephalomyelitis (ADEM) after Zika

• An acute multiple sclerosis-like illness, closely following typical Zika illness.
• 2 patients reported in Pernambuco State, Brazil.

No Evidence of Severe Zika Infection in Immunosuppressed, including HIV

- 2 case reports of fatal Zika infection in Colombia
  - An adult with lymphoblastic leukemia
  - A child with myeloid leukemia
- No evidence of more severe disease or prolonged viremia or shedding
- Likewise little evidence in dengue

Management of Zika Infection

• No treatment for the disease or complications except supportive care

• Avoid getting infected in the first place
  – Use EPA-registered insect repellant containing DEET.
  – Wear protected clothing (long sleeves, long pants and socks).
  – Stay in places with air conditioning or window and door screens.
  – Or sleep under a mosquito net.

• Try to prevent people with acute illness from spreading it further
  – During the acute illness avoid being bitten by *Aedes* mosquitoes.
  – Travelers to endemic regions wear DEET during trip and 3 weeks after return
  – Women avoid pregnancy for 2 months after illness or return from trip
  – Men and women abstain or practice protected sex for 6 months after acute illness
  – Do not donate blood for 4 months after acute illness
Counseling Patients on Pregnancy Planning
Updated October 3, 2016

- Patients diagnosed with acute Zika infection (rash, fever, joint pain, etc.)
  - Women – wait at least 2 months from onset of symptoms to conceive.
  - Men – wait at least 6 months from onset of symptoms for unprotected sex.

- Patients asymptomatic but possibly exposed in travel or sex
  - Women - wait at least 2 months from possible exposure to conceive.
  - Men – wait at least 6 months from onset of symptoms for unprotected sex.

- Patients asymptomatic but living in areas with Zika transmission
  - “Talk with [your] patients about pregnancy plans during a Zika outbreak, the potential risks of Zika, and how they can prevent Zika infection . . . and strategies to prevent unwanted pregnancy.” (CDC)
  - Time pregnancy to avoid the Zika epidemic season (warm season). (PAHO)
Diagnosis of Zika Infection

– **During the acute illness**, test for the viral RNA by PCR.
  - Blood is 51% sensitive (best in first 5 days of illness)
  - Saliva is 81% sensitive
  - **Urine is 92% sensitive**
    - Urine and saliva tests remain positive longer than blood.

– **After end of acute illness**, test blood for IgM antibodies.
  - Cross-reactivity with dengue infection or Japanese encephalitis vaccine (international travelers), confirm positives by the **plaque reduction neutralization test (PRNT)**
  - Presently testing is done on blood and urine.

Initial CDC study of 53 Zika patients
Who Should Get Zika Testing?

- Person with >1 Zika symptom within 4 weeks of:
  - Travel to an area with Zika transmission (see cdc.gov/zika/geo) OR
  - Unprotected sex with a partner who spent time in such an area.
- Pregnant woman*
  - Travel to Zika area during pregnancy or 8 weeks before conception
  - Unprotected sex with a partner who spent time in such an area
- Patient with Guillain-Barre syndrome with exposure history
- Infant born to a woman with positive/inconclusive Zika test
- Infant with microcephaly etc. born to woman with exposure history
- Patient with compatible illness and alternate mode of acquisition (e.g., transfusion, transplant)

*Women with exposure wanting to get pregnant are not being tested for now. (Supposed to avoid pregnancy for 2 months and have protected sex for 6 months).
Sources of Testing for Zika

- Dallas County Health and Human Services (DCHHS) provides free testing of blood and urine for patients meeting the criteria.
  - PCR
  - IgM and IgG
  - Special blood and urine specimen preparation provided by:
    Outpatient labs of Baylor, Medical City and Methodist
    (Physician completes form from DCHHS website and Rx for Zika testing)

- Commercial testing of blood and urine
  - Viracor, LabCorps and Quest
    - PCR ($165)
    - IgM and IgG ($700)
      - CDC or DCHHS labs run PRNT on all IgM positives

http://www.dallascounty.org/department/hhs/zika.html
Diagnosis in the Developing Fetus

• Diagnosis
  – Microcephaly can be detected in utero by ultrasound but generally not until late second trimester (22-24 weeks).
    • When interruption of pregnancy is illegal in Texas.
    • Not highly sensitive either.
    • Hydrocephalus can mask microcephaly during pregnancy.
  – Other severe brain damage may be detected earlier by ultrasound, CT or MRI
  – Infection of the placenta or fetus may prolong PCR detection of Zika RNA in maternal blood.*
  – (Amniotic fluid can be tested for Zika by PCR, but no longer recommended.)

*Driggers et al. *NEJM* 2016 (June); 374: 2142.
How To Contain Autochthonous Spread from Importations? Travel Volume to the U.S. from Zika Transmission Zones

Zika Spreads Explosively in Favelas with Plastic Trash and Old Tires Plus Windows without Screens

- In the U.S., ubiquitous AC, screens, and trash removal greatly retard spread.
- Greatest vulnerability in Florida & Gulf Coast
CDC Strategy for Eradicating a Zika Focus

- Surveillance for autochthonous cases (formed where found)
- Issue a **Zika Alert** for a square mile around the case (3-5 times further than an *Aedes* mosquito ranges).
- Travel warning and resident education (avoid bites)
- Intense mosquito control
  - Mosquito surveillance
  - Door-to-door inspection to eliminate water sources
  - Ground spraying
  - Aerial spraying???
- Continue until no new cases for 3 mosquito incubation periods (7) (3x14=42 days)

What Can We Do To Protect Ourselves?

• Women living in areas of ongoing Zika transmission
  – Avoid pregnancy until epidemic is over.
  – Time pregnancy for 1st trimester to avoid high-transmission season (summer).

  CDC, PAHO and WHO are avoiding recommendations.
What Can We Do To Protect Ourselves?

- Eliminate trash, tires and other standing water.

- Use **Mosquito Dunks** for unavoidable standing water (e.g., bird baths, French drains, AC towers, flower pots, baby pools, neglected swimming pools).
  
  - Contains *Bacillus thuringiensis israeliensis* (BTI)
  
  - Secretes 4 proteins toxic to mosquito larvae.
  
  - One dunk kills mosquito larvae in 100 sq ft of water
  
  - Lasts 30 days
  
  - Toxic only to mosquito larvae, no resistance develops.

What Can We Do To Protect Ourselves?

- Install and maintain mosquito traps around yard.

*Trap-N-Kill* – developed by U.S. Army (requires maintenance)

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What Can We Do To Protect Ourselves?

• Travel
  – Safe to travel to areas with no *Aedes aegypti*, no Zika epidemic, and anywhere above 6,500 ft. elevation
  – Anywhere if not pregnant or spouse of pregnant woman
  – Exposed, avoid pregnancy 2 mo., protected sex 6 mo.
What Can We Do To Protect Ourselves?

• Future elimination of *Aedes aegypti*
  – Genetically modified mosquitoes
  – “Perifocal” insecticide treatment
Genetically Modified Mosquitoes to Suppress *Aedes aegypti*

- **Past approach:** Irradiated sterile male mosquitoes eradicated screw worm from the southern US, Mexico and Belize in 1950-1985
- **New Approach:** GM male mosquitoes are produced by gene editing
  - Males released into environment fertilize females with dud sperm; offspring die soon after hatching.
- 2009 experimental trials in Cayman Islands, Panama and Brazil reduced *Aedes aegypti* populations by 99%.
- GM male mosquitoes do not bite, and die soon after fertilizing females, so have no effect on other species.
- Field trials in Florida and Brazil approved but pending public comment.
- Purdue University poll: 78% of Americans support GM mosquitoes.
- A focal urban solution, not practical for continental eradication.

“Perifocal” Insecticide Treatment

- Key characteristic
  - Aedes is a “skip ovipositor”
  - Lays a small number of eggs in many sites

- “Perifocal” Treatment
  - Field staff find infested containers and spray them plus surrounding meter with DDT or newer persistent insecticide (deltamethrin in polymer).
  - As the female Aedes goes about depositing eggs, she has a high probability of contacting the residual insecticide.
  - Eradicated Aedes aegypti from South and Central America by 1962

Reiter. *PLOS Negl Trop Dis.* 2016 (June): 1-4
Ultimate Solution

Continental herd immunity with a polyvalent arboviral vaccine that does not cause GBS:

Zika
Dengue
Chikungunya

(Yellow fever, Japanese B and Rift Valley viruses)

Years away
How will Zika Virus Affect Us This Year?

• Conditions ripe all along the Gulf Coast, Texas to Florida
  – Poverty
  – Uncontrolled trash dumping
  – No air conditioning and poorly fitting, or no, window screens
  – Abundant *Aedes* aegypti* mosquitoes (history of Dengue &
    Chikungunya outbreaks)
  – Hot weather, periodic rains
• General forecast
  – Small outbreaks in Florida and the Gulf Coast this summer with a few
    cases of microcephaly this winter but no GB syndrome
  – Possible year round persistence in the Florida Keys.
  – Probably no spread in DFW area.
Ob/Gyn Grand Rounds
October 27, 2016

Zika
The Arbovirus *du Jour*

Robert W. Haley, M.D.
Division of Epidemiology, Department of Internal Medicine
University of Texas Southwestern Medical Center at Dallas
How Did Zika Spread to Brazil by 2015?

- First theory: travel from Easter Island
  - But air travel to Easter Island is primarily to Chile (no cases).
- Second theory: World Cup in June-July 2014
  - Recife, Natal and Salvador, N.E. Brazil, but no S Pac teams
- Third theory: Va’a Sprints in Rio in August 2014
  - Outrigger canoe teams from Polynesia, Cook Is., Easter Is.
“Molecular Clock” Analysis

• Based on the constant rate of mutation of Zika’s ssRNA, found that the Brazilian clade shared commonality with the French Polynesian virus.

• The predominant Brazilian clade (B) arose around December 2013.

• The common ancestor (clade A) of the Brazilian and French Polynesian clades arose around May-June 2013.

• This coincided with increasing travel from Zika-active countries related to the FIFA Confederations Cup Soccer Tournament in Brazil in June 2013.

• It included a soccer team from Tahiti.

Rodriguez Faria et al. Science 2016 (April); 352: 345.
Coincidence of GBS with Zika, not Dengue, 2012-2015, Bahia State, Brazil

dos Santos et al. *NEJM* - Advance publication, Sept 2, 2016 (Online Appendix).
Incidence per 100,000 population of Zika and GBS by Age and Sex, Bahia State and El Salvador

$I_{Zika}$ did not increase with age.

$I_{GBS}$ increased with age.

dos Santos et al. *NEJM* - Advance publication, Sept 2, 2016 (Online Appendix).
Table 1. Summary of number of microcephaly cases per 1 000 live births reported annually in the fourteen Brazilian states that investigate microcephaly; 2010–2014; 2015 data as of 28 November

<table>
<thead>
<tr>
<th>State</th>
<th>2009–2013*</th>
<th>2010–2014b</th>
<th>2015, as of 28 November</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yearly average number of live births (LB)</td>
<td>Yearly average number of microcephaly cases</td>
<td>Number of microcephaly per 1 000 LB</td>
</tr>
<tr>
<td>Pernambuco</td>
<td>140 264</td>
<td>8.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Paraíba</td>
<td>47 998</td>
<td>4.2</td>
<td>0.09</td>
</tr>
<tr>
<td>Rio Grande do Norte</td>
<td>47 698</td>
<td>1.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Sergipe</td>
<td>34 477</td>
<td>1.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Alagoas</td>
<td>44 331</td>
<td>3.4</td>
<td>0.08</td>
</tr>
<tr>
<td>Bahia</td>
<td>211 660</td>
<td>10.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Piauí</td>
<td>48 989</td>
<td>3</td>
<td>0.06</td>
</tr>
<tr>
<td>Ceará</td>
<td>128 112</td>
<td>6.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Rio de Janeiro</td>
<td>219 876</td>
<td>12.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Tocantins</td>
<td>24 586</td>
<td>1.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Maranhão</td>
<td>119 069</td>
<td>3</td>
<td>0.03</td>
</tr>
<tr>
<td>Goiás</td>
<td>90 559</td>
<td>3</td>
<td>0.03</td>
</tr>
<tr>
<td>Distrito Federal</td>
<td>43 935</td>
<td>2.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Mato Grosso do Sul</td>
<td>41 421</td>
<td>0.8</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1 242 975</strong></td>
<td><strong>62.8</strong></td>
<td><strong>0.05</strong></td>
</tr>
</tbody>
</table>

Adapted from [48]

* The denominator used for this calculation is the average number of live births per year (2009–2013)

Data source: a) [50], b) [48]