Emerging Arboviruses in the Western Hemisphere

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Fraser Health
Overview

• What are arboviruses?
• Which ones occur in the Western Hemisphere?
• Zika Virus
  • Emergence and Epidemiology
  • Virology
  • Clinical features
Arboviruses

- Transmitted by bite of hematophagous arthropod
  - mosquitoes, ticks, midges, and sandflies
- After ingestion of a blood meal from an infected host, viruses multiply within tissues (salivary glands) of the arthropod to a high titre
- Passed on to humans or other vertebrates during insect biting
Arboviruses

• 4 families of virus: Flaviviridae, Bunyaviridae, Reoviridae, Togaviridae
• 80 different viruses causing human infection
• Some infect humans only occasionally or cause only mild illness, whereas others are of great medical importance and can cause large epidemics and mortality/morbidity
Arboviruses

• Most are zoonoses (animal reservoirs, birds and mammals); man usually an accidental host.
  • exception: dengue virus
• Vertebrate Hosts: mammals (primates, rodents, marsupials, bats) and birds.
• Reservoir Hosts: become infected by the virus and produce high-titre viremias enabling virus transmission to occur; generally not susceptible to disease.
  • May have more than one reservoir host species
• Disseminating Hosts: may move virus from an area of active transmission to another location.
  • birds
  • humans
  • arthropod vectors may also disseminate disease if they are carried on air, marine, rail or road transport.
    • Most likely mechanism for introduction of WNV into the USA in 1999
Dengue

- Originated in Africa-spread to New World in 1600
- Now in 28 Western countries
- Most common arbovirus worldwide

- Breakbone fever
- Hemorrhagic fever
- Shock
Yellow fever

- Fulminant Liver failure
- Viral Hemorrhagic Fever
West Nile Virus

- First cases in Western Hemisphere-New York 1999
- 80% infected with WNV are asymptomatic
- < 1% develop a serious, sometimes fatal meningocencephalitis
Chikungunya = “to walk bent over” Tanzanian language (joint pains)
Feb 1, 2016 Public Health Emergency

WHO declares Zika a Public Health Emergency of International Concern, PHEIC
Zika virus

- 50nm, enveloped, RNA
- Flavivirus
- Closely related to dengue, yellow fever, Japanese encephalitis, and West Nile virus
- 2 lineages: African and Asian lineage
- Virus spreading in Americas is most closely related to the Asian strain that circulated in French Polynesia during the 2013–2014 outbreak
Zika Virus

• Initially isolated from a rhesus monkey in Zika forest of Uganda in 1947
• 1954: first 3 human cases in Eastern Nigeria
• Limited to sporadic cases or small clusters until 2007
• 2007 outbreak in Yap Island of Micronesia
  • rash, conjunctivitis, and arthralgia
  • 5000 infections (total population of 6700)
  • No severe disease, hospitalizations or deaths
• 2014 outbreak in French Polynesia
  • 30,000 infections
  • Guillain-Barre reported
  • 17 cases of neurologic malformations among fetuses (reported retrospectively in 2015)
• Outbreaks in New Caledonia (2014), Easter Island (2014), Cook Islands (2014), Samoa (2015), and American Samoa (2016)
• Endemic in Africa and in South Asia (India, Indonesia, Thailand, Vietnam, and Malaysia)
Zika emerges in Western Hemisphere in 2015

Brazil May, 2015

• Outbreak (1.3 million cases) of locally acquired infections
• Increase in the number of infants born with microcephaly: 8301 cases in Brazil (2 July, 2016)
  • 2000 confirmed cases of congenital zika in Latin America (mostly Brazil) (PAHO, Sep, 2016)

• Possibly introduced in 2014 during World Canoe Championship held in Rio de Janeiro
### Zika cases in the Americas 2015-2016

**PAHO, WHO (22 Sep 2016)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Autochthonous</th>
<th>Imported</th>
<th>Incidence</th>
<th>Deaths</th>
<th>Confirmed congenital</th>
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<tbody>
<tr>
<td></td>
<td>Suspected</td>
<td>Confirmed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>0</td>
<td>0</td>
<td>282</td>
<td>0</td>
<td>1</td>
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<tr>
<td>USA</td>
<td>0</td>
<td>43</td>
<td>3314</td>
<td>0.01</td>
<td>25</td>
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<tr>
<td>Brazil</td>
<td>196,976</td>
<td>78,421</td>
<td>0</td>
<td>131</td>
<td>1949</td>
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<tr>
<td>French Guiana</td>
<td>9710</td>
<td>483</td>
<td>10</td>
<td>3693</td>
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<tr>
<td>Guadeloupe</td>
<td>29,850</td>
<td>379</td>
<td>0</td>
<td>6418</td>
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<tr>
<td>Martinique</td>
<td>36,100</td>
<td>12</td>
<td>0</td>
<td>9119</td>
<td>12</td>
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<tr>
<td>Jamaica</td>
<td>4,946</td>
<td>83</td>
<td>0</td>
<td>179</td>
<td>0</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>500,557</strong></td>
<td><strong>120,785</strong></td>
<td><strong>3846</strong></td>
<td><strong>62</strong></td>
<td><strong>2066</strong></td>
</tr>
</tbody>
</table>

- 47 countries in Americas
- 3 counties in Florida: Miami-Dade, Palm Beach, Pinellas
- GBS: 12 countries
In comparison to Dengue and CHIKV

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Dengue</td>
<td>1,398,876</td>
<td>2,712,632</td>
<td>1,515,824</td>
<td>2,888,330</td>
<td>1,146,590</td>
<td>9,662,252</td>
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<tr>
<td>Chikungunya</td>
<td>–¹</td>
<td>111</td>
<td>1,147,515</td>
<td>726,478</td>
<td>114,199</td>
<td>1,988,303</td>
</tr>
</tbody>
</table>

Table 1  Comparison of the number of cases of dengue, chikungunya and Zika in the region of the Americas, 2012–2016 (as of May 20, 2016). Source: PAHO.
Transmission of Zika Virus to Humans

- Mosquito bite
- Maternal-fetal
- Sexual transmission from infected males
- Laboratory exposure
- Blood transfusion
- Organ transplant
Sylvatic Cycle

Urban Cycle
Aedes mosquito

**Aedes aegypti**
- Urban
- main type of mosquito spreading Zika, dengue, chikungunya,
- anthropophilic (prefer to feed on people); more likely to spread Zika
- rests in sheltered dark areas inside houses
- peak feeding time is midmorning and late afternoon
- female feeds twice during a single gonotrophic cycle
- average life span 8-14 days

**Aedes albopictus**
- Rural
- Asian Tiger mosquito
- can live in a broader temperature range and cooler temperatures than A. aegypti.
- feeds on animals and humans
Aedes aegypti

Aedes albopictus
Aedes Distribution in USA
Female mosquito can transmit Zika to its offspring
Culex mosquitoes do not transmit Zika

- most widespread and abundant mosquito species in the United States
- resistant to Zika virus infection, even when exposed to high levels of the virus in bloodmeals
Typical Zika Symptoms

- Fever
- Rash, often pruritic, maculopapular
- Conjunctival hyperemia
- Palate petechiae
- Arthralgia/myalgia
- Facial or Periarticular edema
- Headache
- GI upset

- Incubation period 3-14 days
- Symptom duration 2-7 days but rash & arthralgia may last > 2 weeks
- 80% asymptomatic
Other Manifestations of Zika Infection

- Uveitis
- Meningoencephalitis
- Guillain Barre Syndrome (GBS)
- ?Memory/learning
- ?Dementia
- ADEM
- Immune thrombocytopenic purpura
Fetal Infection

- Microcephaly
- Collapse of skull
- Absent or poorly developed brain structures
- Defects of the eye, spinal cord
- Hearing loss
- Impaired growth
- Club foot, contractures of joints
- Hydrops fetalis
- Miscarriage, stillbirth
Congenital Infection: Case Series from Brazil

Lancet 2016, Victoria et al
• 602 babies with congenital infection (Nov 19, 2015-Feb 27, 2016)
• 20% had brain abnormalities but normal sized heads (infection >30wks gestation)
• No history of rash during pregnancy in 1/3 of congenital infections

NEJM 2016, Brasil et al
• 72 pregnant women with rash due to Zika (Sep 2015 to Feb 2016)
• 29% risk of adverse fetal effects (brain abnormalities, fetal death, IUGR)
• CNS abnormalities were seen in fetuses infected as late as 27 weeks of gestation
Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities

NEJM June 2, 2016

- 33 year old Finnish woman; at 11 weeks of pregnancy went for a holiday in Mexico, Guatemala and Belize in late November, 2015; recalled mosquito bites especially in Guatemala
- 5 day illness with ocular pain, myalgia, fever, rash
- Serology 4 weeks after illness: +IgG & IgM
- Zika RNA found in maternal serum at 16 & 21 wk GA (*4 weeks and 10 weeks after symptoms*)
- Fetal u/s: normal at week 13,16,17
- GA wk 19: major fetal brain abnormalities on u/s and MRI, no microcephaly nor intracranial calcifications
- Pregnancy terminated at 21wk GA
- Autopsy of fetus: diffuse cerebral thinning, high zika RNA load, viral particles detected by EM, IH and culture in brain, neuronal apoptosis in cortex, volume loss in subventricular zone
Prolonged Shedding of Zika virus Associated with Congenital Infection

NEJM Sep 22, 2016

• Case from Sao Paulo Brazil
• Mother had Zika infection during 26\textsuperscript{th} week of pregnancy: fever, pruritic maculopapular rash, headache, conjunctival hyeremia, swelling & pain of hands and feet
• Male baby born on Jan 2, 2016 with microcephaly and reduced brain parenchyma, calcifications
• Baby PCR positive on day 54 in serum, saliva & urine; serum still positive on day 67, negative on day 216
• Baby at 6 months of age showing neuropyschomotor developmental delay, global hypertonia, spastic hemiplegia
Radiologic Findings of Congenital Zika Virus Infection

Calcifications

Ventriculomegaly

Cortical atrophy
• 20 year old mom, asymptomatic during pregnancy, fetal u/s abnormal at 23GW
• Severe ventriculomegaly, marked parenchymal thinning and/or atrophy, calcification, sloping forehead, and elevation of the hypoplastic cerebellar vermis with hypoplastic cerebellar hemispheres.
• Brainstem is thin, and the midbrain is foreshortened. The spinal cord is irregular, thin, and nonvisualized in parts, and then thicker and possibly mineralized.
• Sloped forehead, redundant skin folds and skull asymmetry
24y mother, rash at 9 wk GA, Fetal u/s abnormal at 19 wk GA
- twins both affected
- severe microcephaly, profound frontal lobe hypoplasia, calcifications,
- Spinal cord is atrophic hypoplasia of the corpus callosum, with prominent fornices
- Cyst or septations within the ventricle
- Cerebellum small and nodular
- Lack of rotation of hippocampi
- Pons flattened
- severe microcephaly with occipital keel-like prominence, and normally developed face
- collapse of the calvarium with extensive overlap of the calvarial bones
- skin rugae (*) on craniogram
Zika Destroys Fetal Mouse Brain Cells

• ZIKV infects different lineages of neuroprogenitor cells (NPC) and immature neurons
• Replicates in these cells with high efficiency
• Suppress proliferation/differentiation
• Triggers apoptosis
Teratogenic Infections (TORCH)

Toxoplasmosis

Others (syphilis, parvovirus, HIV)

Rubella

CMV

Herpes & VZV
CDC Guidelines for Pregnancy and Newborns

- For Women with possible exposure to Zika virus
  - If Zika diagnosed, wait at least **8 weeks** after symptom onset to attempt conception.
  - If NO symptoms develop, wait at least **8 weeks** after last date of exposure before attempting conception

- Guidance for Pregant women (July 28, 2016):
  - Lab testing Flowchart
  - Fetal ultrasound (ACOG guideline)

- First 12 months of life for infants with possible congenital zika infection (Augus 19, 2016): **Table**
Fetal Ultrasounds for Pregnant Women exposed to ZIKV

• Recommended regardless of laboratory findings

• Timing:
  • Early u/s at 16-18 weeks gestation (WG)
  • ≥4 weeks after maternal exposure and every 2-4 weeks
  • At least one exam between 28-33 WG
Amniocentesis & PCR Testing of Amniotic Fluid

- Offered if abnormal u/s and/or positive or inconclusive maternal zika lab results
- Timing: 21WG and at least ≥6 weeks post-exposure
Newborn Assessment
CDC Guideline
# Newborn Assessment

## CDC Guideline

## Outpatient Management Checklist

<table>
<thead>
<tr>
<th>Row</th>
<th>Description</th>
<th>2 weeks</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
<th>4-6 months</th>
<th>9 months</th>
<th>12 months</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Infant with abnormalities consistent with congenital Zika syndrome and laboratory evidence of Zika virus infection*</td>
<td>☐ Thyroid screen (TSH &amp; T4)</td>
<td>☐ Neuro exam</td>
<td>☐ Neuro exam</td>
<td>☐ Thyroid screen (TSH &amp; T4)</td>
<td>☐ Ophthalmology exam</td>
<td>☐ Repeat audiology evaluation (ABR)</td>
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<tr>
<td></td>
<td>Routine preventive health care including monitoring of feeding and growth</td>
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<td></td>
<td>☐ Routine and congenital infection-specific anticipatory guidance</td>
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<td></td>
<td>☐ Referral to specialists, including evaluation of other causes of congenital anomalies as needed</td>
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<td></td>
<td>☐ Referral to early intervention services (See Page 3, Checklist 2)</td>
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<tr>
<td></td>
<td>☐ Continue to evaluate for other causes of congenital anomalies</td>
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<td></td>
<td>☐ Further management as clinically indicated</td>
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<tr>
<td>2</td>
<td>Infant with abnormalities consistent with congenital Zika syndrome and negative for Zika virus infection</td>
<td>☐ Ophthalmology exam</td>
<td>☐ ABR</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>Infant with no abnormalities consistent with congenital Zika syndrome and laboratory evidence of Zika virus infection*</td>
<td>☐ Monitoring of growth parameters (HC, weight, and height), developmental monitoring by caregivers and health care providers, and age-appropriate developmental screening at well-child visits (See Page 3, Checklist 3)</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>Infant with no abnormalities consistent with congenital Zika syndrome and negative for Zika virus infection</td>
<td>☐ Monitoring of growth parameters (HC, weight, and height), developmental monitoring by caregivers and health care providers, and age-appropriate developmental screening at well-child visits</td>
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</tbody>
</table>
Sexual transmission

- Virus can remain in semen longer than in blood
  - Maximum reported is 80 days
- Can be transmitted from symptomatic or asymptomatic male to female (or male)
  - Via vaginal, anal or oral (mouth to penis)

CATMAT recommendations for couples where male has traveled to area of active zika transmission

**Woman is pregnant**
- use condoms consistently or abstain from sex for the duration of the pregnancy.

**Other couples concerned about sexual transmission**
- man has confirmed Zika virus infection or clinical illness consistent with Zika virus disease should consider using condoms or abstaining from sex for at least 6 months after onset of illness.
- man resides in an area with active Zika virus transmission but has not developed symptoms of Zika virus disease might consider using condoms or abstaining from sex while active transmission of zika persists.
Lab acquired Zika Infection

- Prior to the current outbreak, there were four reports of laboratory acquired Zika virus infections, although the route of transmission was not clearly established in all cases.
- 1 case of laboratory-acquired Zika virus disease in the United States
  - Researcher in Pittsburgh contracted Zika virus after needle stick accident; 1 week later developed symptoms
CDC: Utah investigates zika infection with unclear transmission route

• Elderly Utah resident who died on June 25
• Deceased patient had traveled to an area with Zika and had high Zika titers in serum (100,000 x higher than average)
• Family member who had been caring for the elderly patient developed symptoms within 1 week, recovered
  • had close contact (kissing and hugging)
Diagnostic testing

Culture for virus
- generally not routinely performed

PCR
- BCCDC
- Serum (EDTA), urine, CSF, amniotic fluid, fresh frozen tissue
- Acute phase (≤ 14 days)

IgM Serology
- NML
- Often positive by day 4-7 of illness
- Persists for 12 weeks
- Cross reactivity with YF, WNV, Dengue
- Confirmatory plaque reduction (PRNT)

Immunohistochemistry
- CDC Atlanta
- Tissues eg. placenta
MAC ELISA

- Materials provided by CDC or NML
- IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA)
- 96 well plate
- 2 overnight incubation steps
- A colorimetric product is generated by the interaction of enzyme and a chromogenic substrate and detected by a spectrophotometer (ELISA reader).
PCR FDA cleared kits for Zika

• CDC Trioplex rRT-PCR
  • Multiplex detects ZIKV, Chikungunya and Dengue RNA
• Focus Diagnostics Zika Virus RNA Qualitative Real-Time RT-PCR
• Altona RealStar Zika Virus RT-PCR Hologic Aptima Zika Virus Assay (transcription-mediated amplification, TMA test)
Treating patients with Zika

- Rest
- Drink fluids to prevent dehydration
- Take acetaminophen (Tylenol®) to reduce fever and pain
- Do not take aspirin or other non-steroidal anti-inflammatory drugs (NSAIDS) until dengue can be ruled out to reduce the risk of bleeding
- Protect from mosquito bites during the first week of illness, when Zika virus can be found in blood
Recommendations for travelers to endemic areas

- CDC recommends that pregnant women not travel to an area with active Zika virus transmission
- Wear long sleeved shirts and pants
- Use approved mosquito repellants
- Stay in lodgings that are screened or air-conditioned
- Sexual preventative measures
- Avoid mosquito bite during 1st week of illness to avoid human/mosquitos/human transmission
## Travel Advisory, WHO

<table>
<thead>
<tr>
<th>Category 1: Countries with a reported outbreak from 2015 onwards#</th>
<th>AMRO/PAHO</th>
<th>Subtotal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anguilla; Antigua and Barbuda; Argentina; Aruba; Bahamas; Barbados; Belize; Bolivia (Plurinational State of); Bonaire, Sint Eustatius and Saba – Netherlands; Brazil; British Virgin Islands; Cayman Islands; Colombia; Costa Rica; Cuba; Curaçao; Dominica; Dominican Republic; Ecuador; El Salvador; French Guiana; Grenada; Guadeloupe; Guatemala; Guyana; Haiti; Honduras; Jamaica; Martinique; Mexico; Nicaragua; Panama; Paraguay; Peru; Puerto Rico; Saint Barthélemy; Saint Kitts and Nevis; Saint Lucia; Saint Martin; Saint Vincent and the Grenadines; Sint Maarten; Suriname; Trinidad and Tobago; Turks and Caicos; United States of America; United States Virgin Islands; Venezuela (Bolivarian Republic of)</td>
<td>47</td>
</tr>
<tr>
<td>WPRO</td>
<td>American Samoa; Fiji; Marshall Islands; Micronesia (Federated States of); Samoa; Singapore; Tonga</td>
<td>7</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>56</strong></td>
<td></td>
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<tr>
<td>Category 2: Countries with possible endemic transmission or evidence of local mosquito-borne Zika infections in 2016</td>
<td>SEARO</td>
<td>3</td>
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<tr>
<td></td>
<td>Indonesia; Maldives; Thailand</td>
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</tr>
<tr>
<td>WPRO</td>
<td>Malaysia*; Philippines; Viet Nam</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td><strong>6</strong></td>
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<td>Category 3: Countries with evidence of local mosquito-borne Zika infections in or before 2015, but without documentation of cases in</td>
<td>AFRO</td>
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<tr>
<td></td>
<td>Gabon</td>
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</tr>
<tr>
<td>PAHO/AMRO</td>
<td>ISLA DE PASCUA — Chile**</td>
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<tr>
<td>SEARO</td>
<td>Bangladesh</td>
<td>1</td>
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<tr>
<td>WPRO</td>
<td>Cambodia; Cook Islands**; French Polynesia**; Lao People’s Democratic Republic; Marshall Islands; Micronesia; New Zealand; Palau; Papua New Guinea; Tonga; Vietnam; Wallis and Futuna</td>
<td>2</td>
</tr>
</tbody>
</table>
Zika vaccine: Sanofi Pasteur awarded $43 million to develop an inactivated vaccine

• Phase 2 Clinical trials in early 2018
• Work on vaccine began in early 2016 with NIH, WRAIR, BARDA
Thanks.

Comments