Update on Zika virus: The latest emerging arbovirus in the Americas

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Research at Osorio’s Lab

• Study of Emerging Viral Diseases
  • Field Studies
    • Dengue, chikungunya, zika, influenza, monkeypox
  • Vaccine Research
    • Dengue, chikungunya, rabies, plague, white nose syndrome, zika, influenza, enterovirus 71, African swine fever
  • Pathogenesis
    • Dengue, zika, chikungunya, monkeypox
Zika- An International Public Health Emergency

• The World Health Organization has declared the Zika virus an international public health emergency, prompted by growing concern that it could cause birth defects

• The infection appears to be linked to the development of unusually small heads and brain damage in newborns (microcephaly)

• As many as four million people could be infected by the end of the year
What is Zika?

- Zika is a mosquito-transmitted virus discovered in the Zika forest in Uganda in 1947

- Family *Flaviviridae*: related to dengue, yellow fever and West Nile viruses

- Transmitted to humans primarily by *Aedes* species mosquitoes that also transmit chikungunya, dengue and yellow fever
Zika Virus Epidemiology

• Before 2007, sporadic human disease cases reported from Africa and southeast Asia

• In 2007, first outbreak reported on Yap Island, Federated States of Micronesia (population 7,391): 73% population infected; 18% symptomatic among infected; no severe disease

• In 2013–2014, >30,000 suspected cases reported from French Polynesia and other Pacific islands: Guillain-Barré syndrome reported following suspected Zika virus infection; possible increase in microcephaly (identified retrospectively after Brazil)

• In May 2015, the first locally-acquired cases in the Americas were reported in Brazil; microcephaly suspected in November; 5,640 cases reported, 583 confirmed and 4,107 under investigation as of Feb 20th
ZIKA - US Current Status (CDC Report-2/26/16)

- **US States**
  - Travel-associated Zika virus disease cases reported: 107
  - Locally acquired vector-borne cases reported: 0
- **US Territories**
  - Travel-associated cases reported: 1
  - Locally acquired cases reported: 39
- **Nine pregnant U.S. women infected with Zika**
  - Two pregnant women have chosen to have abortions.
  - Two pregnant women suffered miscarriages
  - One gave birth to an infant with serious birth defects
  - Two delivered healthy infants
  - Two are still pregnant
- **10 more cases of pregnant women are being investigated**

Aedes aegypti mosquito distribution

Asian Tiger Mosquito (*Ae. Albopictus*)

The most invasive mosquito in the world
Alternative dengue, chik and zika vector
Zika virus Transmission Cycles

- Sylvatic (jungle) cycle
- Epidemic (urban) cycle
Other Modes of Transmission

• Documented or likely
  – Intrauterine resulting in fetal loss or congenital infection
  – Intrapartum from viremic mother to newborn
  – Sexual
  – Blood transfusion
  – Laboratory exposure

• Theoretical concern
  – Organ or tissue transplantation
  – Breast milk
Zika Virus Diagnostics

- Reverse transcriptase-polymerase chain reaction (RT-PCR) for viral RNA in serum collected ≤7 days after illness onset
- Serology for IgM and neutralizing antibodies in serum collected ≥4 days after illness onset
- Plaque reduction neutralization test (PRNT) for ≥4-fold rise in virus-specific neutralizing antibodies in paired sera
- Immunohistochemical staining (IHC) for viral antigens or RT-PCR on fixed tissues
Serology Cross-reactions with other Flaviviruses

- Zika virus serology can be positive due to antibodies against related flaviviruses (e.g., dengue and yellow fever viruses)
- Neutralizing antibody testing may discriminate between cross-reacting antibodies in primary flavivirus infections
- Difficult to distinguish infecting virus in people previously infected with or vaccinated against a related flavivirus
Clinical Manifestations

- Fever, rash, arthralgia, myalgia, conjunctivitis, headache
- Incubation period of a few days to a week
- Duration of illness typically several days to a week
- Severe disease requiring hospitalization uncommon. Fatalities are rare
- Guillain-Barré syndrome reported in patients following suspected Zika virus infection

Zika virus and microcephaly in Brazil

- Brazil Ministry of Health reported a substantial increase in number of babies born with microcephaly in 2015; true baseline unknown

- Zika virus infection identified in several infants born with microcephaly (including deaths) and several other fetal losses

- Others cases have tested negative or been attributed to other causes

- Proportion of the reported microcephaly cases that are due to Zika virus infection is unknown

- Incidence of congenital infection and microcephaly also unknown
Zika Virus Associated with Microcephaly

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Marko Kolenc, M.Sc., Katarina Resman Rus, M.Sc., Tina Vesnauer Vipotnik, M.D.,
Vesna Fabjan Vodušek, M.D., Alenka Vizjak, Ph.D., Jože Pižem, M.D., Ph.D.,
Miroslav Petrovec, M.D., Ph.D., and Tatjana Avšič Županc, Ph.D.

In this report, we describe the case of an expectant mother who had a febrile illness with rash at the end of the first trimester of pregnancy while she was living in Brazil. Ultrasonography performed at 29 weeks of gestation revealed microcephaly with calcifications in the fetal brain and placenta. After the mother requested termination of the pregnancy, a fetal autopsy was performed. Micrencephaly (an abnormally small brain) was observed, with almost complete agyria, hydrocephalus, and multifocal dystrophic calcifications in the cortex and subcortical white matter, with associated cortical displacement and mild focal inflammation. ZIKV was found in the fetal brain tissue on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, with consistent findings on electron microscopy. The complete genome of ZIKV was recovered from the fetal brain.
Factors contributing to ZIKA spread

• Host
  – Lack of ZIKA-specific immunity in human populations

• Virus ?

• Environment
  – Mosquito population
  – Globalization
  – Climate changes
Countries or territories with reported local transmission of Zika virus (as of Feb 2016)
Osorio’s lab  Efforts on Zika

- Member of Zika Global Task Force (from Global Virus Network)
- First documentation of autochthonous transmission in Colombia (2nd to Brazil in the number of cases)
- Members of ZEST (Zika Experimental Science Team) at UW. Developing a non-human primate animal model. Lead by Dr. David O’Connor, Ted Golos, Thomas Fredrick, and Saverio Capuano
- Developed a mouse model to study Zika. Developing vaccines and antivirals
- Studying a biological approach (*Wolbachia*) to block viral transmission from *Aedes aegypti*
- Development of a Field Site to release *Wolbachia* as a biological approach to control Dengue, chikungunya and Zika (Medellin, Colombia)
- Developing a field cohort study in Colombia of pregnant women infected with Zika
- Creation of a Center in Colombia to study Tropical and Emerging Infectious Diseases
Zika Task Force – Global Virus Network

GVN Zika Task Force Chair

SCOTT C. WEAVER, MS, PhD
Director, Institute for Human Infections and Immunity
Scientific Director, Galveston National Laboratory
John Sealy Distinguished University Chair in Human Infections & Immunity

GVN Zika Task Force
Field Studies of Emerging Arboviruses

Colombia

Santa Marta

Sincelejo

Medellín

Leticia

Ecuador

Argentina

UW-Madison

USA
Detection of autochthonous ZIKV transmission in Sincelejo, Colombia

Camacho et al. EID, In Press  
Photo: Cynthia Goldsmith, Centers for Disease Control and Prevention
ZIKV causes lethal infection in mice

Aliota et al. PLoS NTD, In Review
ZIKV viremia peaks 2d PI

A

- • Young mice
- □ Adult mice

B

- • $10^5$ PFU
- □ 103 PFU
- ▲ $10^2$ PFU
Zika virus in rhesus macaques

Project ZEST: Zika Experimental Science Team
NHP Advantages

- Exact timing, dose, and strain of virus
- Serial sampling
- Invasive sampling
- Immune responses and pregnancy similar to humans
- Outstanding tools available for studying immunology and pathogenesis

(e.g., virus quantification and evolution, measuring immune responses, evaluating vaccines and therapeutics)
Key Questions (non pregnancy)

• Does Asian lineage ZIKV infect macaques?
• What are the viral dynamics in plasma, urine, saliva, feces, CNS, and semen?
• Are there long-lived reservoirs where ZIKV persists?
• What are the clinical and immunological indicators of infection?
• Does primary ZIKV infection protect from homologous and heterologous secondary infection?
• What are the correlates of protective immunity?
Key Questions (pregnancy)

• Is fetal development impacted by ZIKV infection in macaques?
• Does timing of ZIKV infection influence fetal pathology?
• How does ZIKV breach maternal/fetal barriers?
• Does ZIKV infection pose a threat to future pregnancies?
• Do pathologies more subtle than microcephaly occur in newborns?
ZIKV-001 Objectives

- Gain familiarity and expertise working with ZIKV-infected animals and clinical samples
- Assess infectivity of three different doses of French Polynesian ZIKV (10E6, 10E5, and 10E4 PFU)
- Dynamics of virus replication in multiple fluids
- Clinical and immunological indicators of infection
Plasma viral loads

- Also detected virus in urine and CSF.
- NK cell changes in blood coincident with virus infection
The Wolbachia Based Biological Control Approach to Eliminate Dengue, Zika, and Chikungunya. Pilot Studies in Bello (Antioquia, Colombia)
Wolbachia
ELIMINATE DENGUE PROGRAM
CURRENT SITES
ELIMINATE DENGUE COLOMBIA

- Universidad de Antioquia – PECET (Programa de Estudio y Control de Enfermedades Tropicales)
- Monash University
- Universidad Nacional de Colombia
- University of Wisconsin
Biological control of Dengue using *Wolbachia* in Bello (Antioquia, Colombia)

<table>
<thead>
<tr>
<th>Population (2014)</th>
<th></th>
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<tbody>
<tr>
<td>Colombia</td>
<td>47,661,787</td>
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<tr>
<td>Antioquia</td>
<td>6,378,132</td>
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<tr>
<td>Medellin</td>
<td>2,410,765</td>
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<tr>
<td>Bello</td>
<td>429,765</td>
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<tr>
<td>Barrio Paris</td>
<td>44,000</td>
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</tbody>
</table>
PARÍS, BELLO, COLOMBIA
Communications and Social Engagement work
Community Consent

Studied area: Paris
Visited houses: 5006
Agree: 4744 (94.8%)
Disagree: 262 (5.2%)
Communications and Social Engagement work

Material and methods used to socialise the project with different stakeholders:

- Sticker
- Comic book
- Loudspeaker announcement
- Portfolio
- Magnet
- Posters
- Song
Communications: Addressing Community Concerns

Hotline-Email

Suggestion Box

Surveys
FEVER CLINIC

Started May 2014

We have attended more than 200 patients
74 confirmed cases of dengue
Field site preparations

Location of confirmed dengue cases (May 2014 – present)

Total patients tested = 174
Total cases = 74
NS1+ = 44
ELISA+ = 56

- DenV 1 (n= 32)
- DenV 2 (n= 4)
- DenV 3 (n= 1)
- No confirmed (n= 31)
Monitoring

BG Sentinel Trap

BG-GAT Gravid Aedes Trap

- BG-Sentinel (n=70)
- BG-GAT (n=30)
- Área: 0,624Km²
*Wolbachia* Mosquito Release Process
Release Routes
How *Wolbachia* spreads in the wild mosquito population

a) 

b) 

c) 

Female

Male

*Wolbachia*
Frequency: wMel in *Ae. aegypti* tested

- Primer periodo de liberación
- Segundo periodo de liberación

\[ n= 3664 \text{ Ae. } aegypti \]
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The C.D.C. testing algorithm for pregnant women who have visited countries in which the Zika virus is spreading. Credit Centers for Disease Control and Prevention