Zika, Chikungunya & Dengue!

José Darío Martínez, MD, FAAD
Professor of Internal Medicine & Dermatology
Chief, Internal Medicine Clinic
University Hospital “JE González”, UANL
Monterrey, México
I do not have any relevant relationships with industry.
Travelers’ diseases

Medical problems in returned travelers

❖ Fever
❖ Acute diarrhea
❖ Skin lesions

Most common skin lesions are:

➢ Cutaneous larvae migrans
➢ Insect bites (bedbugs)
➢ Bacterial infections
➢ Rash
Rash & fever in travelers

Most common causes in the Americas

- Malaria
- **Dengue fever**
- Spotted fever (*rickettsia*)
- Yellow fever
- West Nile fever
- **Chikungunya fever**
- Zika fever
Arbovirus infections

Arthropod-borne virus

Most common arbovirus in the Americas

- Dengue fever
- Yellow fever
- West Nile fever
- Chikungunya fever
- Zika fever
# Taxonomy of some important Arbovirus

*Clin Exp Vaccine Res* 2014;3:58-77

<table>
<thead>
<tr>
<th>Family</th>
<th>Genus</th>
<th>Important Species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Togaviridae</strong></td>
<td><em>Alphavirus</em></td>
<td><em>Chikungunya</em>, Mayoro, EEE, WEE, VEE virus, etc.</td>
</tr>
<tr>
<td>Single-stranded positive-sense DNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flaviviridae</strong></td>
<td><em>Flavivirus</em></td>
<td>West Nile, <em>Dengue</em>, <em>Zika</em>, Yellow fever, KFD, etc.</td>
</tr>
<tr>
<td>Single-stranded positive-sense DNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bunyaviridae</strong></td>
<td><em>Bunyavirus</em></td>
<td>California encephalitis, Oropouche, Turlock Rift valley fever, Sandfly fever virus, etc.</td>
</tr>
<tr>
<td>Single-stranded negative-sense RNA</td>
<td><em>Phlebovirus</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Nairovirus</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Hantavirus</em></td>
<td></td>
</tr>
<tr>
<td><strong>Reoviridae</strong></td>
<td><em>Orbivirus</em>, <em>Coltivirus</em></td>
<td>African horse sickness, Blue tongue viruses</td>
</tr>
<tr>
<td>Double-stranded RNA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Travelers’ maladies

THERAPY IN PRACTICE

Got the Travel Bug? A Review of Common Infections, Infestations, Bites, and Stings Among Returning Travelers

Matthew P. Vasievich1 · Jose Dario Martinez Villarreal2 · Kenneth J. Tomecki1

© Springer International Publishing Switzerland 2016
Arbovirus Infections

Focus on:

- **Zika**: transmission, muco-cutaneous manifestations, fetal malformations, neurologic disease, diagnosis
- **Chikungunya**: cutaneous and articular manifestations
- **Dengue**: skin lesions, warning signs of severe disease, prevention, new vaccine
Zika fever

Overview

- Emerging mosquito-borne pathogen
- *Flavivirus*
- Was isolated in *Zika forest* in Uganda in 1947
- Transmitted by *Aedes aegypti* mosquito
- First epidemic occurred in 2007 in *Micronesia*

*Emerging Infect Dis* 2015;21(1):84-86
Zika fever

Epidemiology

❖ During 2007-2013 few cases in travelers returning from Africa or SE Asia were reported

❖ First cases of ZF in The Americas were reported in Brazil in 2015

❖ New vector: *Culex quinquefaciatus*

Vasievich MP, Martínez JD, Tomecki KJ.
Zika CDC map (December 14, 2016)
Zika fever

Transmission

- Mosquito bite
- Mother-to-fetus
- Sexual intercourse
- Blood transfusion
- Breast-feeding?

CDC, 2016
Zika fever

Clinical facts

❖ Asymptomatic in most cases (misdiagnosed)
❖ Incubation period: 3-8 days
❖ **Mild fever** (37.8 °C-38.5 °C)
❖ Arthralgia (small joints in hands & feet): 65%
❖ Headache, retroorbital pain

*JAMA Dermatol 2016 DOI:10.1001/jamadermatol.2016.1433*
Zika fever

Muco-cutaneous signs

- Skin rash: 90%
- Nonpurulent conjunctivitis: 55%
- Oral enanthem
- Pruritus

JAMA Dermatol 2016
DOI:10.1001/jamadermatol.2016.1433
Zika fever

Diagnosis I

❖ Serum RT-PCR: rapid, sensitive, and specific test (first week)

❖ Ab anti ZV: IgM & IgG (second week): cross reaction with Dengue

❖ TrioPlex Real-time RT-PCR
  - CDC’s new text for DF, CHIKF & ZF (Sept. 21, 2016)
  - Not FDA approved yet, only in emergencies

Emerging Infect Dis 2015;21(1):84-86
Zika fever

Diagnosis II

- **Urine RT-PCR**: useful in travelers (2 weeks)
- In **pregnant women**:
  - Fetal ultrasound
  - Amniocentesis (RT-PCR)

*Emerging Infect Dis 2015;21(1):84-86*

*CDC: Zika fever recommendations in pregnant women, 2016*
Zika fever

DDX

- Dengue fever
- Chikungunya fever
- Viral rash
- Drug reaction

Emerging Infect Dis 2015;21(1):84-86
Zika fever

Complications

❖ **Neurologic**: Guillain-Barré syndrome
  ➢ Incidence difficult to assess

❖ **Microcephaly**: feared in pregnant women during the first trimester (weeks 12-16)
  ➢ Most cases reported in Brazil

❖ About **5% of zika cases** in pregnant women in US (PR) had birth defects*

*MMWR CDC, June 16, 2017*
Interim Guidelines for Pregnant Women During a Zika Virus Outbreak — United States, 2016

Emily E. Petersen, MD; J. Erin Staples, MD, PhD; Dana Meany-Delman, MD; Marc Fischer, MD; Sascha R. Ellington, MSPH; William M. Callaghan, MD; Denise J. Jamieson, MD

Pregnant woman with history of travel to an area with Zika virus transmission http://wwwnc.cdc.gov/travel/notices/

Pregnant woman does NOT report clinical illness consistent with Zika virus disease during or within 2 weeks of travel

Test for Zika virus infection

Positive or inconclusive test for Zika virus infection

Fetal ultrasound to detect microcephaly or intracranial calcifications

Offer amniocentesis for Zika virus testing

Negative test(s) for Zika virus infection

Fetal ultrasound to detect microcephaly or intracranial calcifications

Fetal ultrasound to detect microcephaly or intracranial calcifications

Either finding present

No findings present

Test pregnant woman for Zika virus infection

Consider amniocentesis for Zika virus testing

Consider serial ultrasounds to detect development of microcephaly or intracranial calcifications

Either finding develops

Either finding present

No findings present
Zika: key points

- Clinical diagnosis is not enough
- IgM and IgG have cross reaction
- PCR is definitive
- Blood
- Urine
- Pregnancy test
- Prognosis
Zika: key points

- Sexual transmission (male)
- Use of condoms
- Maternal-fetal transmission, breast-feeding?
- Blood transfusion
- Risk of Guillain-Barré syndrome
- How long the virus live in our system?
Zika: pregnancy guidelines summary

- PCR: essential in diagnosis
- Obstetrician consult
- Possible malformations: US
- Follow up: mother & child
- Breast-feeding:
  - If late pregnancy or perinatal infection, not recommended (case #3)
Zika: microcephaly
Zika fever

Prevention & treatment

❖ Essential in pregnant women (or unaware)
❖ Appropriate clothing and use of repellents (DEET)
❖ Counselling before travel (travelers’ disease)
❖ Acetaminophen
❖ Supportive therapy as needed
❖ If pregnant: US, then amniocentesis to detect transplacental ZV disease
Fundiadora Park, Monterrey, México
Chikungunya fever

Overview

❖ **Alphavirus**

❖ Three serotypes (Asian, E/C/S African and W African)

❖ **Chikungunya:** african word (Makonde dialect) which means “that which bends up”

❖ Unlike DF, CHIKF results in greater and prolonged morbidity than mortality

*Med Clin N Am* 2012;96:1225-1255
Chikungunya fever

**Vector**
- Female mosquito
- *Aedes aegypti*
- *Aedes albopictus* (Asian tiger mosquito)
- Daylight: dawn & dusk
- Outdoors (*A aegypti* indoors also)
- Transmission: infected person to healthy person (via mosquito bite)
Chikungunya fever vectors: Aedes aegypti & Aedes albopictus
Chikungunya fever

Epidemiology

- Came from Africa, India, Indonesia
- **Arrive to America on Dec. 2013**
- Caribbean islands (first cases)
- March 2014: > 8000 cases
- **Travelers´ disease**
- Spreading rapidly into The Americas
Chikungunya fever

Key facts

❖ It is transmitted by *A aegypti*
❖ CHIKV strains mutate
❖ Outbreak: La Reunion Island (2005-06)
❖ Facilitating transmission by *A albopictus*
❖ Mutation in the viral envelope gene E1
❖ Very high ability to adapt to various environments
❖ Movement of goods and people
Chikungunya fever

World cases as of 1952 to 2006
CHIKF in The Americas!

**Hot spots:** Central America, Haiti, Dominican Republic, Colombia, Venezuela, and Brazil

June, 2015 (PAHO)
- 366,000 SC
- 10,800 CC
- 54 deaths

December 30, 2015
- **México:** 11,199 local cases (PAHO)
- **México City:** 160 cases
- Casualties unknown
## CHIKV in US 2015

June 1, 2016 (First local case reported in Brownsville, Texas since 2014)

<table>
<thead>
<tr>
<th>State</th>
<th>Travel-associated cases (N=43)</th>
<th>Locally-transmitted cases (N=0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Arkansas</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Colorado</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Florida</td>
<td>12 (28)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Indiana</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Kentucky</td>
<td>2 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Maryland</td>
<td>4 (9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Missouri</td>
<td>3 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>New Jersey</td>
<td>3 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>New York</td>
<td>9 (21)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ohio</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>2 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Texas</td>
<td>3 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Washington</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
CHIKV CDC (April 22, 2016)
Chikungunya fever

Clinical picture

- 3-28% patients are asymptomatic
- 4 of 5 patients have symptoms
- **Incubation period:** 7 days (1-12)
- Fever
- **Arthritis**
- Muscle pain, headache
Chikungunya fever

Skin lesions

❖ Maculopapular rash
  ➢ 50% of cases
  ➢ 2-5 days after fever starts
  ➢ Acral rash

❖ Melanosis

❖ Melanonichia

❖ Vesicles, bullae

❖ Genital ulcers
Chikungunya fever

Articular involvement

- **Acute**: high fever, arthralgia/arthritis, migrating polyarthritis, symmetric affection, no bleeding (last 3-10 days)

- **Subacute**: 2-3 months after, distal polyarthritis, depression, fatigue, weakness

- **Chronic**: arthralgia > 3 months, *mimicking* RA/PsA (93% [3m], 53% [15m], 47% [24m])
Chikungunya fever

Risk factors for severe disease

- Newborns
- Older age (> 65 years)
- Initial severe acute disease
- Co-morbidities: DM, HBP, HD
- Pre-existing joint disease: RA, PsA
Chikungunya fever

Diagnosis

- **RT-PCR**: most sensitive, rapid test, can detect CHIKV in the first week
- **Serology**: MAC-ELISA: IgM (+ in 2-6 days)
- **Serology**: CHIKV IgG 4-fold elevation (+ in 7 days, can last for years)

*Eur J Int Med 2012;23:325-329*
Chikungunya fever

**DDx**

- Dengue
- Zika
- Malaria
- Leptospirosis
- Menigococcemia
- Drug eruption
Chikungunya fever

Complications

❖ Articular chronic pain like RA/PsA
❖ Can affect unborn babies
❖ **Low mortality** (mortality associated with comorbidities)
❖ **No second infection**
❖ Can detonate autoimmune diseases ➤ SLE, SA
Chikungunya fever

Treatment

❖ No vaccine available
❖ No specific antiviral treatment
❖ Acetaminophen (drug of choice)
❖ NSAID’s
❖ Bed rest (mosquito net)
❖ Fluids

Palace of Fine Arts, México City
Overview

- Warm climate, rainy season
- *Flavivirus*
- *Aedes aegypti* mosquito
- Female mosquito (bites in daytime)
- Most prevalent arthropod-borne virus
- Emerging disease
- Illness can go from mild to fatal disease
Dengue mosquito
Dengue fever

Dengue virus sero-types (4)

- **DENV1** (most common)/DENV 2, 3 (more severe)
Dengue fever

Epidemiology

- Worldwide
- 2.5 billion people at risk
- DENV cause 50-100 million cases of DF
- 250-500,000 cases of DHF per year
- 25,000 deaths per year
- US: Texas outbreak (25 cases) occurred in 2005
- México 2016 PAHO: >200,000 C/31 D/4 Sero-types
Dengue map 2016 (CDC)
Dengue fever

Clinical facts

- 60-80% dengue cases are asymptomatic
- **Incubation period**: 2-8 days
- **Acute febrile illness**: headache, high fever, myalgia, arthralgia (**“breakbone” fever**), retro-orbital pain, fatigue
- **Faint macular rash** (2-6 days into illness)
- **Gums bleeding, nosebleeds, bruising**
WHO definition of dengue fever: probable case

*Travel Med and Infect Dis* 2009;7:278-283

- **Acute febrile illness (2 or +)**
  - Headache
  - **Retro-orbital pain**
  - Myalgia
  - Arthralgia
- **Rash**
- Hemorrhagic manifestations
- Leukopenia
- **Serology (+)**
Dengue fever

Clinical syndromes (WHO)

❖ Approximately 1% of patients will progress to one of these during the critical phase in days 4-7 of illness:

➢ Dengue hemorrhagic fever (DHF)
➢ Dengue shock syndrome (DSS)

Dengue fever

Warning signs of severe disease

❖ Abdominal pain
❖ Persistent vomiting
❖ Pleural effusion or ascites
❖ Mucosal bleeding

➢ These signs may occur at or after defervescence
➢ DHF or DSS may be evolving

Dengue Diagnosis

❖ Clinical suspicion
❖ Travel to endemic areas (2 weeks before)
❖ Serologic tests to detect antidengue Ab
  ➢ IgM (positive at day 5 of illness)
  ➢ IgG (recurrent infection)
❖ RT-PCR (first 4-5 days)
❖ NS1 (rapid test)
Dengue

DDx

- Chikungunya fever
- Zika
- Malaria
- Leptospirosis
- Menigococcemia
- Drug eruption
Dengue

Prevention

❖ Vaccine: not approved by the FDA yet
❖ Use of repellents (DEET) on exposed skin and/or clothing
❖ DEET
  ➢ Not for infants (< 2 months old)
  ➢ Children and adults: DEET (15-30%), no more than 30% in small children
Dengue Fever Vaccine

Original Article
Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

Methods: Children 9-16 yrs old, from Colombia, Brazil, México, Puerto Rico, and Honduras, in June 2011 to March 2012. Doses 0, 6, 12 months.

Results: > 20,800 children (2/3 vaccine, 1/3 placebo), vaccine safety was good.

Discussion: 60.8% overall efficacy, works well in all 4 serotypes, 80.2% vs. hospitalization, and 95.5% vs. severe dengue cases. Protection against DF starts with the first dose, but two more doses are needed to increase the Ab response and long lasting protection.

Note: in México this vaccine was approved by Cofepris (12/9/15)
Dengvaxia: tetravalent vaccine
Dengue

Key points to avoid spread DF

- Avoid sick patient to get a bite from healthy mosquitoes
- Use of mosquito nets among sick patients
- In travelers usually it is a mild disease
- Patients with DF history can have the next time a more severe form of DF
- Dengue vaccine has been approved in México & Brazil
Dengue

Management

- Dengue fever:
  - Bed rest, liquids
  - Isolation (mosquito net)
  - Actaminophen

- DHF/DSS:
  - Hospitalization
  - ICU
  - Supportive care
Arbovirus infections

Public health strategies

- Focused in *A. aegypti* a domestic mosquito (water filled containers)
- *A. albopictus* breeds in the woods (water filled leaves)
- These facts lead us to a difficult vector eradication

*Vector borne and Zoonotic Diseases, 2016;16(2)*
## DF, CHIKF & ZF: Clinical Similarities

Table by José Darío Martínez, MD

<table>
<thead>
<tr>
<th>Feature</th>
<th>Dengue</th>
<th>Chikungunya</th>
<th>Zika</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vector</strong></td>
<td><em>Aedes aegypti</em></td>
<td><em>Aedes aegypti</em></td>
<td><em>Aedes aegypti</em></td>
</tr>
<tr>
<td><strong>Geo Area</strong></td>
<td>Worldwide</td>
<td>Worldwide</td>
<td>Worldwide</td>
</tr>
<tr>
<td><strong>Incubation</strong></td>
<td>2-8 days</td>
<td>1-12 days</td>
<td>3-8 days</td>
</tr>
<tr>
<td><strong>Asymptomatic</strong></td>
<td>60-80%</td>
<td>&lt;30%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td><strong>Fever ≥39 °C</strong></td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Arthralgia/myalgia</strong></td>
<td>+/-</td>
<td>+++/+</td>
<td>++/+</td>
</tr>
<tr>
<td><strong>Vaccine</strong></td>
<td>Yes (Not FDA app)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>DEET</td>
<td>DEET</td>
<td>DEET</td>
</tr>
<tr>
<td>Feature</td>
<td>Dengue</td>
<td>Chikungunya</td>
<td>Zika</td>
</tr>
<tr>
<td>------------------</td>
<td>--------</td>
<td>-------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Bleeding</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eyes/face</td>
<td>Pain</td>
<td>Melanosis</td>
<td>Red eye, pain</td>
</tr>
<tr>
<td>Arthritis</td>
<td>-</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Itch</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Feature</td>
<td>Dengue</td>
<td>Chikungunya</td>
<td>Zika</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------</td>
<td>-------------</td>
<td>-------</td>
</tr>
<tr>
<td>Chronic arthritis</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Guillain-Barré</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Shock</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>STD</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Recurrence</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rx</td>
<td>Supportive</td>
<td>Supportive</td>
<td>Supportive</td>
</tr>
</tbody>
</table>
DF, CHIKF, ZF

Summary

❖ These mosquitoes can cause significant morbidity and mortality among international travelers
❖ Counseling to travelers
❖ Prevention is basic
❖ Clinicians must be aware of clinical presentation
❖ CHIKV & ZF are emerging diseases in The Americas
❖ Serology confirmation is essential
DF, CHIKF, ZF

Summary

❖ No vaccines approved by the FDA yet
❖ In México & Brazil a DF vaccine was approved
❖ CHIKV cycle last longer than DV
❖ **Zika is more dangerous than DF & CHIKF**
❖ Rx: acetaminophen, supportive therapy
❖ Genetic modified mosquitoes introduced in Brazil
❖ **What is next? Mayoro virus? Yellow fever?**
Thank you! Gracias!

Email: jdariomtz@yahoo.com.mx

El Castillo, Chichen Itzá, Yucatán, México