The Aedes Threat: Dengue, Chikungunya & Zika fever

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F006 The Aedes Threat: Dengue, Chikungunya & Zika fever

DISCLOSURES
I do not have any relevant relationships with industry.
José Darío Martínez, MD
In this topic I am going to discuss some FDA approved drugs and some that are used off-label.
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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
Table 4-02. Skin lesions in returned travelers, by type of lesion

<table>
<thead>
<tr>
<th>Skin Lesion</th>
<th>Percentage (n = 4,742)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous larvae migrans</td>
<td>9.8</td>
</tr>
<tr>
<td>Insect bite</td>
<td>8.2</td>
</tr>
<tr>
<td>Skin abscess</td>
<td>7.7</td>
</tr>
<tr>
<td>Superinfected insect bite</td>
<td>6.8</td>
</tr>
<tr>
<td>Allergic rash</td>
<td>5.5</td>
</tr>
<tr>
<td>Rash, unknown etiology</td>
<td>5.5</td>
</tr>
<tr>
<td>Dog bite</td>
<td>4.3</td>
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<tr>
<td>Superficial fungal infection</td>
<td>4.0</td>
</tr>
<tr>
<td>Dengue</td>
<td>3.4</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>3.3</td>
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<tr>
<td>Myiasis</td>
<td>2.7</td>
</tr>
<tr>
<td>Spotted fever group rickettsiae</td>
<td>1.5</td>
</tr>
<tr>
<td>Scabies</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Rash & fever in travelers

Most common causes in the Americas

- Malaria
- **Dengue fever**
- Spotted fever (*rickettsia*)
- Yellow fever
- West Nile fever
- **Chikungunya** fever (emerging disease)
- **Zika** fever (new kid on the block)
Travelers´ maladies

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
Dengue fever

Overview

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

Dengue virus serotypes

- DENV 1-4 (RNA virus)
- **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
- Mexico 2015: 18,000 new cases
The Aedes Threat

Aedes aegypti mosquitoes are more likely to spread viruses like Zika, dengue, chikungunya and other viruses than other types of mosquitoes such as Aedes albopictus mosquitoes.

These maps show:
- CDC's best estimate of the potential range of Aedes aegypti and Aedes albopictus in the United States.
- Areas where mosquitoes are or have been previously found

These maps DO NOT show:
- Exact locations or numbers of mosquitoes living in an area
- Risk or likelihood that these mosquitoes will spread viruses

Maps have been updated from a variety of sources. These maps represent CDC's best estimate of the potential range of Aedes aegypti and Aedes albopictus in the United States. Maps are not meant to represent risk for spread of disease.
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
- Supportive serology
Dengue rash: faint, itchy
Dengue rash

“White islands in a sea of red”
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 or tenderness
- Persistent vomiting
- Pleural effusion or ascites
- **Mucosal bleeding**
  - These signs may occur at or after defervescence
  - DHF or DSS may be evolving

*Clev Clin J Med 2012;79(7):474-482*
WHO definition of dengue hemorrhagic fever

All must be present:
- Fever > 2-7 days
- Hemorrhagic tendencies: tourniquet test (+), mucosal, GI bleeding, injections sites bleeding, hematemesis or melena
- Thrombocytopenia (< 100,000/mm)
- Evidence of plasma leakage (rise/low hematocrit)
- Signs of plasma leakage (pleural effusion, ascitis)
WHO definition of dengue shock syndrome
Travel Med and Infect Dis 2009;7:278-283

- All of the 4 criteria for DHF plus evidence of circulatory failure:
  - Rapid and weak pulse
  - Narrow pulse pressure (<20 mm/Hg)
  - Hypotension
  - Cold clammy restless
  - Hypothermia
  - Abdominal pain
  - Hepatomegaly
  - Mild to deep shock
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)
- PCR (first 4-5 days)
- NS1 (rapid test)
Dengue

DDx

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

- **Vaccine:** not approved by the FDA yet
- **Use of repellents (DEET)** on exposed skin and/or clothing
- **DEET**
  - Not for infants
  - Children and adults: DEET (15-30%), no more than 30%
Sanofi's $1.5B dengue vaccine shows Phase III promise!

- Asian people
- Cover all 4 DENV serotypes (low efficacy in type 2)
- 3 doses (0, 6, 12 months)
- Overall efficacy 56.5%
- Reduce 88.5% of DHF cases
- Not recommended for travelers/not FDA approved
Original Article

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

Methods: Children 9-16 yrs old, from Colombia, Brazil, Mexico, 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 Mexico this vaccine was approved by Cofepris (12/9/15)
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 Mexico & Brazil
Prevention (fumigation) with Avate: cypermethrine and boric acid
Dengue Management

- **Dengue fever:**
  - Bed rest, liquids
  - Isolation (mosquito net)
  - Paracetamol (pain relief)

- **DHF/DSS:**
  - Hospitalization
  - ICU
  - Supportive care
Dengue inpatient management
Fundidora Park, Monterrey, México
Chikungunya fever

Overview

- **Alphavirus**: *Togaviridae* virus (RNA)
- 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
Chikungunya fever in the U.S.
Chikungunya fever in the news

July 04, 2014
US: Four chikungunya cases reported in Boston area
Via The Boston Globe: 4 chikungunya cases reported in Boston among travelers to Caribbean.
Chikungunya fever in Texas!
Confirmed local cases: July 25, 2014
Chikungunya fever map

June 2, 2014
Chikungunya fever world map

CDC: Dec. 2, 2014
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
- **Mexico**: 11,000 local cases (SSA)
- **Mexico City**: 160 cases
- Casualties unknown
### Table 1. Laboratory-confirmed chikungunya virus disease cases reported to ArboNET by state—United States, 2015 (as of February 24, 2015)

<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>(%)</td>
</tr>
<tr>
<td>Arkansas</td>
<td>1</td>
<td>(2)</td>
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<tr>
<td>Colorado</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td>Florida</td>
<td>12</td>
<td>(28)</td>
</tr>
<tr>
<td>Indiana</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td>Kentucky</td>
<td>2</td>
<td>(5)</td>
</tr>
<tr>
<td>Maryland</td>
<td>4</td>
<td>(9)</td>
</tr>
<tr>
<td>Missouri</td>
<td>3</td>
<td>(7)</td>
</tr>
<tr>
<td>New Jersey</td>
<td>3</td>
<td>(7)</td>
</tr>
<tr>
<td>New York</td>
<td>9</td>
<td>(21)</td>
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<tr>
<td>Ohio</td>
<td>1</td>
<td>(2)</td>
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<tr>
<td>Pennsylvania</td>
<td>2</td>
<td>(5)</td>
</tr>
<tr>
<td>Texas</td>
<td>3</td>
<td>(7)</td>
</tr>
<tr>
<td>Washington</td>
<td>1</td>
<td>(2)</td>
</tr>
</tbody>
</table>
Chikungunya fever

Clinical picture

- 3-28% patients are asymptomatic
- Incubation period: 7 days (1-12)
- Fever
- Arthritis
- Muscle pain, headache
- Maculopapular rash, 50% of cases, 2-5 days after fever starts
Chikungunya fever rash
CHIKF rash
Chikungunya fever

Clinical syndromes

- **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])
CHIKF rare images from India

Courtesy Dr. Arun Inamadar, Bijapur, India

Int J Dermatol 2008;47:154-159
Chikungunya fever

Risk factors for severe disease

- Newborns
- Older age (> 65 years)
- Co-morbidities like DM, HBP, HD
- Pre-existing joint disease
- Initial severe acute disease
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
- Malaria
- Leptospirosis
- Menigococcemia
- Drug eruption
- Zika fever (new kid on the block): Mexico’s first case reported as 11/18/15 (imported from Colombia)
Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial

Lee-Jah Chang MD a †, Kimberly A Dowd PhD b †, Floreliz H Mendoza RN a, Jamie G Saunders BSN a, Sandra Sitar MSc a, Sarah H Plummer NP a, Galina Yamshchikov MSc a, Uzma N Sarwar MD a, Zonghui Hu PhD c, Mary E Enama PA-C a, Robert T Bailer PhD a, Richard A Koup MD a, Richard M Schwartz PhD a, Wataru Akahata PhD a, Gary J Nabel MD a, John R Mascola MD a, Theodore C Pierson PhD b, Barney S Graham MD a, Dr Julie E Ledgerwood DO a, the VRC 311 Study Team
Chikungunya fever

Treatment

- No vaccine available
- No specific antiviral treatment
- **Paracetamol** (drug of choice)
- NSAID’s
- **Bed rest (mosquito net)**
- Fluids

Chikungunya fever

Complications

- Articular chronic pain like RA/PsA
- MTX has been used for chronic arthritis in Europe
- Can affect unborn babies
- Low mortality
- Mortality associated with comorbidities
Chikungunya fever

Bullets to remember

- Emerging disease in The Americas
- Prevention similar as Dengue
- Unlike dengue, no second infection
- CHIKF will behave like DF in US (according to CDC officials), July 18, 2014
- *A aegypti & A albopictus* are very versatile mosquitoes
CHIKV CDC (Sept. 2, 2014)
CHIKV CDC (April 22, 2016)
Palace of Fine Arts, Mexico City
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 on 2015

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

Vasievich MP, Martinez JD, Tomecki KJ.
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
- Nonpurulent conjunctivitis: 55%
- Maculopapular rash: 90%

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

Diagnosis

- **Serum RT-PCR**: rapid, sensitive, and specific test (first week)
- **Ab anti ZV**: IgM & IgG (second week)
- **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
- All are transmitted by the same mosquitoes: *Aedes aegypti* & *Aedes spp.*

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

Complications

- **Neurologic:** Guillain-Barré syndrome
- **Microcephaly:** most feared in pregnant women during the first trimester (weeks 12-16)
- 4,783 cases reported in Brazil (Jan. 30, 2016)
- First case in US was reported in Hawaii (Jan. 15, 2016) in a traveler to Brazil
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

Pregnant woman reports 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

Either finding present

No findings present

Consider amniocentesis for Zika virus testing

Either finding develops

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
Zika fever map in the Americas: Brazil
Zika fever map (Dec. 2015)

Figure 2. Countries with reported confirmed autochthonous cases of Zika virus infection in 2015, as of 4 December

Note: Map does not indicate the extent of the autochthonous transmission in the countries.
A person in Dallas County, Texas, has contracted the Zika virus through sexual contact with an infected person who had visited a country where an outbreak has been identified. Local health officials confirmed via the Dallas County Health and Human Services Twitter account, writing “Dallas County’s 1st case of #Zika thru sex was acquired from someone who traveled to Venezuela, confirmed case did not travel.”

**Trending in the U.S.:**

- Zika may have been sexually transmitted in 14 cases: CDC (02/23/16) Reuters
- Florida reports 223 cases (40 pregnant), 1 baby with microcephaly. All imported cases (June 28, 2016). AFP
Zika fever & Pro Sports (May 6, 2016)

- Baseball scraps Puerto Rico series amid Zika concerns
- MLB moved the series
Zika & Olympic Games 2016

Pau Gasol to consider freezing sperm to avoid Zika. June 16, 2016
The Americas: countries with active Zika transmission (CDC: June 30, 2016)
Zika fever

Public health strategies

- Focused in *A. aegypti* that thrives and breeds close to homes (water filled containers)
- Meanwhile *A. albopictus* breeds in less accessible areas (water filled leaves of plants)
- These facts lead us to a difficult vector erradication
- *A. alboticus* tends to displace *A. aegypti*

Vector borne and Zoonotic Diseases, 2016;16(2)
Zika fever

Prevention & treatment

- Essential in pregnant women (or unaware)
- Appropriate clothing and use of repellents (DEET)
- Counselling before travel (travelers’ disease)
- Paracetamol
- Supportive therapy as needed
- If pregnant: US, then amniocentesis to detect transplacental ZV disease
The US Aedes Threat

Aedes aegypti mosquitoes are more likely to spread viruses like Zika, dengue, chikungunya than other types of mosquitoes such as Aedes albopictus mosquitoes.

- These maps show CDC's best estimate of the potential range of Aedes aegypti and Aedes albopictus in the United States.
- These maps include areas where mosquitoes are or have been previously found.
- Shaded areas on the maps do not necessarily mean that there are infected mosquitoes in that area.

*Maps have been updated from a variety of sources. These maps represent CDC's best estimate of the potential range of Aedes aegypti and Aedes albopictus in the United States. Maps are not meant to represent risk for spread of disease.*

<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>Up to 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>No*</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>DEET</td>
<td>DEET</td>
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</table>
DF, CHIKF & ZF: clinical & lab differences
Table by Jose Dario Martinez, MD

<table>
<thead>
<tr>
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<th>Dengue</th>
<th>Chikungunya</th>
<th>Zika</th>
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<tbody>
<tr>
<td>Bleeding</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Eyes</td>
<td>Pain</td>
<td>Melanosis</td>
<td>Red eye</td>
</tr>
<tr>
<td>Arthritis</td>
<td>-</td>
<td>+++</td>
<td>++</td>
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<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>
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<td>-----------------------</td>
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<tr>
<td>Chronic arthritis</td>
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</tr>
<tr>
<td>Guillain-Barre</td>
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<td>++++</td>
</tr>
<tr>
<td>Shock</td>
<td>+</td>
<td>-</td>
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<td>STD</td>
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<td>Blood transfusion</td>
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<tr>
<td>Microcephaly</td>
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<td>-</td>
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<tr>
<td>Recurrence</td>
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<td>Rx</td>
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<td>Supportive</td>
<td>Supportive</td>
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</table>
DF, CHIKF, ZF

Summary

- These mosquitoes can cause significant morbidity and mortality among international travelers
- Counseling to travelers
- Prevention is essential
- Clinicians must be aware of clinical presentation
- CHIKV & ZF are emerging diseases in The Americas
Summary

- Serology confirmation is essential
- No vaccines approved by the FDA yet
- In Mexico & Brazil a DF vaccine was approved
- Zika fever has arrived to The Americas
- ZF threatens pregnant women
- Rx: paracetamol, supportive therapy
- Genetic modified mosquitoes introduced in Brazil
Mosquitoes remind us that we are not as high up on the food chain as we think.

Email: jdariomtz@yahoo.com.mx
Thank you!

"In theory there is no difference between theory and practice. In practice there is."
— Yogi Berra

"You can observe a lot by watching"
— Yogi Berra

El Castillo, Chichen Itzá, Yucatán, México