Zika, Chikungunya & Dengue!

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

José Darío Martínez, MD, FAAD
Zika, Chikungunya & Dengue!

DISCLOSURES
I do not have any relevant relationships with industry.
Zika, Chikungunya & Dengue!

José Darío Martínez, MD, FAAD
In this topic I am going to discuss some FDA approved drugs and some that are used off-label.
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>
<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>
</tr>
<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>
</tr>
<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
Zika, Chikungunya & Dengue!

Focus on:

- **Zika:** transmission, muco-cutaneous manifestations, fetal malformations, diagnosis
- **CHIKF:** cutaneous and articular manifestations
- **Dengue:** update, new vaccine
- **Tables showing:**
  - Similarities, differences, complications, prevention
US Aedes Threat

Estimated range of *Aedes aegypti* and *Aedes albopictus* in the United States, 2016*

*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.

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

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

Vasievich MP, Martínez JD, Tomecki KJ.
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

- **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

- **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**
- **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
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 CDC map (December 14, 2016)
Zika fever

Public health strategies

- Focused in *A. aegypti* that thrives and breeds close to homes (water filled containers)
- Meanwhile *A. albopicus* 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)
- Acetaminophen
- Supportive therapy as needed
- If pregnant: US, then amniocentesis to detect transplacental ZV disease
Zika: key points

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

- Sexual transmission (male)
- Use of condoms
- Fetal transmission (female), breast milk?
- Blood transfusion
- Risk of Guillian-Barré syndrome
- How long the virus live in our system?
Zika: pregnancy dilemma

- 3 months pregnancy
- PCR: essential in diagnosis
- Obstetrician consult
- Possible malformations
- Follow up: mother & child
- Breast-feeding:
  - Not recommended
Interim Guidelines for Pregnant Women During a Zika Virus Outbreak — United States, 2016

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

The Boston Globe

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
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: as of 2/24/2015
### CHIKV in US 2015

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

#### 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>
</tr>
<tr>
<td>Ohio</td>
<td>1</td>
<td>(2)</td>
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<td>Pennsylvania</td>
<td>2</td>
<td>(5)</td>
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<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
- 4 of 5 patients have symptoms
- **Incubation period:** 7 days (1-12)
- Fever
- Arthritis
- Muscle pain, headache
Chikungunya fever

Skin signs

- Maculopapular rash
  - 50% of cases
  - 2-5 days after fever starts
- Melanosis
- Melanonichia
- Vesicles, bullae
- Genital ulcers
Chikungunya fever

Articular involvement

- **Acute:** high fever, arthralgia/arthritis, migrating polyarthralgia, 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)
- 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)

Chikungunya fever

DDx

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

Treatment

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

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

Complications

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

June 2, 2014
CHIKV CDC (April 22, 2016)

Current or previous local transmission of chikungunya virus
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
- Most cases are seen by Rheumatologists
Palace of Fine Arts, México City
Dengue fever

Overview

- Warm climate, rainy season
- Dengue virus (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 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
- **México 2016 PAHO**: >200,000 C/31 D/4 ST
Dengue map 2016 (CDC)
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 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*
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
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

Dengvaxia™
Powder and solvent for suspension for injection
Polvo y disolvente para suspensión inyectable

Dengue tetravalent vaccine (live, attenuated)
Vacuna tetravalente contra el dengue (de virus vivos atenuados)

Powder (1 dose) in vial + 0.5 mL of solvent in a pre-filled syringe with 2 separate needles - Pack size of 1
Indication: Prevention of Dengue disease caused by Dengue Serotypes 1, 2, 3 and 4 in individuals
9 through 45 years of age living in endemic areas.

Subcutaneous (SC) use after reconstitution
Subcutanea (SC) después de la reconstrucción

SANOFI PASTEUR

Manufactured by:
Sanofi Pasteur
Lyon, France
Imported by:
Sanofi Pasteur, Inc.
Makati City, Philippines

Caution: Foods, Drugs, Cosmetics & Cosmetics Act prohibits dispensing
without prescription.
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**
Prevention (fumigation) with Avate: cypermethrine and boric acid
Dengue

Management

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

- **DHF/DSS:**
  - Hospitalization
  - ICU
  - Supportive care
Dengue inpatient management
### 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>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>Yes (Not FDA app)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>DEET</td>
<td>DEET</td>
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# DF, CHIKF & ZF: clinical & lab differences

Table by José Darío Martínez, MD

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<thead>
<tr>
<th>Feature</th>
<th>Dengue</th>
<th>Chikungunya</th>
<th>Zika</th>
</tr>
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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, 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>
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DF, CHIKF & ZF: complications & Rx
Table by José Darío Martínez, MD

<table>
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<tr>
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<th>Dengue</th>
<th>Chikungunya</th>
<th>Zika</th>
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</thead>
<tbody>
<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>
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</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>
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</tr>
<tr>
<td>Rx</td>
<td>Supportive</td>
<td>Supportive</td>
<td>Supportive</td>
</tr>
</tbody>
</table>
Advertising at the airports & in the streets in México!
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
Summary

- No vaccines approved by the FDA yet
- In México & Brazil a DF vaccine was approved
- CHIKF cycle last longer than DF
- Zika is more dangerous than DF & CHIKF
- Rx: acetaminophen, supportive therapy
- Genetic modified mosquitoes introduced in Brazil
- What is next? Mayoro virus? Yellow fever?
Mosquitoes remind us that we are not as high up on the food chain as we think.
Dermatology & Baseball…

“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
Thank you! Gracias!

Email: jdariomtz@yahoo.com.mx

El Castillo, Chichen Itzá, Yucatán, México