UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

KILLER BITES:
Mosquito-Borne Viruses

Jon Mark Hirshon, MD, MPH, PhD
Professor, Department of Emergency Medicine
University of Maryland School of Medicine

Aedes Aegypti

Disclosures

- Conflicts of Interest:
  - Pfizer consultant related to Sickle Cell Disease

Presentation Objectives

- Identify at least 3 mosquito-borne viruses potentially transmitted in the Continental U.S.
- Briefly discuss arboviruses and vectors
  - Include review of disease epidemiology
- Discuss West Nile, Dengue and Zika Viruses

ARBOVIRUSES AND VECTORS

Mosquito-Borne Viruses

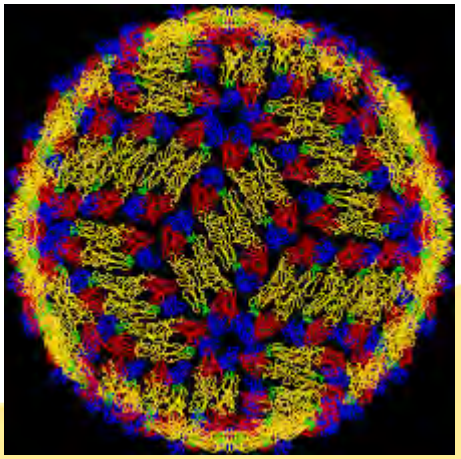
- West Nile Virus
- Dengue
- Zika Virus
- Chikungunya
- Yellow Fever
- St. Louis Encephalitis
- Jamestown Canyon Virus
- Western Equine Encephalitis
- Eastern Equine Encephalitis
- La Crosse Encephalitis

And many others…

Terms

- **Arboviruses:**
  - **AR**thropod-**BO**rne virus
- **Arthropods**
  - E.g: mosquitos, ticks, sandflies
- **Flaviviridae (family)**
  - Flavivirus (genus)
    - Single stranded RNA viruses

Dengue Virus



www.purdue.edu/uns/html4ever/020307.Kuhn.dengue.html

Arboviruses

- Transmitted by arthropods
- Can have rare person-to-person transmission
  - Blood borne
    - Transfusion, sharing needles
  - Organ transplantation
  - Breast feeding
  - Intrauterine
  - Sexual transmission

Aedes albopictus

en.wikipedia.org/wiki/Aedes_albopictus

Major Arbovirus Viral Families

- **Family *Bunyaviridae***
  - *Rift Valley, Crimean–Congo hemorrhagic*
- **Family *Flaviviridae***
  - *Dengue, West Nile, Zika, Yellow Fever*
- **Family *Reoviridae***
  - *Equine encephalosis*
- **Family *Togaviridae***
  - *Chikungunya, Western equine encephalitis*

Flaviviridae: Flavivirus

- **Mosquito-borne viruses**
  - Dengue virus group
    - *Dengue virus* (DENV)
  - Japanese encephalitis virus group
    - *Japanese encephalitis virus* (JEV)
    - *Murray Valley encephalitis virus* (MVEV)
    - *St. Louis encephalitis virus* (SLEV)
    - *West Nile virus* (WNV)

- **Mosquito-borne viruses (cont.)**
  - Spondweni group
    - *Spondweni virus*
    - *Zika virus* (ZIKV)
  - Yellow fever virus group
    - *Yellow fever virus* (YFV)

- **Tick-borne viruses**
  - Mammalian tick-borne virus group
    - *Kyasanur forest disease* virus (KFDV)
    - *Tick-borne encephalitis virus* (TBEV)

Vector for:
Dengue virus, Yellow Fever virus, Chikungunya virus, and Zika virus

Photo From: https://colekcolek.com/2012/07/26/first-in-the-world-dengue-fever-vaccine/

DENGUE FEVER

Dengue Fever: "Break-bone Fever"

Virus genus	Flavivirus
Transmission	Mosquito-borne (*Aedes sp)*
Amplifying host	Humans/primates
Global Distribution	Primarily tropical and subtropical (similar to Yellow Fever)
U.S. Continental Distribution	Rarely South Texas (Found in Puerto Rico, the U.S. Virgin Islands, Samoa and Guam)
Vaccine	None currently available in US
Treatment	Symptomatic

Worldwide Tropical Distribution

https://www.cdc.gov/dengue/epidemiology/index.html

Dengue Viruses

- Four serotypes
  - Provides long-term serotype specific immunity
  - Short-term cross-immunity
- All serotypes can cause severe/fatal disease
- Most important arboviral disease
  - >2.5 billion people at risk globally
  - **Dengue hemorrhagic fever (DHF)** mortality rate 2%-5%.
    - Untreated- mortality rate as high as 50%

Dengue Fever – Mode of Transmission

Infected mosquito

Healthy person

Infected person

Incubation Period: 3 to 14 days
Most commonly 4 to 7 days

Dengue fever is not spread by contact with infected persons.

Diagnosis of Dengue

- **Good Clinical Acumen**
- First 7 days of illness
  - viral RNA can often be identified in serum
  - RT-PCR is the preferred test
    - Dengue, Zika, Chikungunya
- Virus specific IgM antibodies may be detectable >4 days after onset of illness.
  - strong cross reactivity with other flaviviruses

Dengue Fever - Symptoms

- **High fever:**
  - Continuous for 2 to 7 days
- **Severe headache**
  - Retro-orbital
- **Joint, muscle, and back pain**
- **Nausea, vomiting**
- **Rash**
  - Including maculopapular
- **May worsen into DHF**
  - Leading to internal bleeding, shock, or even death.

Dengue Treatment

- Symptomatic treatment
- Hydration
- Avoid aspirin and non-steroidal
  - Use acetaminophen
- Monitor hematocrit and platelets

DHF Criteria

- Fever lasting 2-7 days
  - May be biphasic
- Hemorrhagic tendencies
  - Positive tourniquet (aka Rumpel-Leede) test
  - Petechiae, ecchymosis or purpura
  - GI bleeding
- Thrombocytopenia (<100,000/mm^3)
- Evidence of plasma leakage
  - Increase in hematocrit >20% above age/sex normal
  - Decrease in hematocrit >20% after volume replacement
  - Signs of plasma leakage
    - e.g. pleural effusions, ascites, hypoproteinemia

DHF Treatment

- Supportive Care
- Careful fluid management
  - Aggressively hydrate if dehydrated
  - Slow/stop intravenous fluids if adequate hydration is present
- Proactive treatment of hemorrhage
  - Platelet and fresh frozen plasma transfusions

Flaviviridae: Flavivirus

- **Mosquito-borne viruses**
  - Dengue virus group
    - *Dengue virus* (DENV)
  - Japanese encephalitis virus group
    - *Japanese encephalitis virus* (JEV)
    - *Murray Valley encephalitis virus* (MVEV)
    - *St. Louis encephalitis virus* (SLEV)
    - *West Nile virus* (WNV)

- **Mosquito-borne viruses (cont.)**
  - Spondweni group
    - *Spondweni virus*
    - *Zika virus* (ZIKV)
  - Yellow fever virus group
    - *Yellow fever virus* (YFV)

- **Tick-borne viruses**
  - Mammalian tick-borne virus group
    - *Kyasanur forest disease* virus (KFDV)
    - *Tick-borne encephalitis virus* (TBEV)

West Nile Virus

www.cdc.gov/vhf/virus-families/flaviviridae.html

Culex pipiens

Vector for:
West Nile virus, Japanese encephalitis, St. Louis encephalitis, and Western and Eastern Equine Encephalitis.

Photo from https://cameronwebb.wordpress.com/tag/culex-pipiens/

WEST NILE VIRUS

West Nile Virus

Virus genus	Flavivirus
Transmission	Mosquito-borne (*Culex sp.*)
Amplifying host	Birds
Global Distribution	Worldwide
U.S. Continental Distribution	Through-out
Vaccine	No human vaccines
Treatment	Symptomatic

West Nile Virus

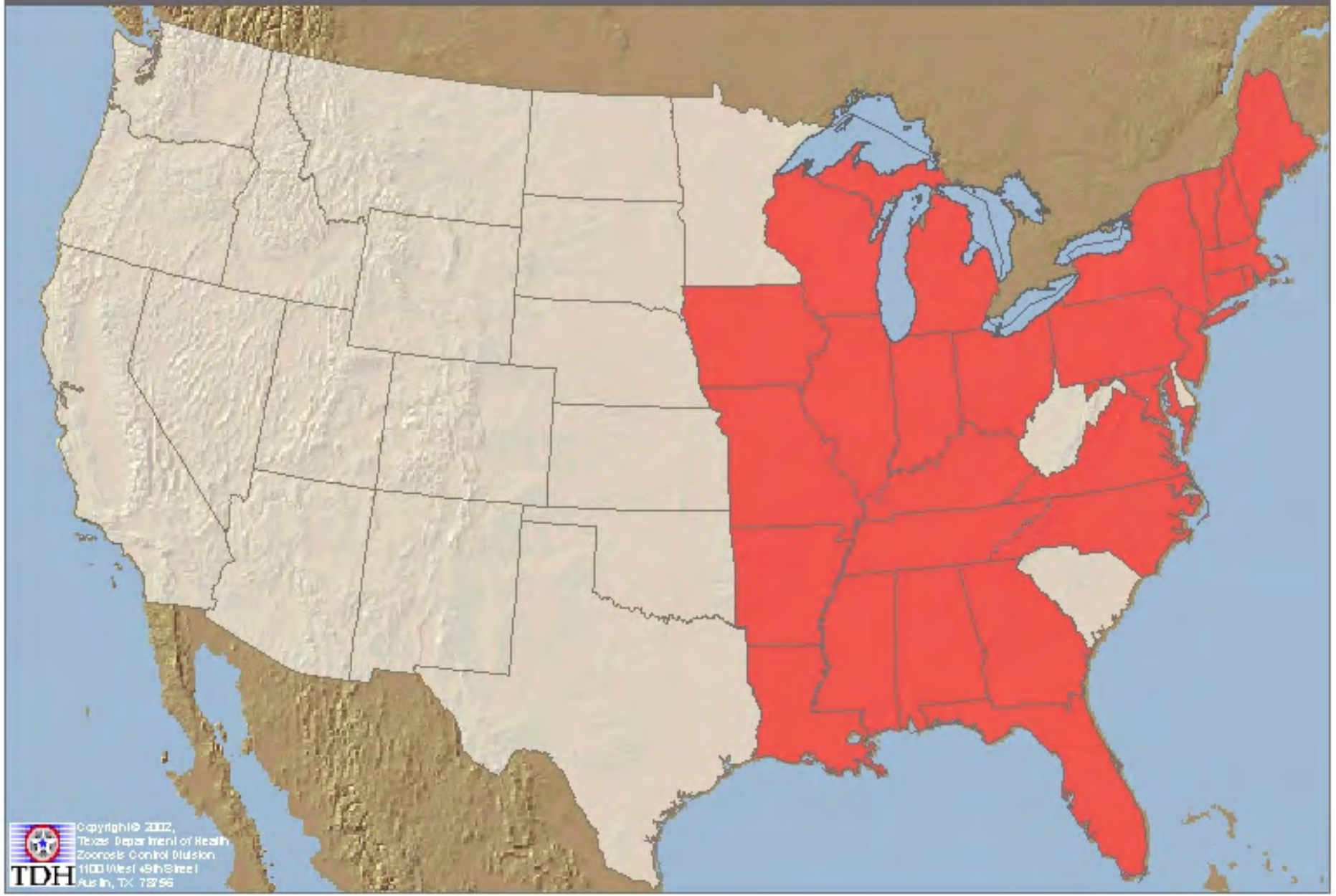
West Nile virus first identified in the West Nile Region of Uganda, Africa in 1937

First cases in the US in 1999…

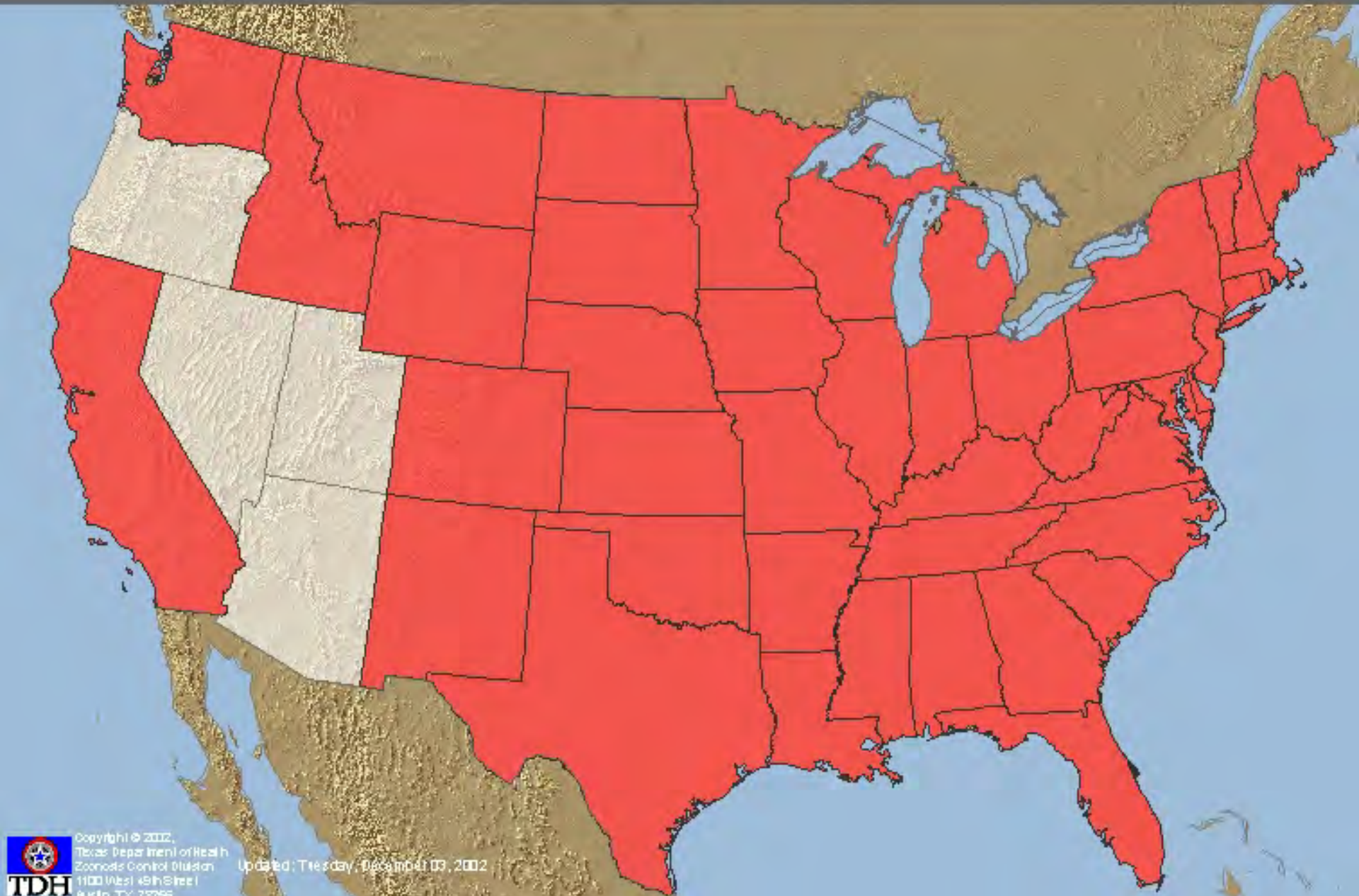
States with Laboratory Confirmed West Nile Virus In Animals or People, 1999

States with Laboratory Confirmed West Nile Virus In Animals or People, 2000

States with Laboratory Confirmed West Nile Virus In Animals or People, 2001



States with West Nile Virus In Animals or People: 2002

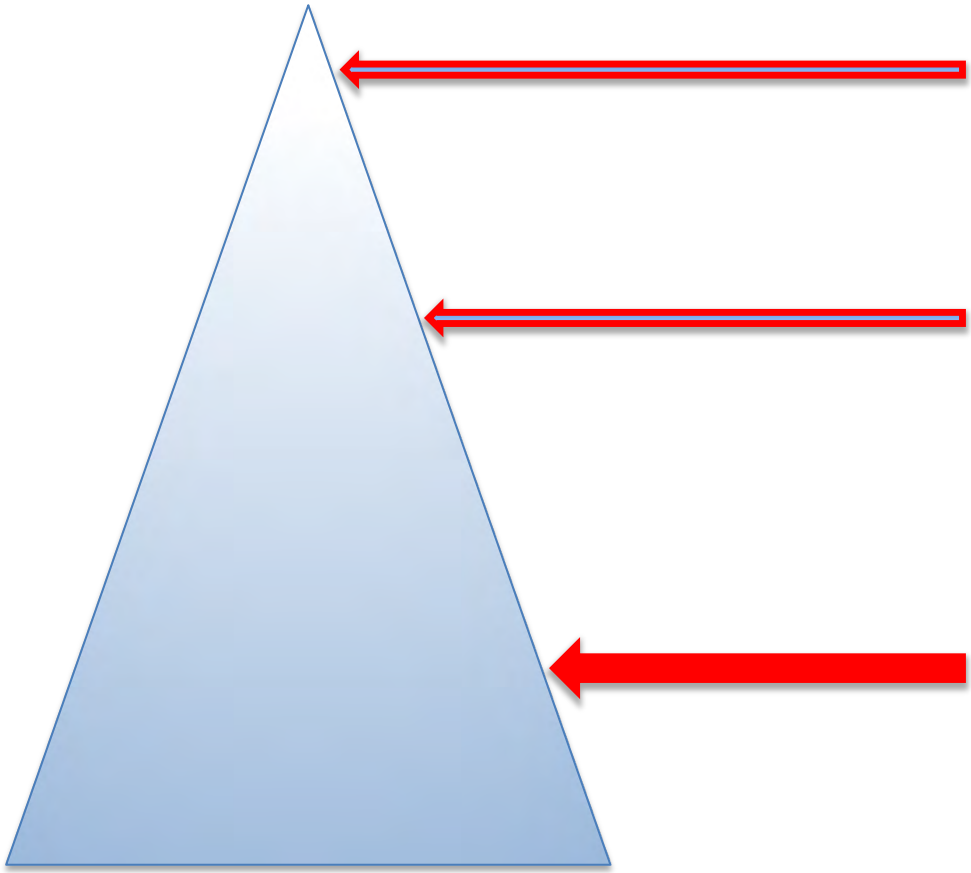


West Nile Virus Activity by State – United States, 2017 (as of January 9, 2018)

WNV in Humans

- **Incubation:** 2 to 14 days
  - Many WNV infections asymptomatic
  - Two forms of clinical disease
- **West Nile fever**
  - Most common form
  - Resembles influenza
  - Most infections resolve within a week
  - Some symptoms, such as fatigue, can persist

Clinical Spectrum of WNV



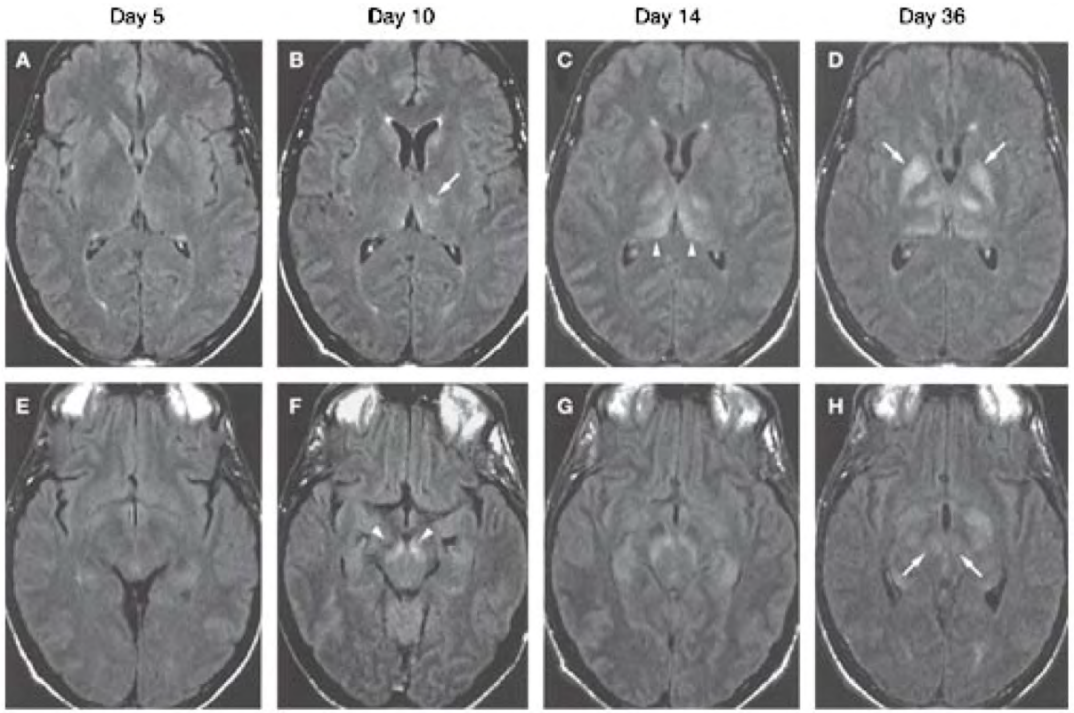
- **Neuroinvasive** (<1%)
- **Febrile illness** (20%-30%)
- **Asymptomatic infection** (70%-80%)

WNV Neuroinvasive Disease

- Occurs rarely (<1%)
  - Progression of West Nile fever
- Can be severe and life-threatening
  - Most cases require hospitalization
- Three syndromes
  - Encephalitis, Meningitis, Acute flaccid paralysis
- Persistent neurological dysfunction may occur
  - 50%-70% need assisted living or rehabilitation
- Case fatality- 10%

Symptoms of Neuro WNV

- Headache
- High fever
- Neck stiffness
- Disorientation
- Coma
- Tremors
- Seizures
- Paralysis



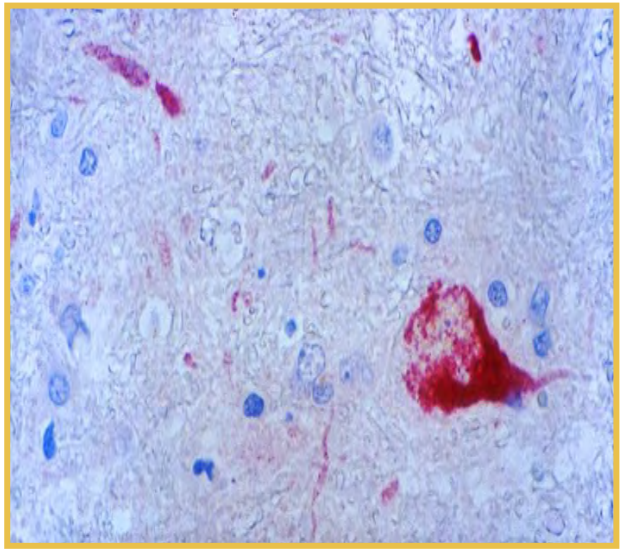
www.nature.com/nrneurol/journal/v2/n5/fig_tab/ncpneuro0176_F4.html

Risk Factors for Severe Disease

- Age >60 y/o
- Hypertension
- Diabetes
- Cancer
- Kidney disease
- H/O organ transplant

WNV Diagnosis in Humans

- **Good clinical acumen**
- Serology
  - Serum or CSF
  - IgM capture ELISA
    - Cross reactions possible
  - Plaque reduction neutralization test
- Detection of virus, antigen, or nucleic acids
  - RT-PCR
  - Immunohistochemistry



Center for Food Security and Public Health, Iowa State University, 2011

WNV Treatment

- Supportive care
- Manage complications
- No proven antiviral or adjuvant therapy

Flaviviridae: Flavivirus

- **Mosquito-borne viruses**
  - Dengue virus group
    - *Dengue virus* (DENV)
  - Japanese encephalitis virus group
    - *Japanese encephalitis virus* (JEV)
    - *Murray Valley encephalitis virus* (MVEV)
    - *St. Louis encephalitis virus* (SLEV)
    - *West Nile virus* (WNV)

- **Mosquito-borne viruses (cont.)**
  - Spondweni group
    - *Spondweni virus*
    - *Zika virus* (ZIKV)
  - Yellow fever virus group
    - *Yellow fever virus* (YFV)

- **Tick-borne viruses**
  - Mammalian tick-borne virus group
    - *Kyasanur forest disease* virus (KFDV)
    - *Tick-borne encephalitis virus* (TBEV)

What is the common name for the *Aedes albopictus* mosquito?

- Common house mosquito
- Southern house mosquito
- That @#$@# mosquito
- Flying tiger mosquito
- Asian tiger mosquito

Aedes albopictus

en.wikipedia.org/wiki/Aedes_albopictus

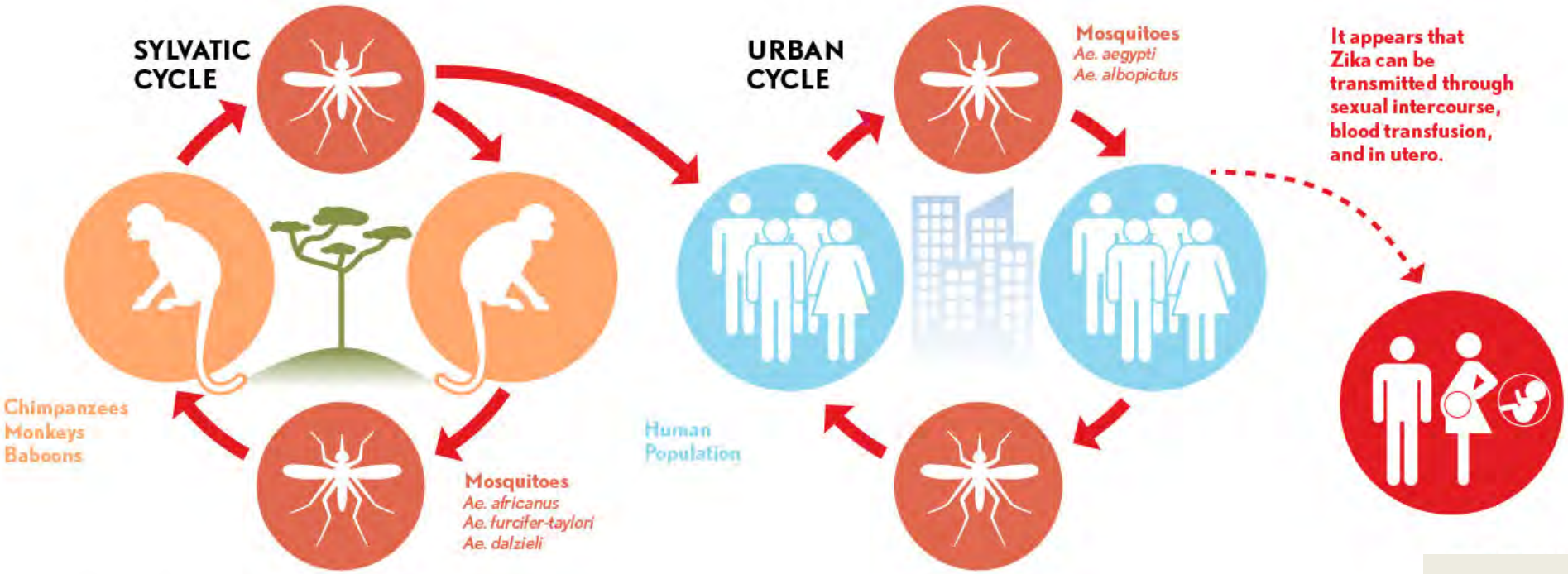
ZIKA VIRUS

Zika Virus

Virus genus	**Flavivirus**
Transmission	**Mosquito-borne *(Aedes sps.)***
Amplifying host	**Humans/primates**
Global Distribution	**Tropical**
U.S. Continental Distribution	**Rarely South Texas, Florida (found in Puerto Rico, the U.S. Virgin Islands)**
Vaccine	**None available**
Treatment	**Symptomatic**

How the Zika Virus Enters the Human Population

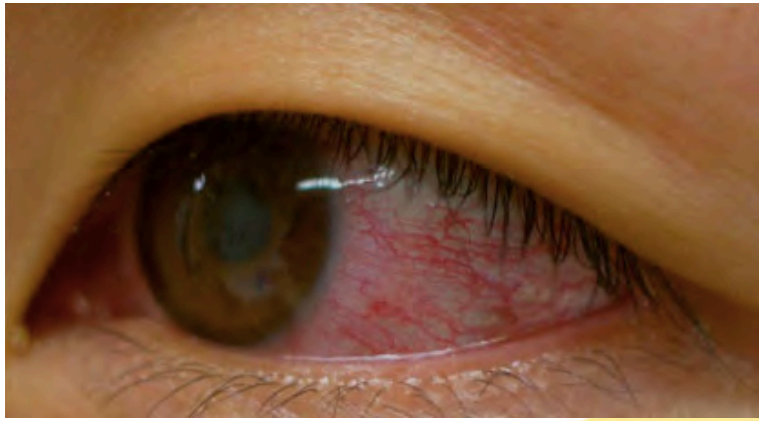
The virus originates with nonhuman primates in tropical rainforests but can infect humans. Warm, urban environments with standing pools of water attract mosquitoes, and can lead to the virus's spread.



Zika Virus Symptoms

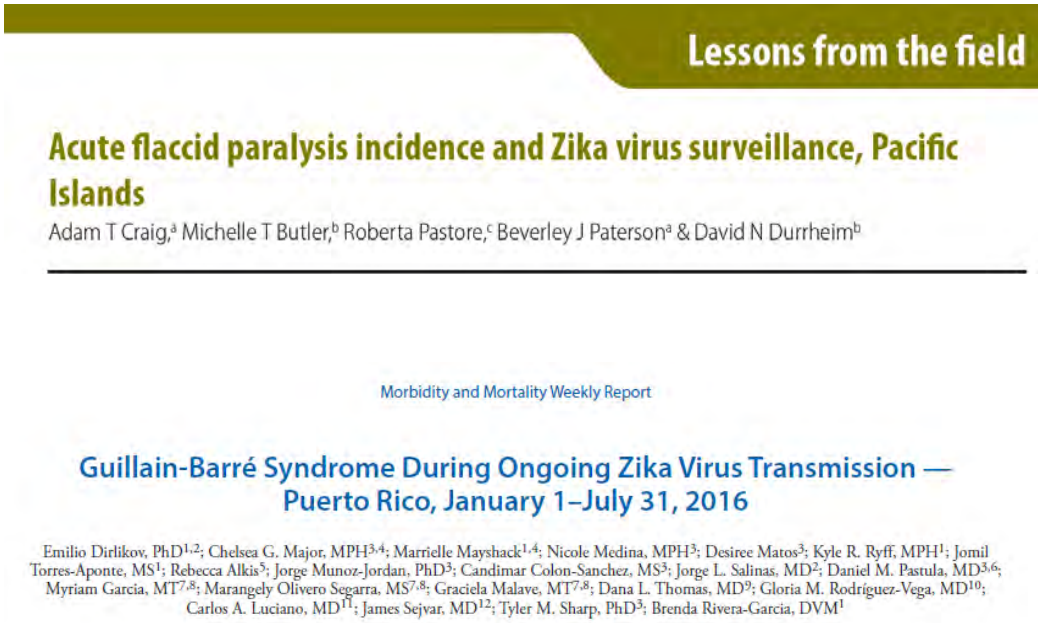
- **Most common symptoms**
  - Fever
  - Rash
  - Muscle and joint pain
  - Conjunctivitis (pink eye)
  - Headache

  Occur 2-14 days after insect bite
- Most illnesses are mild
- Symptoms last 5 days
- Death is rare



Zika Virus Complications

- Guillain-Barre Syndrome (GBS): muscle weakness/ paralysis; can affect breathing
  - Lasts weeks to months
  - 1 in 20 die
- Meningoencephalitis
- Myelitis
- Peripheral neuropathy



Lessons from the field

Acute flaccid paralysis incidence and Zika virus surveillance, Pacific Islands

Adam T Craig,[a] Michelle T Butler,[b] Roberta Pastore,[c] Beverley J Paterson[a] & David N Durrheim[b]

Morbidity and Mortality Weekly Report

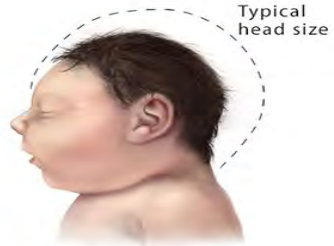
Guillain-Barré Syndrome During Ongoing Zika Virus Transmission — Puerto Rico, January 1–July 31, 2016

Emilio Dirlikov, PhD[1,2]; Chelsea G. Major, MPH[3,4]; Marrielle Mayshack[1,4]; Nicole Medina, MPH[3]; Desiree Matos[3]; Kyle R. Ryff, MPH[1]; Jomil Torres-Aponte, MS[1]; Rebecca Alkis[5]; Jorge Munoz-Jordan, PhD[3]; Candimar Colon-Sanchez, MS[3]; Jorge L. Salinas, MD[2]; Daniel M. Pastula, MD[3,6]; Myriam Garcia, MT[7,8]; Marangely Olivero Segarra, MS[7,8]; Graciela Malave, MT[7,8]; Dana L. Thomas, MD[9]; Gloria M. Rodríguez-Vega, MD[10]; Carlos A. Luciano, MD[11]; James Sejvar, MD[12]; Tyler M. Sharp, PhD[3]; Brenda Rivera-Garcia, DVM[1]

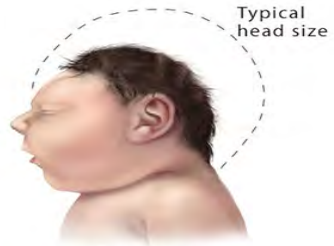
Congenital Zika Syndromes

- **Microcephaly (small head)*****
- Other defects
  - Hearing/vision problems
  - Seizures
  - Developmental delay/cognitive impairment/absent or poorly developed brain structures
  - Intracranial calcifications
  - Miscarriage, stillbirth
  - Limb abnormalities,
  - Impaired growth
- A lifelong problem!


Baby with Typical Head Size



Baby with Microcephaly



Baby with
Severe Microcephaly

Zika Diagnosis & Treatment

- No currently available commercial test
- RT-PCR during first week of illness
- Treatment is symptomatic and supportive

Zika Virus – The next big thing?

- "Zika is not contagious in the way that Ebola is, nor is it as lethal (fever, rash, joint pain) but it appears to strike in an especially cruel way – depressing brain growth in babies born to infected mothers. And like so many other pathogens that preceded it, the Zika virus has seemingly whirled out of nowhere, reinforcing how difficult it is to predict confidently which ones will go rogue. It only appeared in Brazil last May and is forecast to affect up to four million across the Americas by the end of this year."

http://www.telegraph.co.uk/news/worldnews/southamerica/12134625/Zika-is-the-latest-face-of-an-ancient-enemy.html

“The World Health Organization announced Thursday it will hold an emergency meeting next to week on how to confront the Zika virus, which it said is spreading explosively in the Americas”

World Health Organization

Public Health Emergency of International Concern

- Extraordinary event which is determined:
  - to constitute a public health risk to other States through the international spread of disease; and
  - to potentially require a coordinated international response

- Implies a situation that
  - is serious, unusual or unexpected
  - carries implications for public health beyond the affected State's national border
  - may require immediate international action

WHO Declaration of PHEIC

- April 2009

  When the **H1N1 pandemic** was still in Phase Three
- May 2014

  With the resurgence of **polio** after its near-eradication
- August 2014

  In response to the outbreak of **Ebola** in Western Africa
- February 2016

  Amid fears the mosquito-borne **Zika** virus is linked to birth defects and spreading rapidly

ARBOVIRUSES

	Distribution	Main Complications	Treatment	Main Vector
Dengue	Tropical/ Subtropical	Hemorrhagic Fever	Supportive	*Aedes sps.*
West Nile	Throughout the US	Neurologic	Supportive	*Culex sps.*
Zika	Tropical/ Subtropical	Congenital	Supportive	*Aedes sps.*

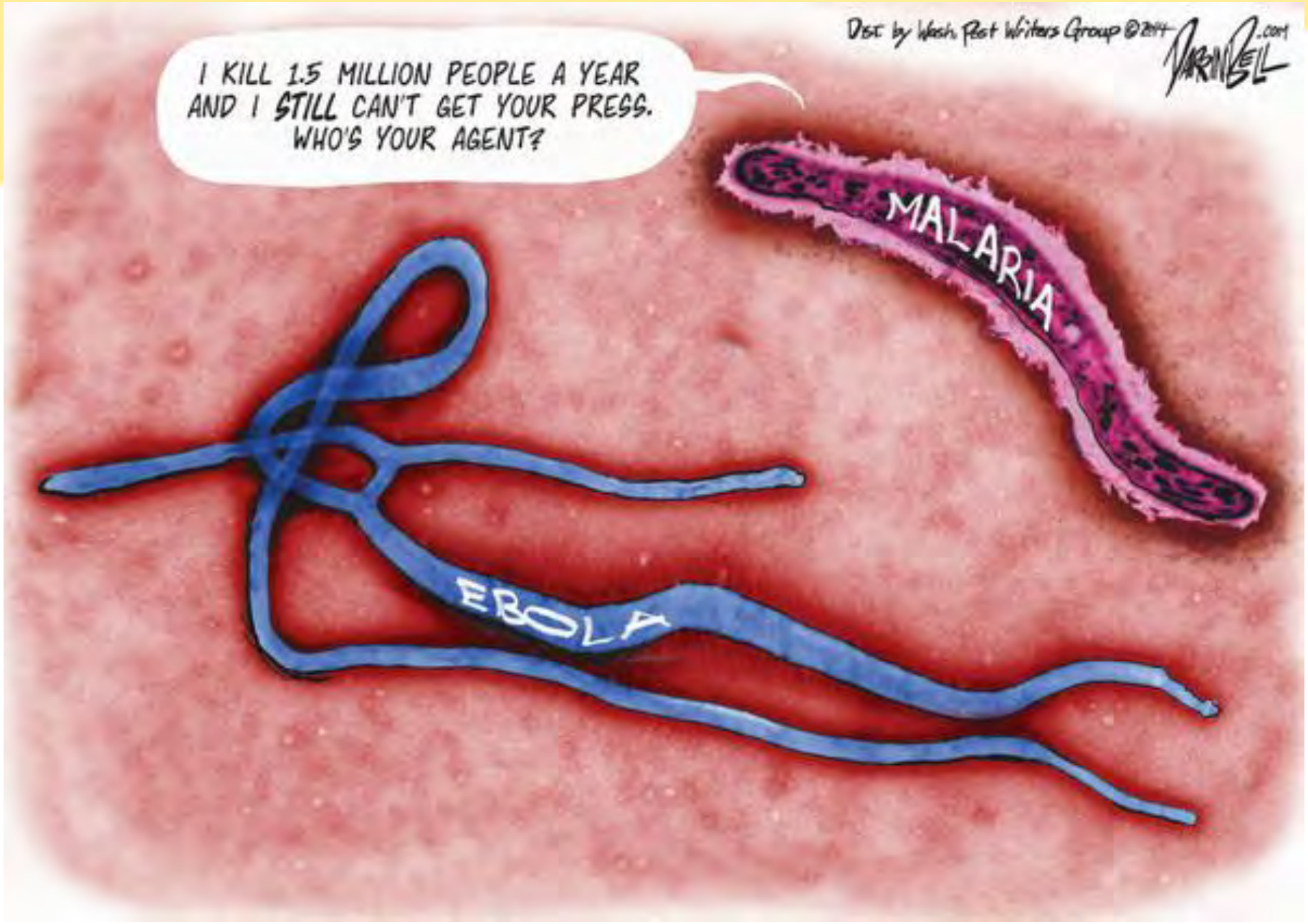
VECTOR BORNE VIRSUSES: PREVENTIVE MEASURES

Prevention Measures: Travelers

- If traveling to an endemic area
  - Wear pants and long sleeved shirts
  - Use approved mosquito repellants
  - Stay in places with screening/air-conditioning
- Pregnant women should avoid travel to Zika endemic areas

Preventive Measures: Sexual Partners

- For patients at risk for sexual transmission
  - Abstain from sex or use a barrier method
    - At least 8 weeks after illness onset if a female partner is likely to have Zika
    - At least 6 months after illness onset if a male partner is likely to have Zika


Dist. by Wash. Post Writers Group ©2014
DARKOW .com
I KILL 1.5 MILLION PEOPLE A YEAR AND I STILL CAN'T GET YOUR PRESS. WHO'S YOUR AGENT?
MALARIA
EBOLA

- jhirshon@acep.org
- jhirshon@umaryland.edu
- Twitter:@DrJonMark

Chikgunya

Virus family/genus	Togaviridae/Alphavirus
Transmission	Mosquito-borne *(Aedes sps)*
Amplifying host	Humans
Global Distribution	Multiple countries
U.S. Continental Distribution	Florida (also found in Puerto Rico and US Virgin Islands)
Vaccine	None available
Treatment	Symptomatic

Yellow Fever

Virus genus	**Flavivirus**
Transmission	**Mosquito-borne *(Aedes sps, Haemagogus sps)***
Amplifying host	**Humans/primates**
Global Distribution	**Primarily tropical and subtropical (similar to Dengue)**
U.S. Continental Distribution	**Not currently in the US**
Vaccine	**Available**
Treatment	**Symptomatic**