# Emerging Pathogens

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**OVERVIEW**

- Definitions
- Arboviral Encephalitides
- Arboviral Hemorrhagic Fevers

# ARBOVIRUSES

- Arboviruses are naturally maintained in cycles by hematophagous arthropods that **biologically** transmit the virus between vertebrate hosts.

- Vector usually becomes infected by ingesting the **viremic blood** from a vertebrate host, or through transovarial transmission, or venereal transmission.

# ARBOVIRUSES

- Typically, the arbovirus does not exert a deleterious effect on the vector.

- However, the virus may be extremely pathogenic to vertebrate hosts, especially tangential (abnormal) hosts.

# Arthropod-borne Viruses

Arboviruses are viruses that can be transmitted to man by arthropod vectors. The WHO definition is as follows:

"Viruses maintained in nature principally, or to an important extent, through biological transmission between susceptible vertebrate hosts by haematophagus arthropods or through transovarial and possibly venereal transmission in arthropods."

Arboviruses belong to three families:

- Togaviruses
- Bunyaviruses
- Flaviviruses

# Types of Transmission Cycles

- Man – arthropod vector - man
  - e.g. dengue, chikungunya, zika, urban yellow fever.
  - Reservoir may be in either man or arthropod vector.
  - In the latter transovarial transmission may take place.
- Animal - arthropod vector - animal
  - e.g. Japanese encephalitis, West Nile virus, jungle yellow fever.
  - The reservoir is a non-human vertebrate animal.
  - The virus is maintained in nature in a transmission cycle involving the arthropod vector and animal. Humans become infected incidentally.
- Both cycles may be seen with some arboviruses such as yellow fever virus.

# Types of Arthropod Vectors of Arboviruses

## Mosquitoes

Japanese encephalitis, dengue, chikungunya, zika, yellow fever, SLE, WNV, EEE, WEE, VEE, LAC, etc.

## Ticks

Crimean-Congo hemorrhagic fever, various tick-borne encephalitides

## Sandflies

Sicilian sandfly fever, Rift valley fever

SLE = St. Louis encephalitis; WNV = West Nile virus; EEE = Eastern Equine encephalitis; WEE = Western Equine encephalitis; VEE = Venezuelan Equine encephalitis; LAC = LaCrosse encephalitis

# Types of Animal Reservoirs of Arboviruses

In some cases, the actual reservoir is not known. The following animals have been implicated as reservoirs:

| | |
|---|---|
| Birds | Japanese encephalitis, SLE, WEE EEE, WNV |
| Pigs | Japanese encephalitis |
| Monkeys | Yellow Fever, dengue (in Old World) |
| Rodents | VEE, Russian Spring-Summer encephalitis, LAC |

# Symptoms/Disease

- Fever, rash, muscle/joint pain - this is usually a non-specific illness resembling a number of other viral illnesses such as influenza, rubella, and enterovirus infections. The patients may go on to develop mild encephalitis or hemorrhagic fever. (e.g. uncomplicated dengue, zika, chikungunya)
- Encephalitis - e.g. WNV, EEE, St Louis encephalitis, Japanese encephalitis.
- Hemorrhagic fever - e.g. yellow fever, complicated dengue, Crimean-Congo hemorrhagic fever.

# Diagnosis

- Serology – antibody detection used to make a diagnosis of past arbovirus infections (IgM - recent, IgG - past).
- Culture - a number of cell lines may be used, including mosquito cell lines. However, it is rarely carried out since many of the pathogens are biosafety level (BSL) 3 or 4 pathogens.
- Direct Detection Tests - e.g, detection of antigen and nucleic acids are available but again there are BSL issues if virus is live.
- Rapid Tests/Kits – may use antibody or antigen (usually inactivated). Quick w/ improved safety.

# Prevention

- Surveillance - of disease and vector populations
- Control of vector - insecticides, environmental manipulation, genetic control, etc.
- Personal protection - screening of houses, bed nets, insect repellants
- Vaccination - available for a number of arboviral infections, e.g., Yellow fever, Japanese encephalitis, Russian tick-borne encephalitis

# Important Mosquito-Borne Viruses

- *Eastern Equine Encephalitis virus (EEE)*
- *Lacrosse Encephalitis virus (LAC)*
- *St. Louis Encephalitis virus (SLE)*
- *West Nile virus (WNV) - in US since 1999*
- Dengue virus (DEN) – recent in South Florida, South Texas and Hawaii
- Chikungunya virus (CHIK)
- Venezuelan Equine Encephalitis virus (VEE)
- Zika virus (ZIKV)
- Japanese Encephalitis virus (JEV)
- Rift Valley Fever virus (RVF)
- Yellow Fever virus (YFV)

Occur regularly in the US. Occur occasionally in the US. Not currently in the US.

# Arboviral Encephalitis - General

- **Seasonal - usually warm months**
- **Incidence varies with time and place - ecological factors**
- **Causative viruses differ greatly in case-infection ratio (clinical to subclinical infection)**
- **Humans are not an important amplifying host**
- **Togaviridae *(Alphavirus)*, Bunyaviridae, Flaviviridae**

# Arboviral Encephalitis - Pathogenesis

- **Initial viremia from lymphoid system - little or no recognized disease during viremic phase**
- **Initial nonspecific symptoms - fever, abdominal pain, vertigo, sore throat, respiratory symptoms**
- **Secondary symptoms - headache, photophobia, vomiting, lethargy, convulsions, coma, death**
- **CNS invasion - CNS disease (encephalitis) from neuronal infection and damage associated with edema & inflammation**

# Arboviruses of the Gulf South

- Eastern equine encephalitis virus (EEEV)
- St. Louis encephalitis virus (SLEV)
- West Nile virus (WNV)

} Bird - Mosquito

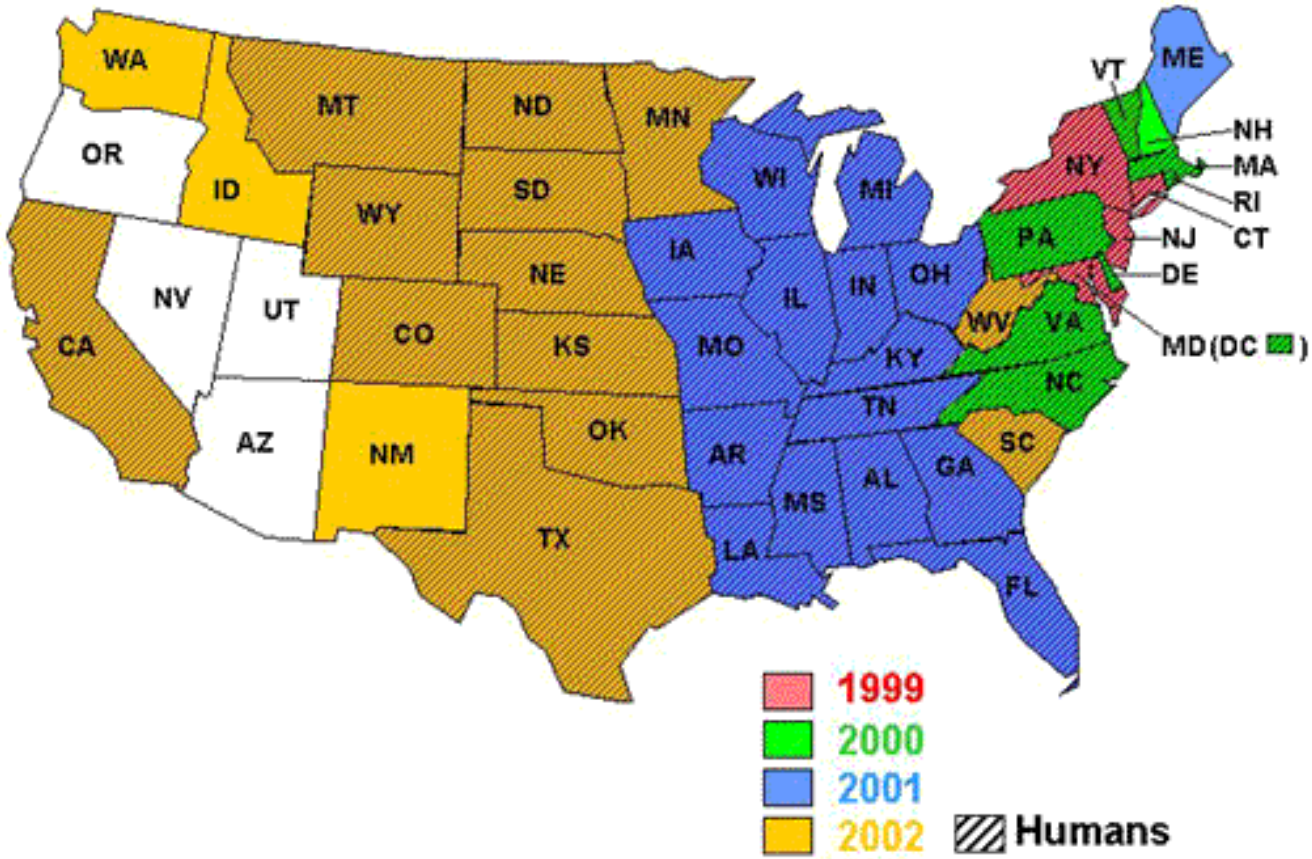
- LaCrosse encephalitis virus (LACV) Rodent - Mosquito
- Dengue virus (DENV)
- Chikungunya virus (CHIKV)
- Zika (ZIKV)

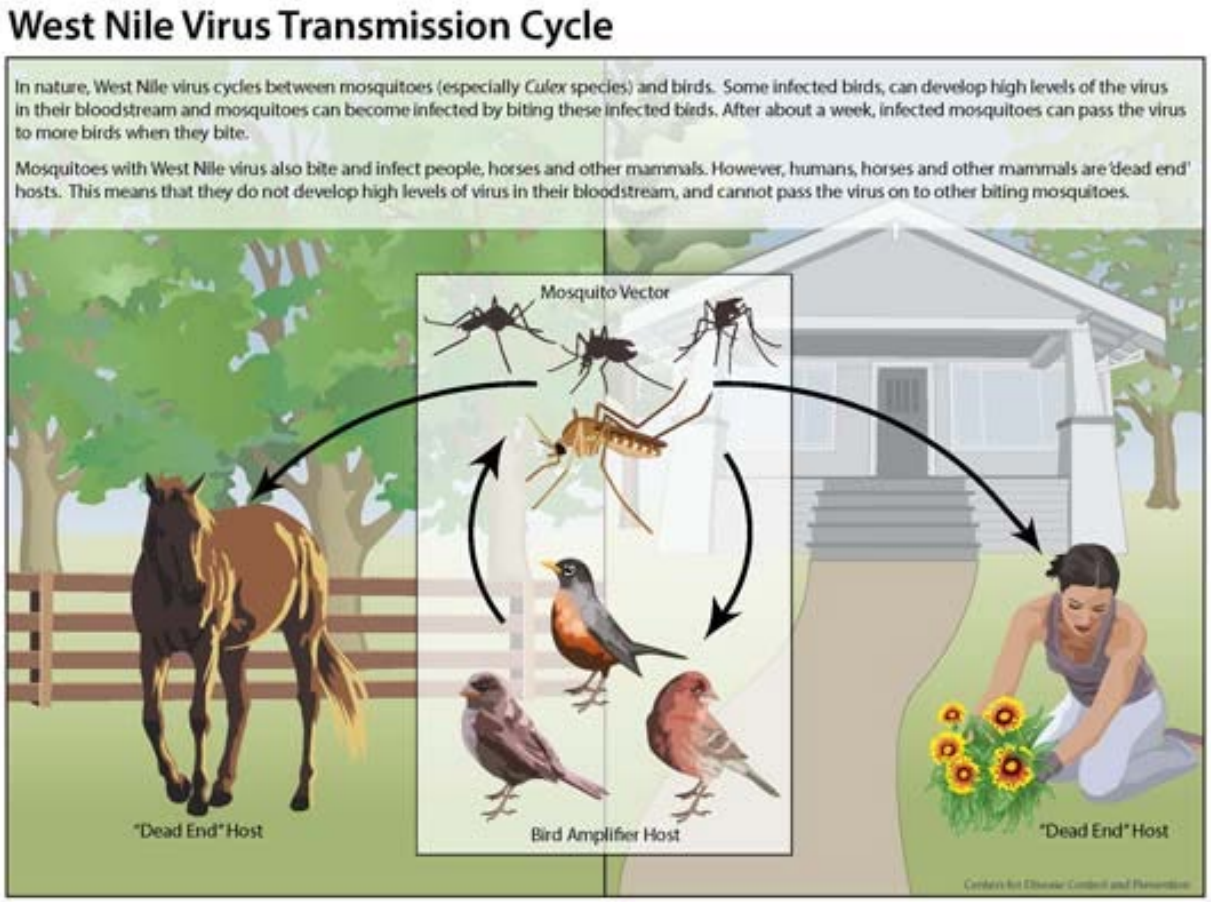
} Human - Mosquito

# West Nile Virus: Background

- First isolated in 1937 in Uganda from blood of a febrile woman.
- Family: Flaviviridae
  - Genus: Flavivirus
  - Japanese Encephalitis Antigenic Complex
  - Complex includes: Alfuy, Japanese encephalitis, Kokobera, Koutango, Kunjin, Murray Valley encephalitis, St. Louis encephalitis, Stratford, Usutu, and West Nile viruses.
- All are transmissible by mosquitoes, many can cause febrile, sometimes fatal, illnesses in humans.

# West Nile Virus in the United States, 1999 - 2002



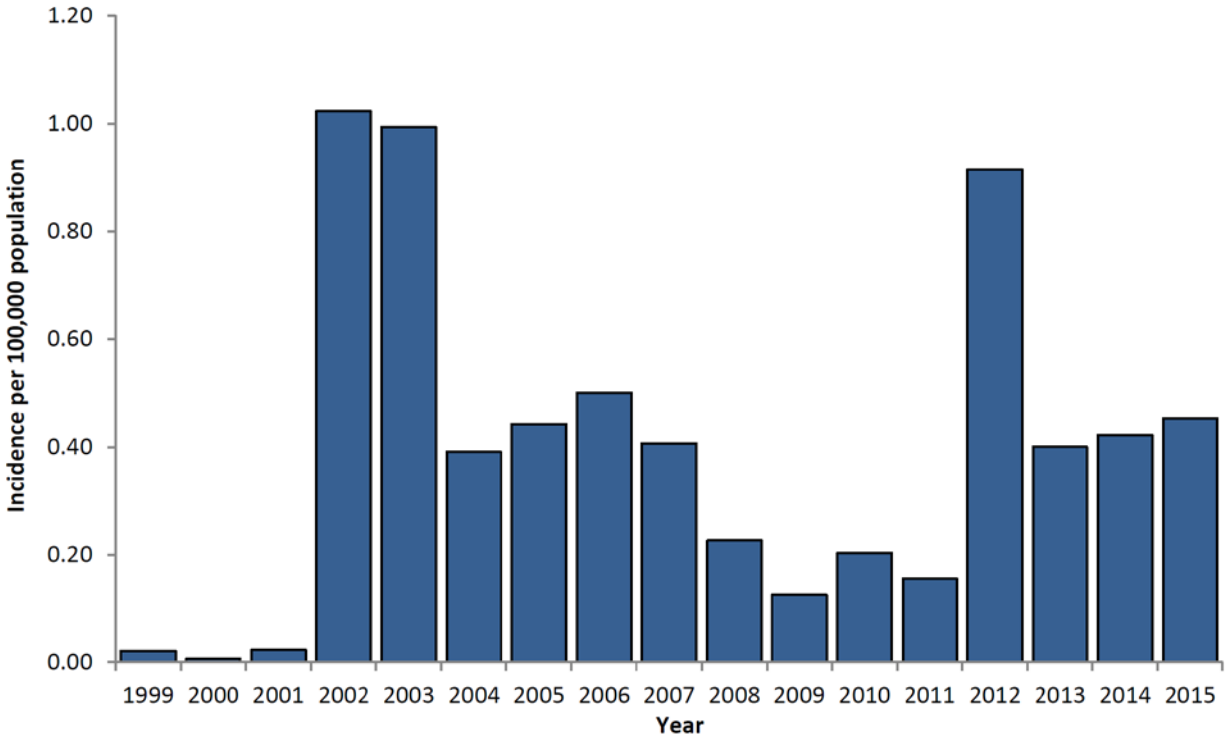



- Tends to be more severe in elderly adults
- In LA, *Cx. quinquefasciatus* and other *Culex* species; also *Aedes albopictus*
- Initially dead birds were an important surveillance indicator

# West Nile Neuroinvasive Disease (NID) in the United States, 1999 - 2012

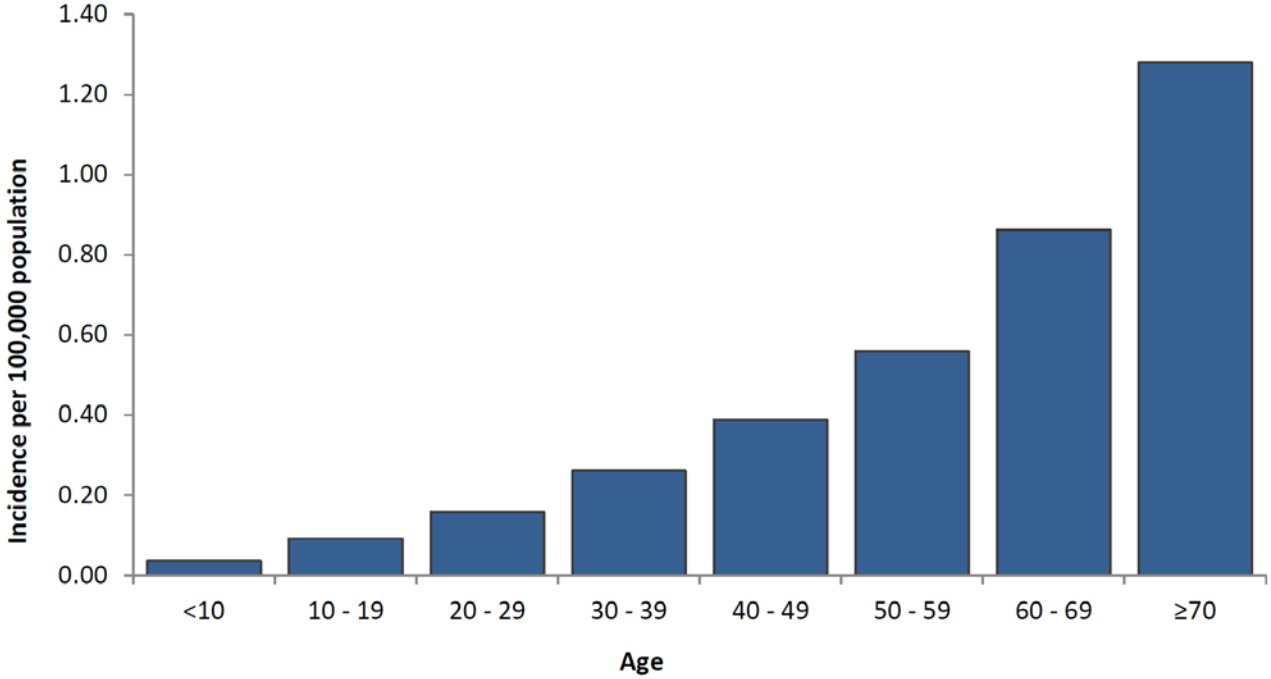
| Year | National WNV NID | National Deaths | National Mortality in Severe WNV |
|---|---|---|---|
| 1999 | 59 | 7 | 11.9% |
| 2000 | 19 | 2 | 10.5% |
| 2001 | 64 | 9 | 14.1% |
| 2002 | 2,946 | 284 | 9.6% |
| 2003 | 2,860 | 264 | 9.2% |
| 2004 | 1,142 | 100 | 8.8% |
| 2005 | 1,294 | 119 | 9.2% |
| 2006 | 1,459 | 177 | 12.1% |
| 2007 | 1,217 | 124 | 10.2% |
| 2008 | 687 | 44 | 6.4% |
| 2009 | 335 | 30 | 9.0% |
| 2010 | 601 | 45 | 7.5% |
| 2011 | 486 | 46 | 9.5% |
| 2012 | 2,734 | 243 | 8.9% |
| 2013 | 1,267 | 119 | 9.4% |
| 2014 | 1,347 | 97 | 7.2% |
| 2015 | 1,455 | 146 | 10.0% |
| 2016 | 1,140 | 94 | 8.2% |
| **Total** | **21,112** | **1,950** | **9.2%** |

**West Nile virus neuroinvasive disease incidence reported to CDC by year, 1999-2015**



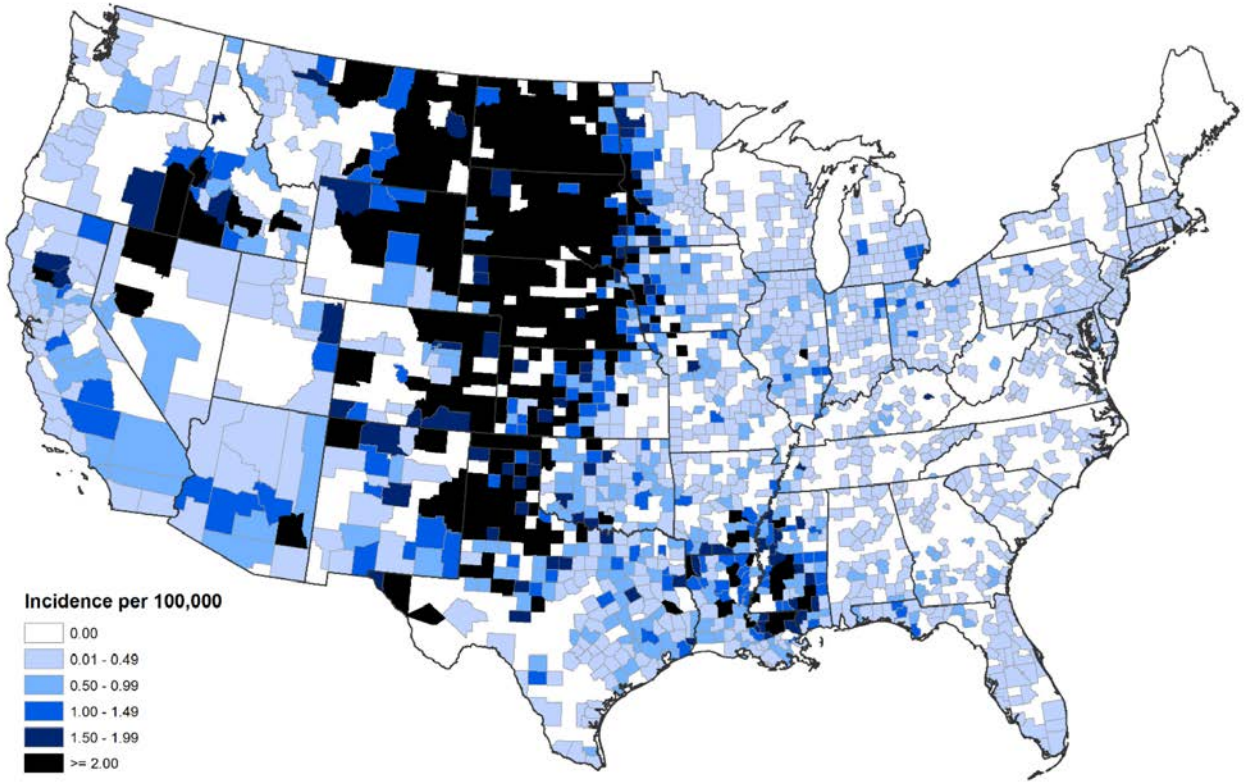

Source: ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention

**Average annual incidence of West Nile virus neuroinvasive disease reported to CDC by age group, 1999-2015**




Source: ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention

**Average annual incidence of West Nile virus neuroinvasive disease reported to CDC by county, 1999-2015**



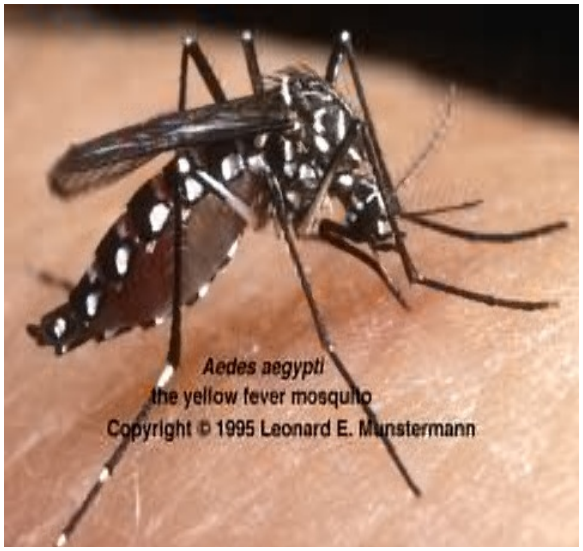
# *Aedes aegypti* Mosquito

**Several different arboviruses are transmitted in similar cycles by this species. What makes it such an effective vector?**

# *Aedes aegypti*

- Dengue/chikungunya/zika transmitted by infected female mosquito
- Primarily a daytime feeder
- Lives in and around human habitation
- Prefers to take blood from humans
- Lays eggs and produces larvae preferentially in artificial containers

*Aedes aegypti*




**Yellow Fever mosquito**

*Aedes albopictus*

**Asian Tiger mosquito**

# *Aedes albopictus*

- **Introduced to the US in 1985 via used tire trade. Found in many of the same habitats as *Aedes aegypti.***
- **Has since spread throughout the eastern US, and to many other countries in the New World.**
- **Known secondary and/or rural vector of dengue virus in SE Asia. But will take blood from many different non-human hosts.**
- **Competent laboratory vector of LaCrosse encephalitis virus, Eastern Equine encephalitis virus, West Nile virus and *Dirofilaria immitis* (dog heartworm).**

Andrew Haddow

# What is Zika?


www.ecologyasia.com

- Zika ia a single stranded positive sense RNA virus in the family Flaviviridae, genus Flavivirus
- Zika is related to other flaviviruses, such as the yellow fever virus, dengue virus and West Nile virus
- The virus was first isolated from a sentinel monkey located in the canopy of the Zika forest in Uganda in 1947, indicating a zoonotic origin of the virus

**Many people infected with Zika virus won’t have symptoms or will only have mild symptoms. The most common symptoms of Zika are:**

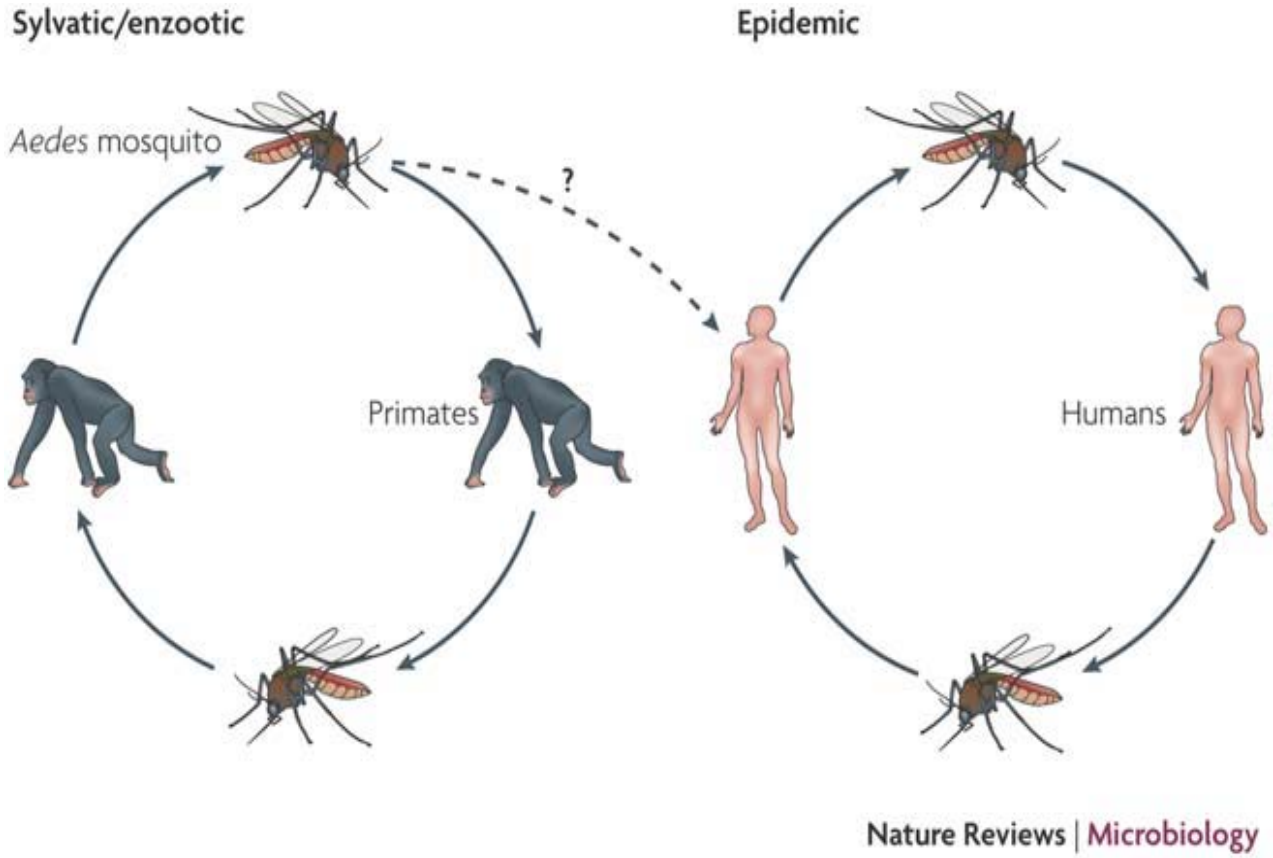
- **Fever**
- **Rash**
- **Joint pain**
- **Conjunctivitis**

**Other symptoms include:**

- **Muscle pain**
- **Headache**

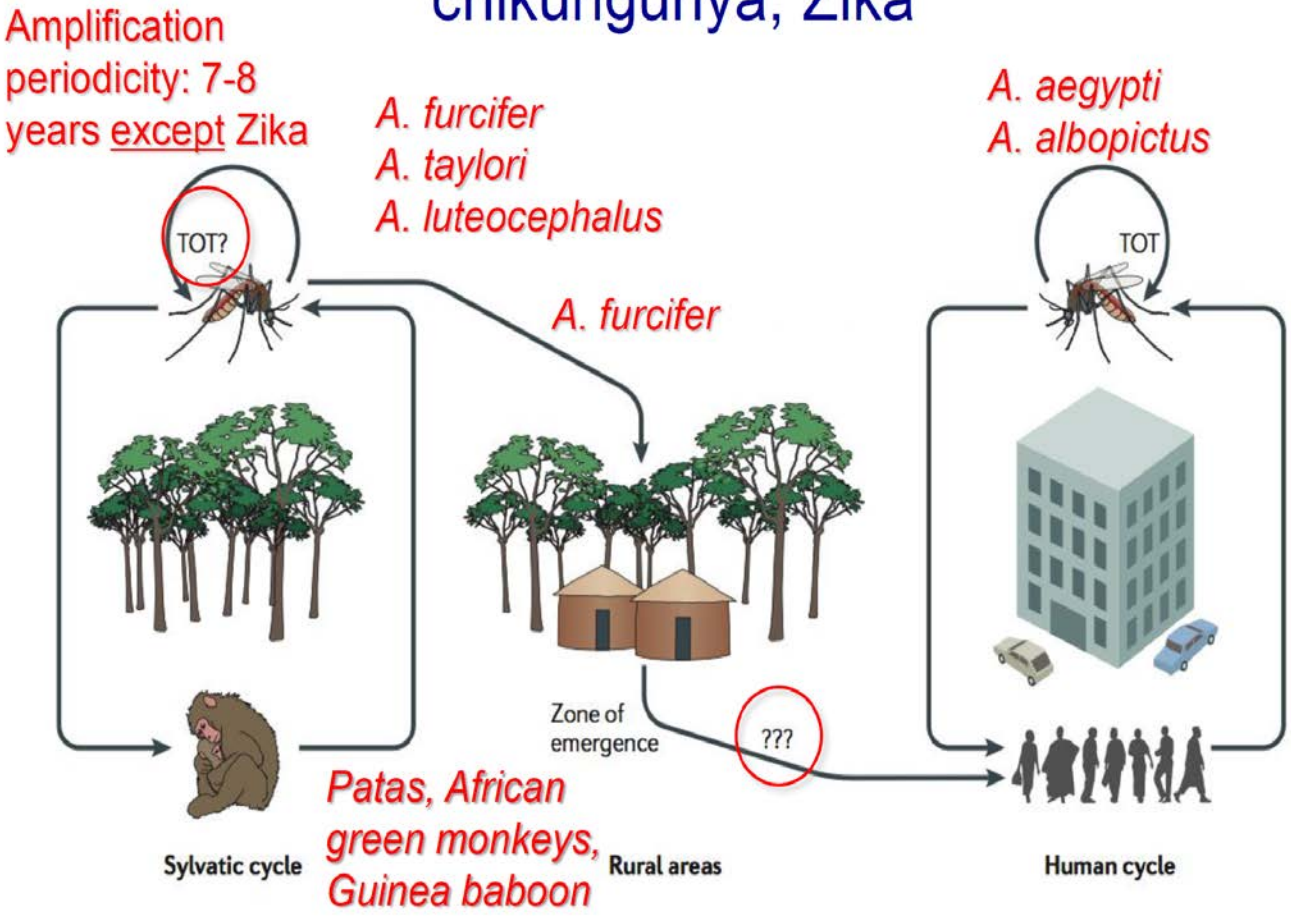
**Zika is usually mild with symptoms lasting for several days to a week. People usually don’t get sick enough to go to the hospital, and they very rarely die of Zika. For this reason, many people might not realize they have been infected. Symptoms of Zika are similar to other viruses spread through mosquito bites, like dengue and chikungunya.**

## Zika Transmission Cycle (also dengue and chikungunya)




- **The mosquito species responsible for transmission in the sylvatic cycle are not the same as those in the epidemic cycle.**
- **Once infected, it takes a mosquito about 10 days before it can transmit to another human.**
- **Human viremia usually lasts about a week.**
- **Only about 20% of infected people have symptoms (fever, rash, joint pain, or conjunctivitis, sometimes muscle pain or headache).**

# **Quartet** of arboviruses in West Africa with history of urban emergence: yellow fever, dengue, chikungunya, Zika



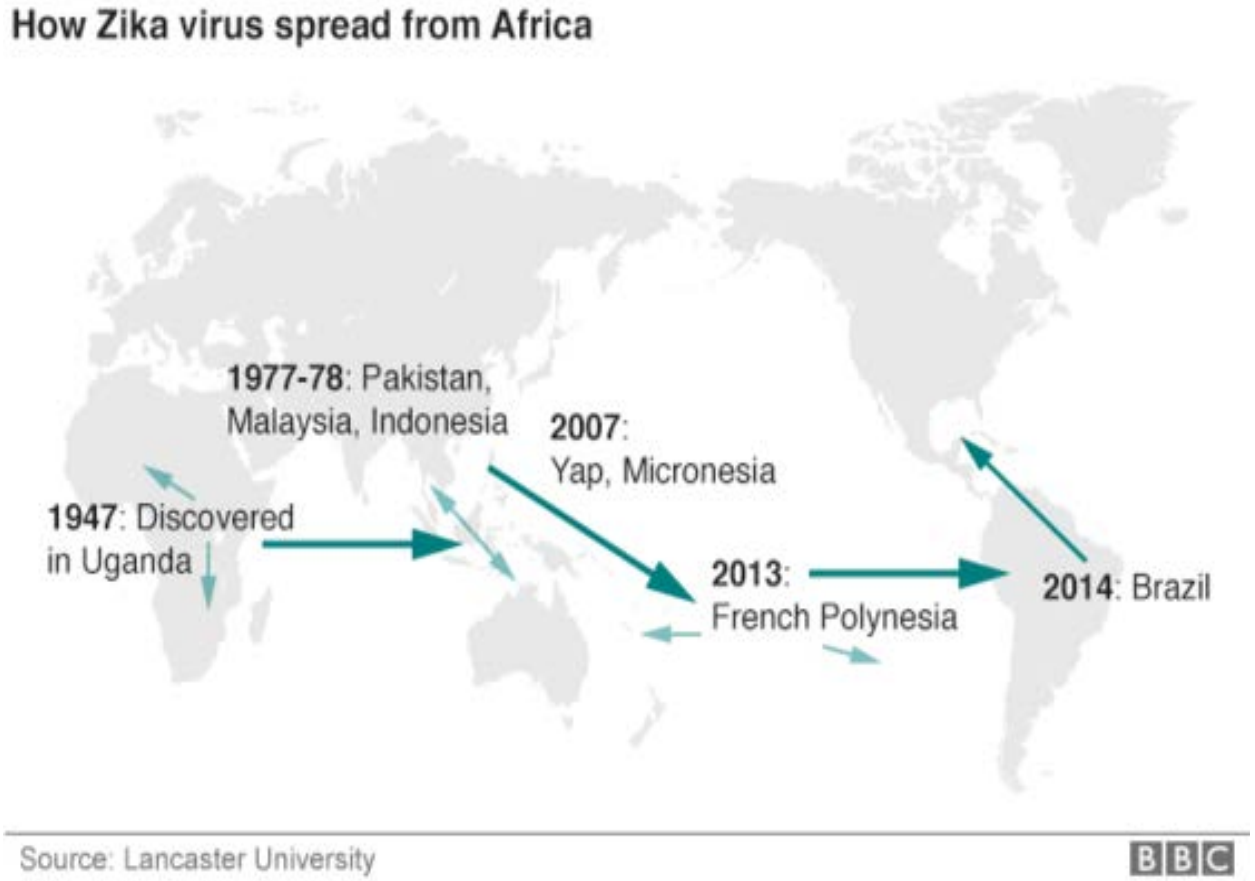

**Scott Weaver, in Potential Research Priorities to Inform Public Health and Medical Practice for Domestic Zika Virus: Workshop in Brief. 2016.**

- **Following initial virus isolation in 1947 and verification of arbovirus status, research on the virus indicated that it was not an important human pathogen in that environment**

- **For decades, the only known human infections were laboratory acquired**

- **In the 1970's and 1980's a few reports from humans and NHP**

- **In 2007 a "small" outbreak on the island of Yap (49 initial confirmed, but 5000 infections indicated through follow up serosurvey)**



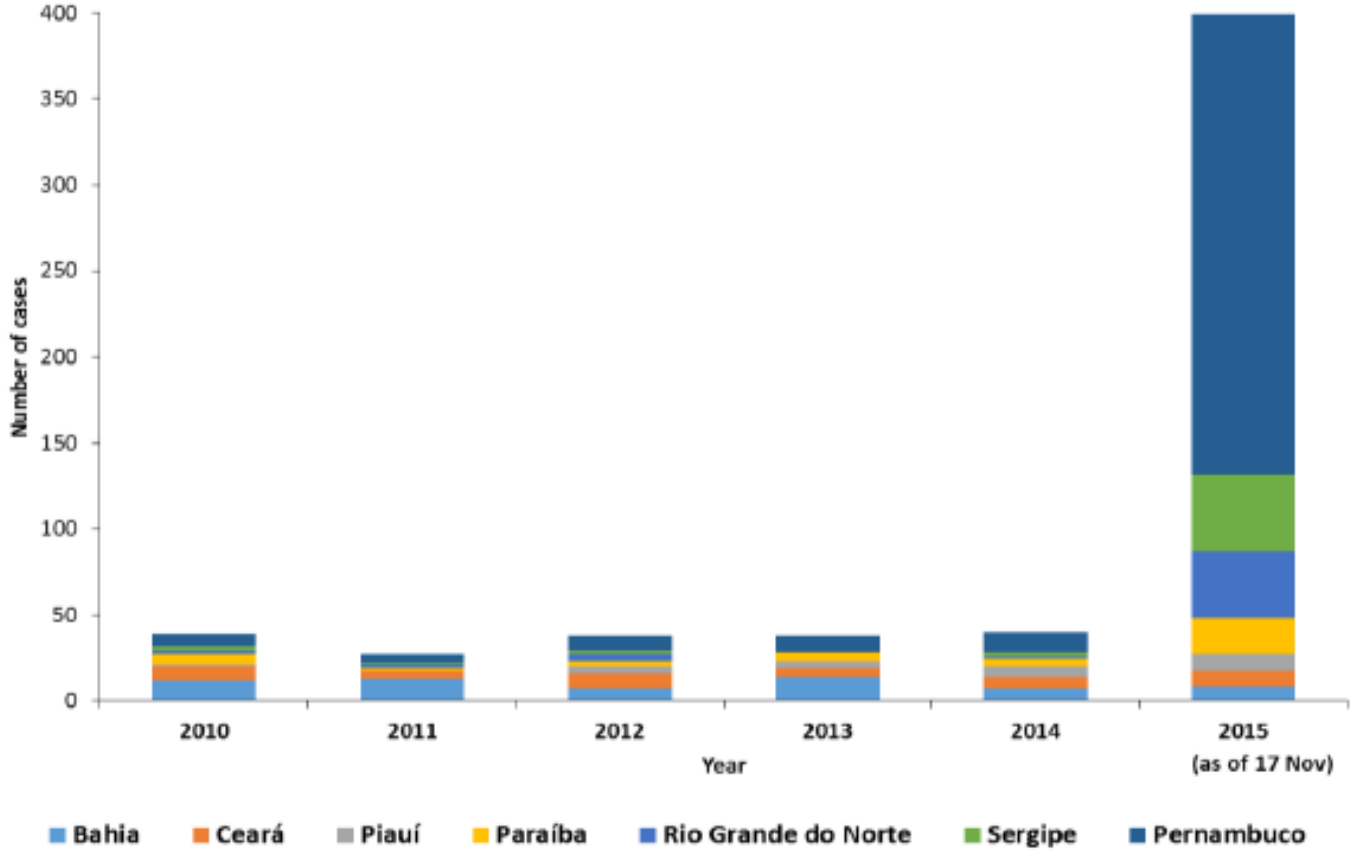
# Soon thereafter…

**First report of sexual transmission of Zika virus (occurred in 2008/published in 2010); in the US from former Tulane PhD student to his wife**


**He was doing field work in Senegal when he acquired the infection.**

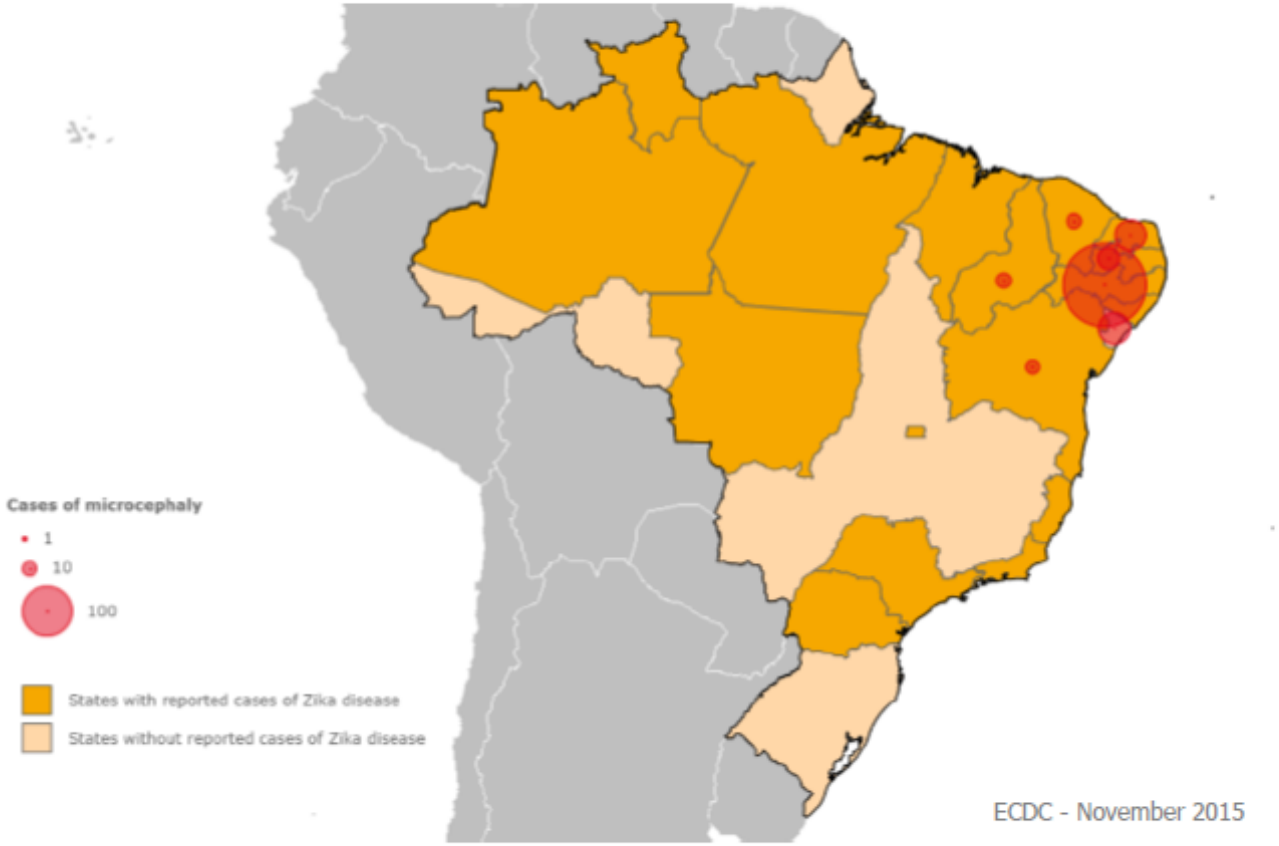

- **In 2013, there was a large outbreak in French Polynesia, with 333 confirmed cases and 19,000 estimated infections.**
- **First association serious symptoms: mainly neurological disorders, including Guillain-Barré syndrome (mild to severe paralysis)**
- **Two congenital infections observed (in utero or during delivery) with no lasting health problems**

**Figure 2. Number of cases of microcephaly reported annually in the seven Brazilian states reporting an unusual increase of microcephaly, 2010–2015**




**RAPID RISK ASSESSMENT Microcephaly in Brazil potentially linked to the ZIKV epidemic – Nov 2015 European Center for Disease Prevention and Control**

**Figure 3. States of Brazil with reported confirmed autochthonous cases of ZIKV virus infection 2014–2015, and reported cases of microcephaly in 2015, as of 17 November 2015.**

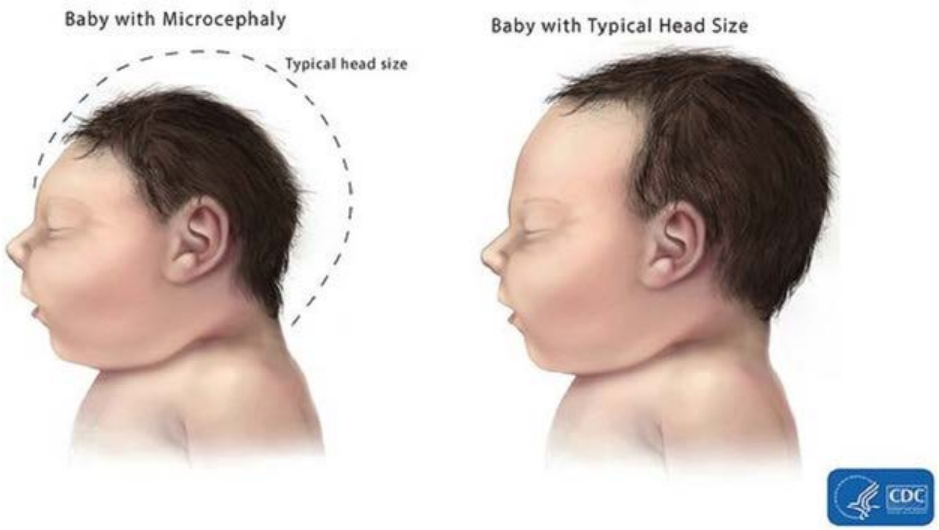



*Adapted from [1] and [40]*

RAPID RISK ASSESSMENT Microcephaly in Brazil potentially linked to the ZIKV epidemic – Nov 2015
European Center for Disease Prevention and Control

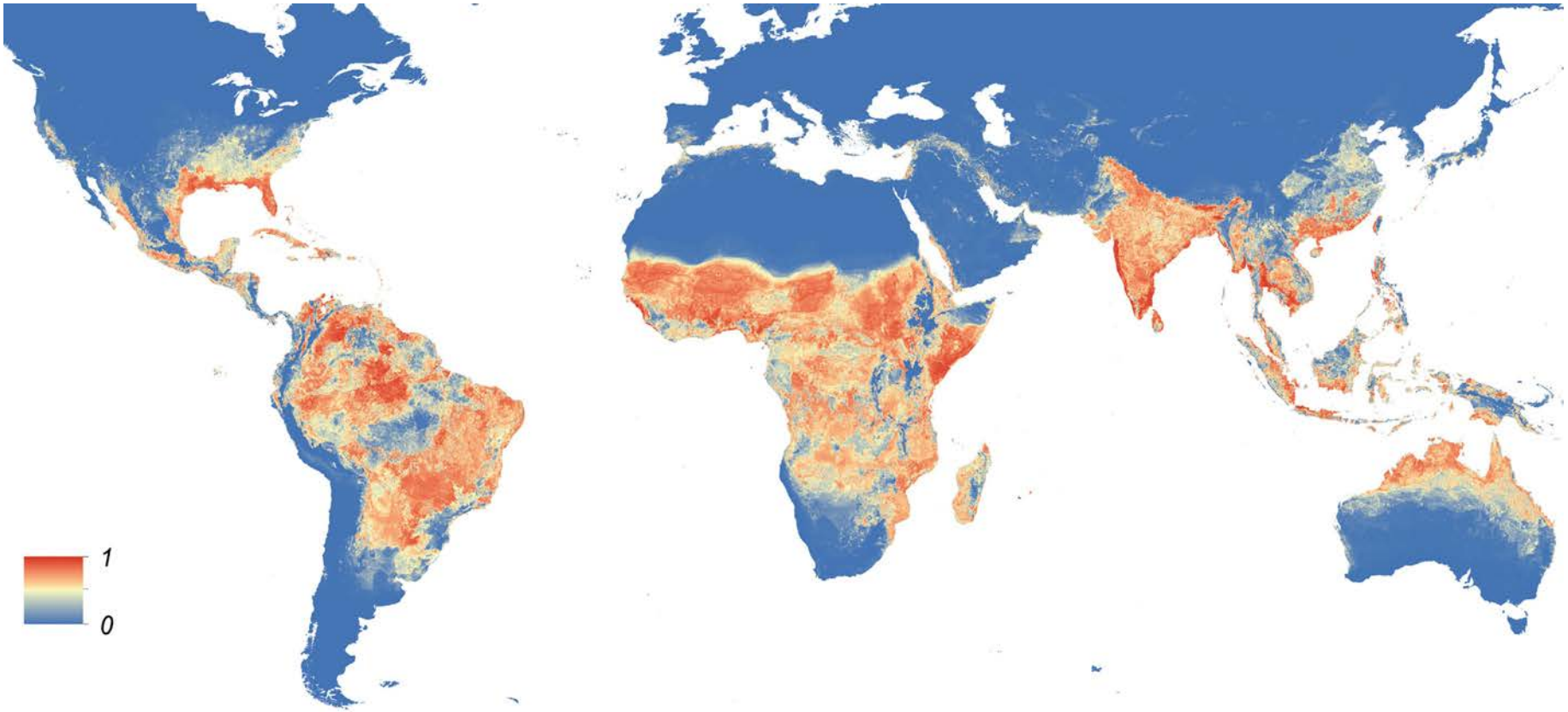
# What is microcephaly?

- Head circumference > 2 SD below mean (for size, gest age)

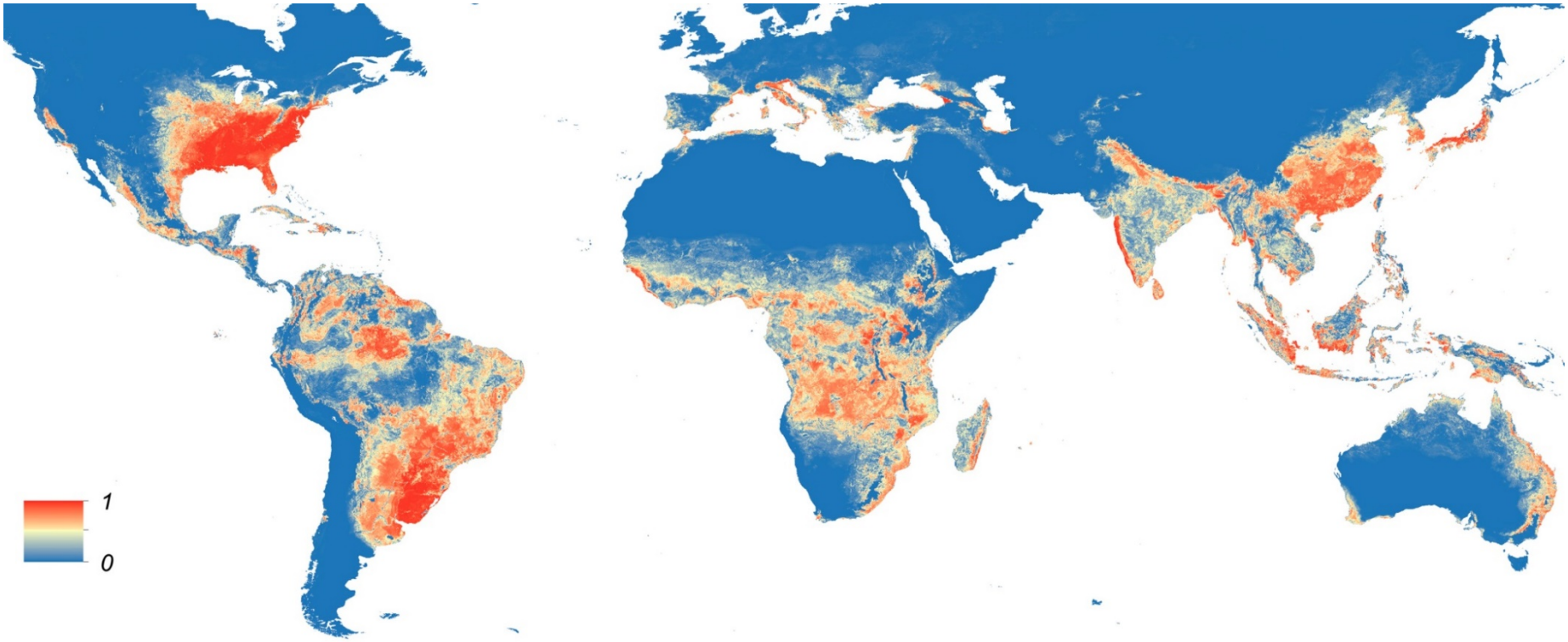



Causes:

- infections in the womb: toxoplasmosis (caused by a parasite found in undercooked meat), rubella, herpes, syphilis, cytomegalovirus and HIV;
- exposure to toxic chemicals: maternal exposure to heavy metals like arsenic and mercury, alcohol, radiation, and smoking;
- genetic abnormalities such as Down syndrome; and
- severe malnutrition during fetal life.



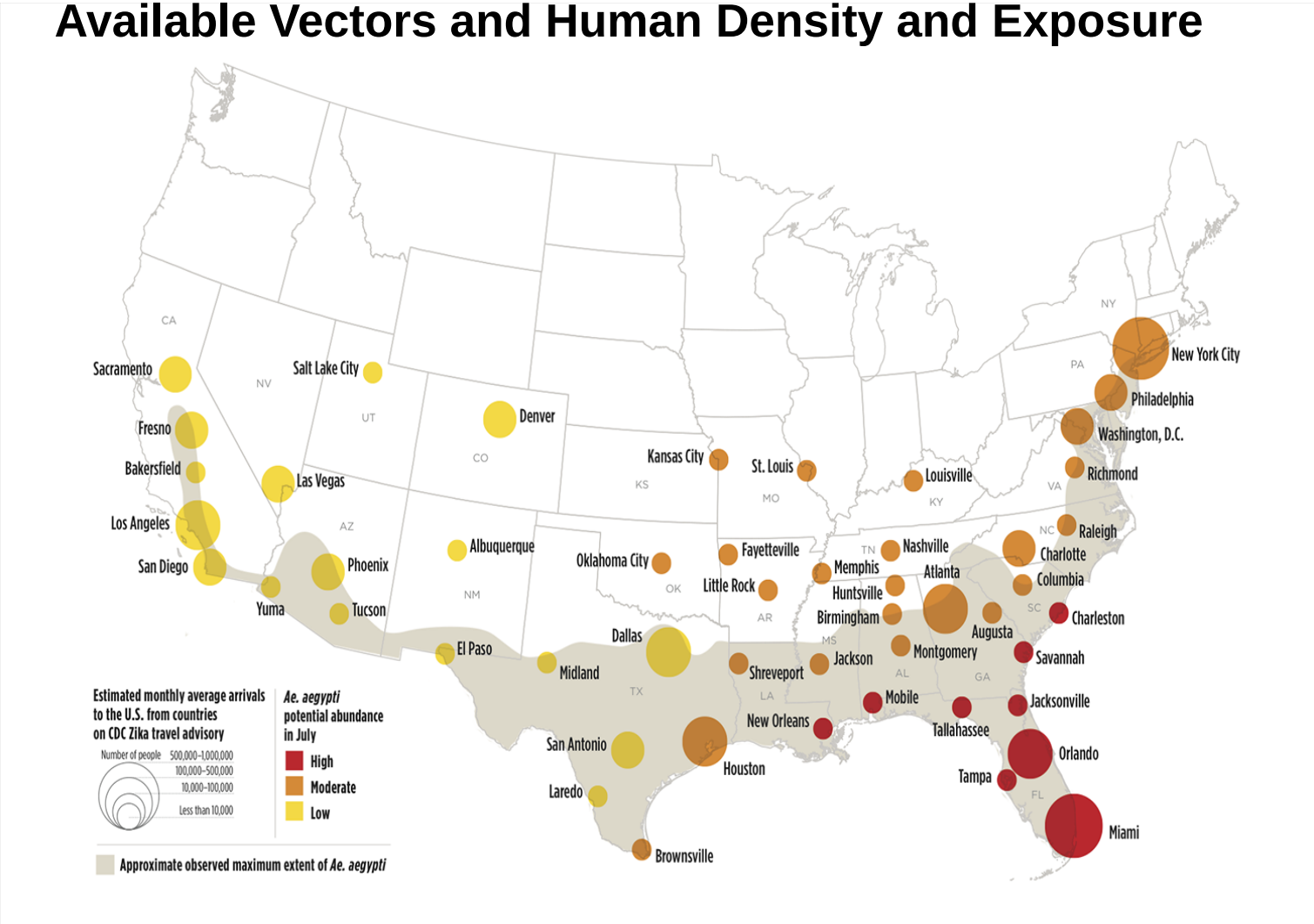

**Global *Aedes aegypti* predicted distribution in 2015.**
**The map depicts the probability of occurrence (blue=none, red=highest occurrence).**




**Global map of the predicted distribution of *Ae. albopictus.* The map depicts the probability of occurrence (from 0 blue to 1 red) at a spatial resolution of 5 km × 5 km.**

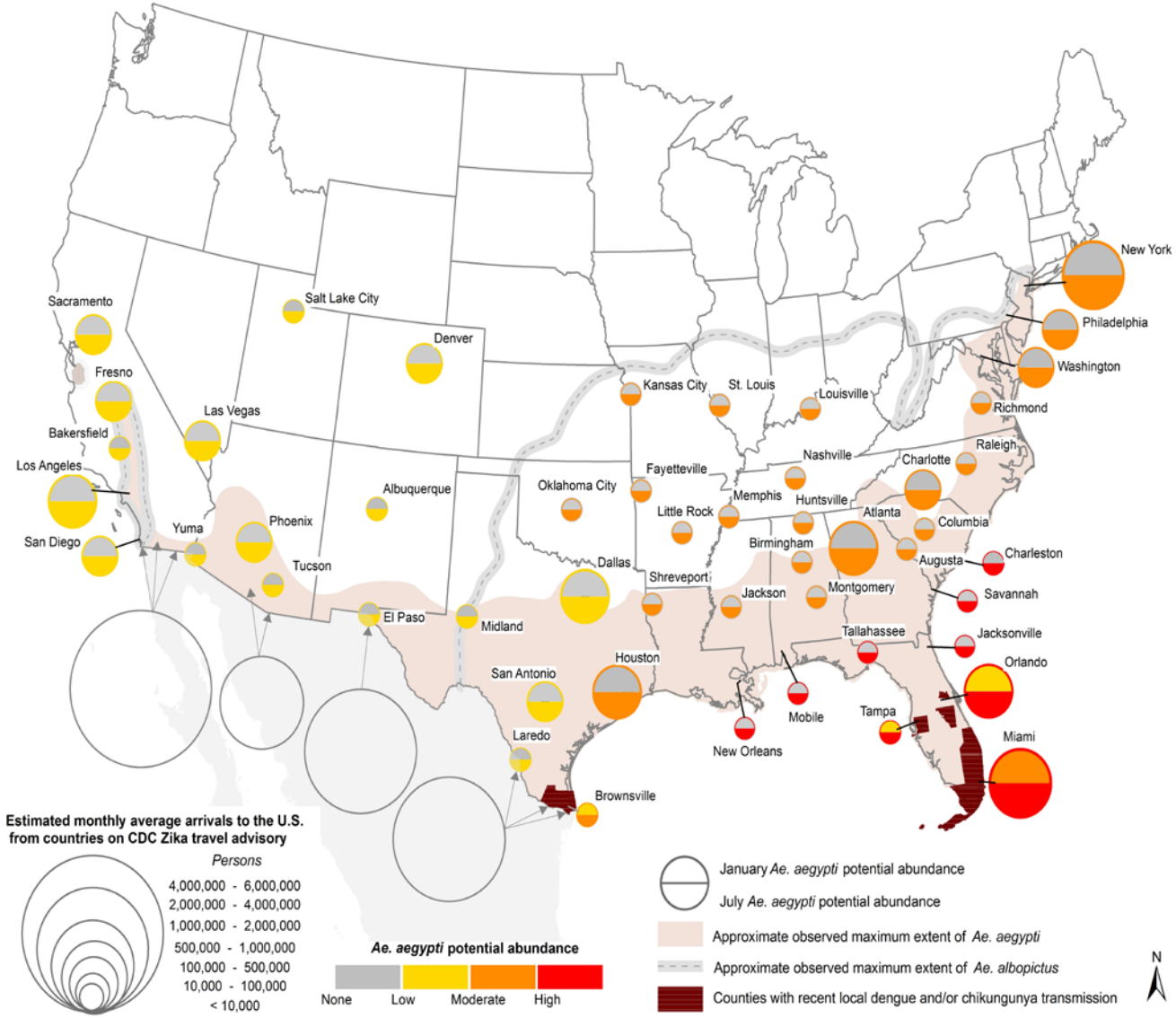
**Kraemer et al, eLife 2015;4:e08347**

# The Potential for Introduction of Zika to the US is Dependent on Available Vectors and Human Density and Exposure




**Many U.S. cities face potential risk in summer of low, moderate, or high populations of the mosquito species that transmits Zika virus (colored circles). The mosquito has been observed in parts of the United States (shaded portion of map) and can establish populations in additional cities because of favorable summertime meteorological conditions. In addiiton, Zika risk may be elevated in cities with more air travelers arriving from Latin America and the Caribbean (larger circles)**

***Image based on data mapped by Olga Wilhelmi, NCAR GIS program***

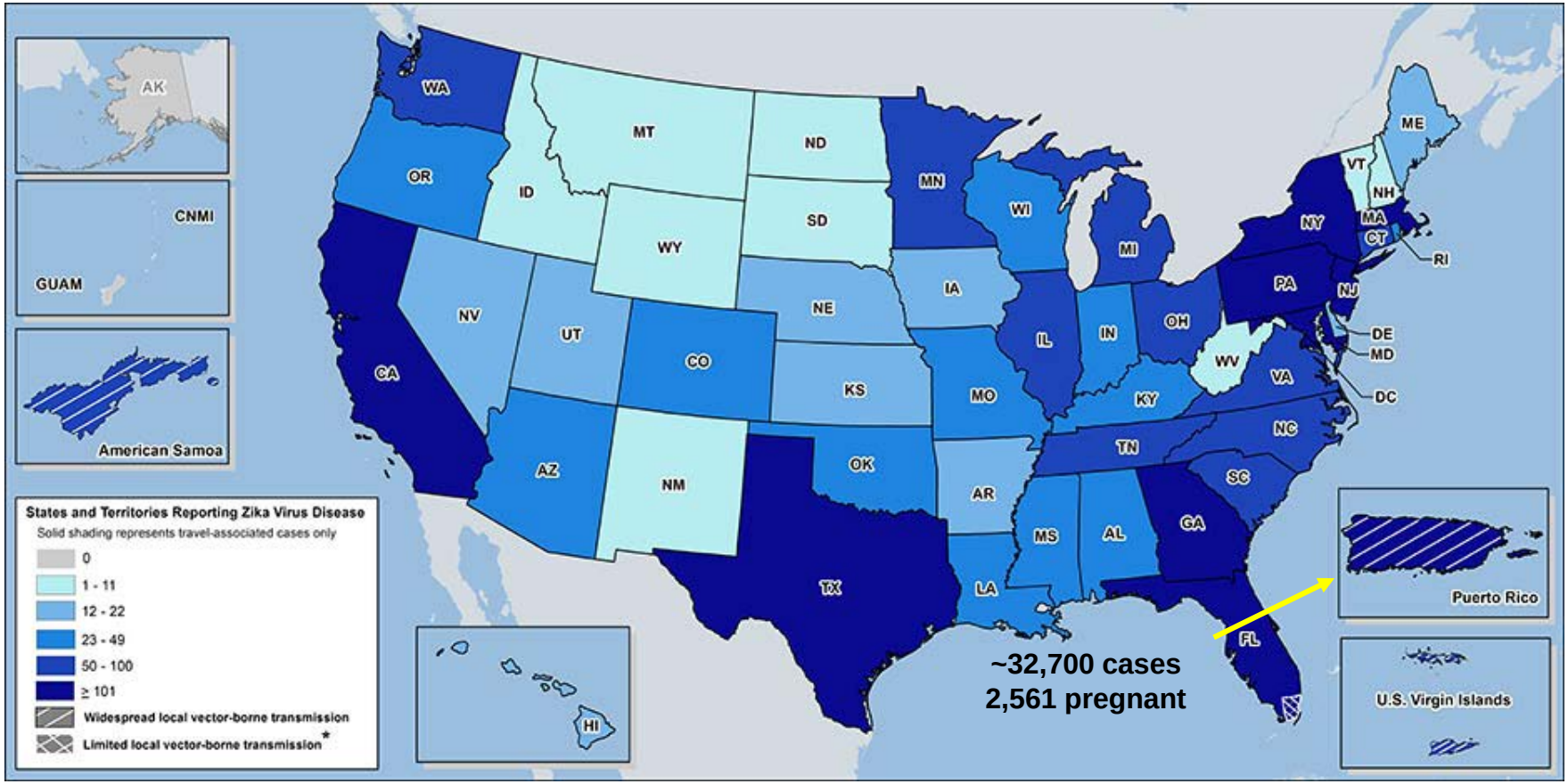



**U.S. map showing:**

**1) *Ae. aegypti* potential abundance for Jan/July (colored circles)**

**2) approximate maximum known range of *Ae. aegypti* (shaded regions) and *Ae. albopictus* (gray dashed lines)**

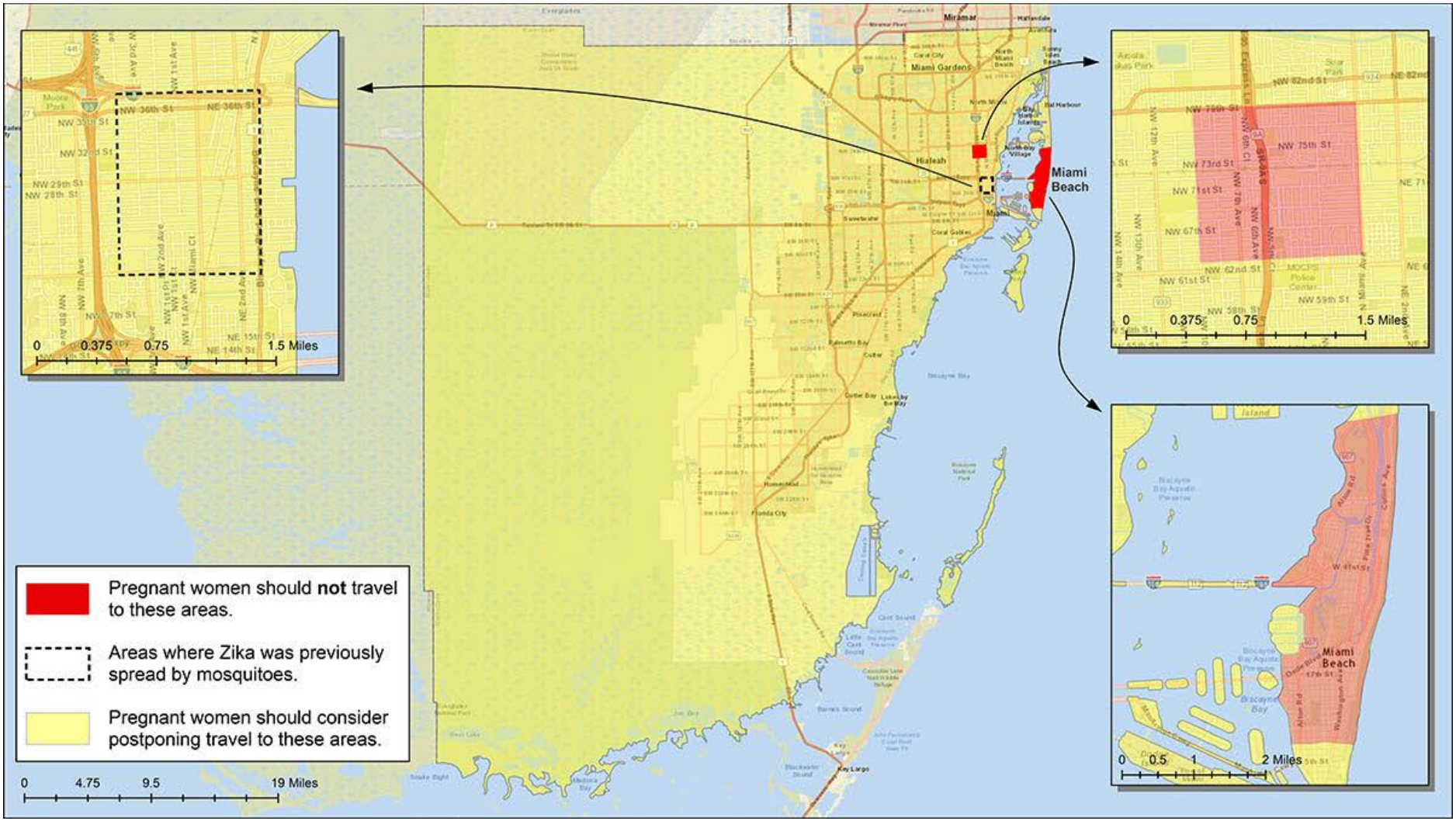
**3) monthly average number arrivals to the U.S. by air and land from countries on the CDC Zika travel advisory**




CDC, As of Nov. 23, 2016

# US States

- **Local transmission in S. FL - 238**
- **Travel-associated Zika virus disease cases reported in 50 states: 4,262**
- **NY, FL, CA and TX account for ~55% of cases**
- **1,114 U.S. pregnant travelers with Zika virus infection had been identified**
- **28 live births with birth defects; 5 pregnancy losses with birth defects**




**Miami-Dade County, FL. Red shows areas where pregnant women should not travel. Yellow shows areas where pregnant women should consider postponing**


# All Countries & Territories with Active Zika Virus Transmission, Nov. 2016

# Dengue Viruses

- Each serotype provides specific lifetime immunity, and short-term cross-immunity
- All serotypes can cause severe and fatal disease
- Genetic variation within serotypes
- Some genetic variants within each serotype appear to be more virulent or have greater epidemic potential (i.e. DEN-2)

## Recent Dengue in the U.S.A. (Hawaii - 2001)

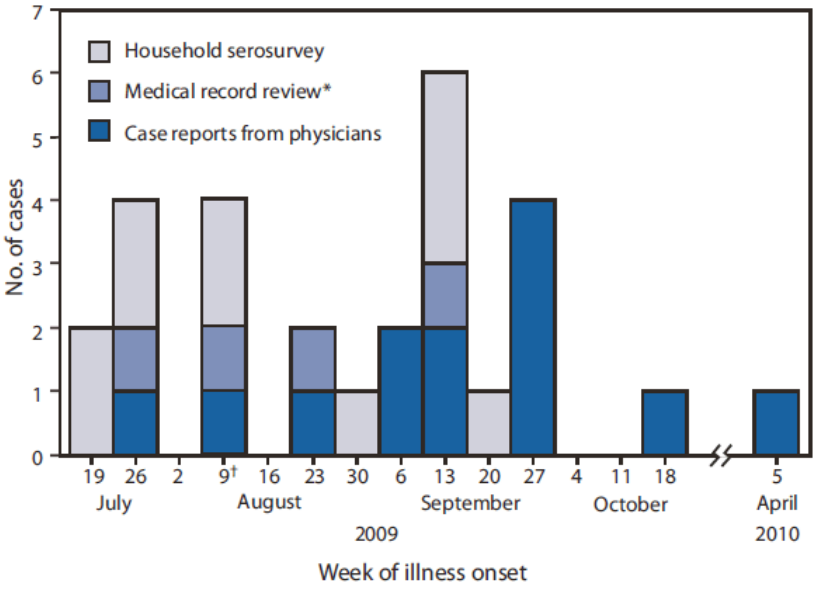
- Through late November 2001, there were 88 cases of dengue in the Hawaiian Islands.
- Most of the cases were in the Hana area of East Maui, a lush, remote part of the island several hours' drive from the main tourist areas.
- But there also were a few cases on other islands, including Oahu and Kauai.
- All cases were classic dengue with no hemorrhagic manifestations.
- Vector was *Aedes albopictus* – *Ae. aegypti* not present in those areas.

# Recent Dengue in the U.S.A. (Texas)

- Dengue epidemics occurred in the USA in the 1800s and the first half of the 1900s
- Recent indigenous transmission:
  - 1980: 23 cases, 1st local cases since 1945
  - 1986: 9 cases
  - 1995: 7 cases
  - 1997: 3 cases
  - 1998: 1 case
  - 1999: 18 cases (51 total, but underreported…)
- 2005 – first DHF case described in Texas

# 2009-2010, Locally Acquired Dengue in Key West, FL

- First Case Identified: Vacationer from Rochester, NY (Den 1)
  - 2009 - 27 cases identified
  - 2010 - 63 cases identified to date
- 2009 Serosurvey
  - 240 sampled:
    13 (5.4%) were IgM+



# 2010: LARGEST DENGUE OUTBREAK IN PUERTO RICO HISTORY (> 21,000 cases)

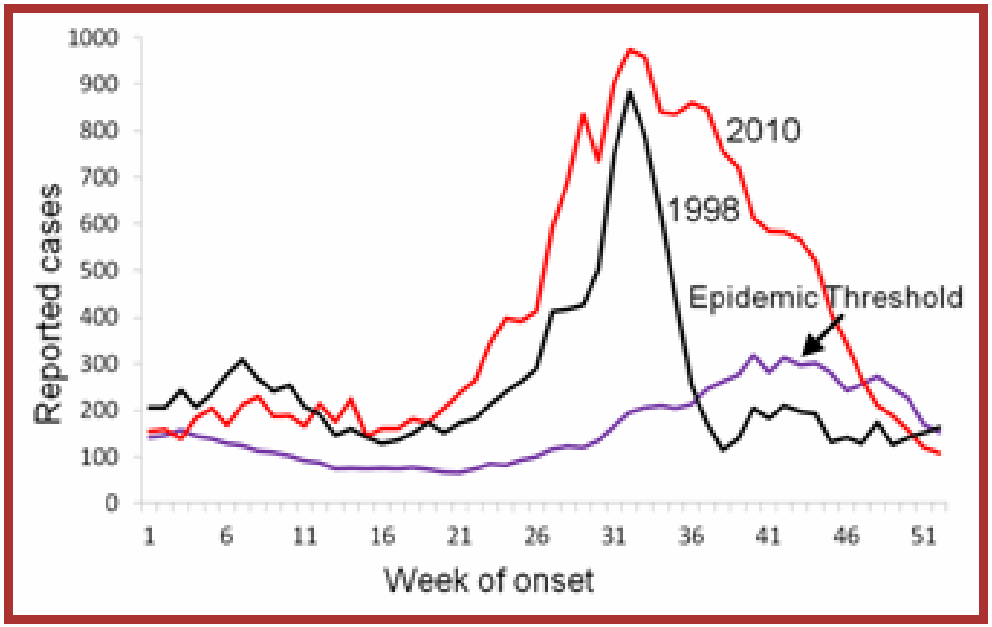
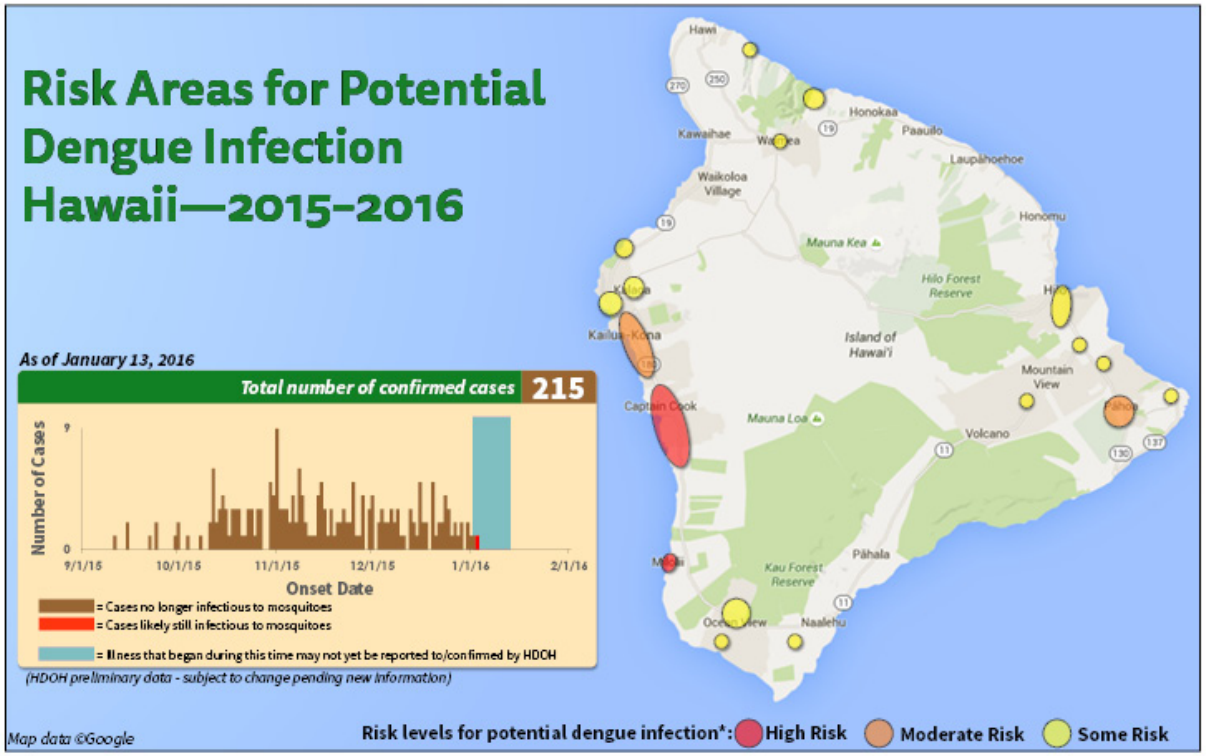



**Figure 1.** Reported dengue cases in Puerto Rico, 1998 and 2010

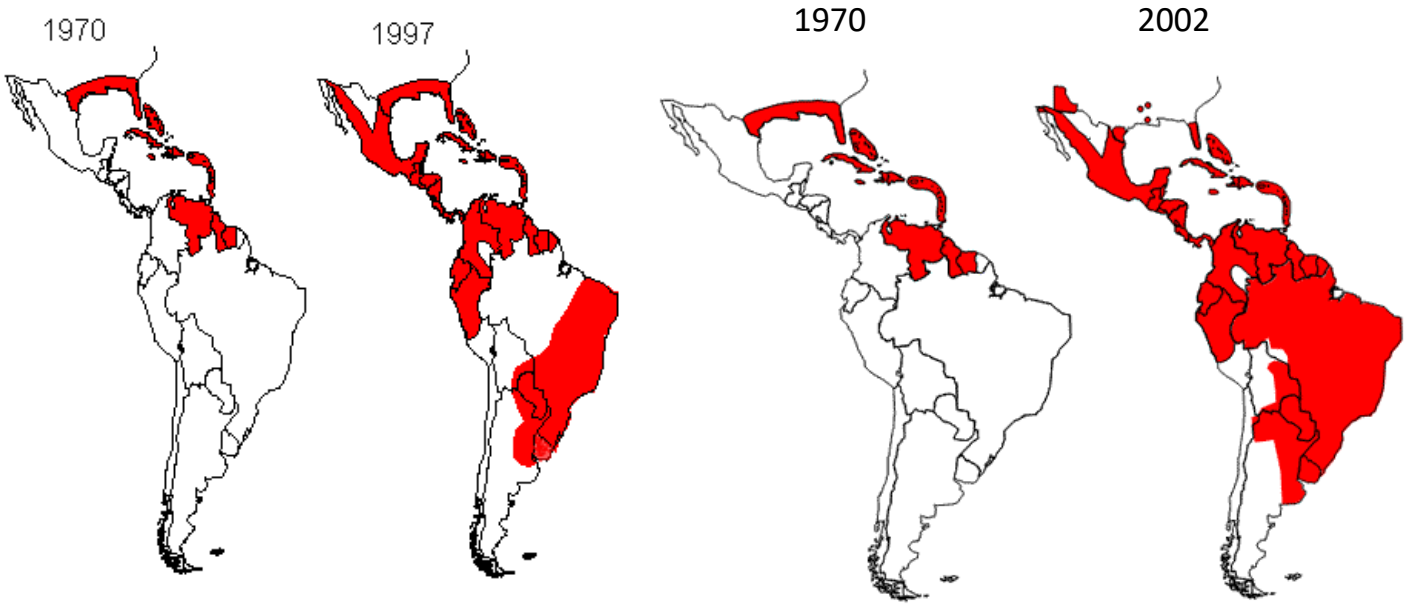



*Risk levels of areas where confirmed cases may have contracted dengue fever are determined by the number of confirmed cases with recent onset dates who reported visiting those areas. Individuals should always protect themselves against mosquitoes and mosquito bites island-wide; extra precaution should be taken in areas of risk. For more information on dengue fever and ways to protect yourself from mosquitoes, visit: http://health.hawaii.gov/docd/dengue-outbreak-2015/


Of the confirmed cases, 201 are Hawaii Island residents and 22 are visitors.

181 cases have been adults; 42 have been children (<18 years of age).

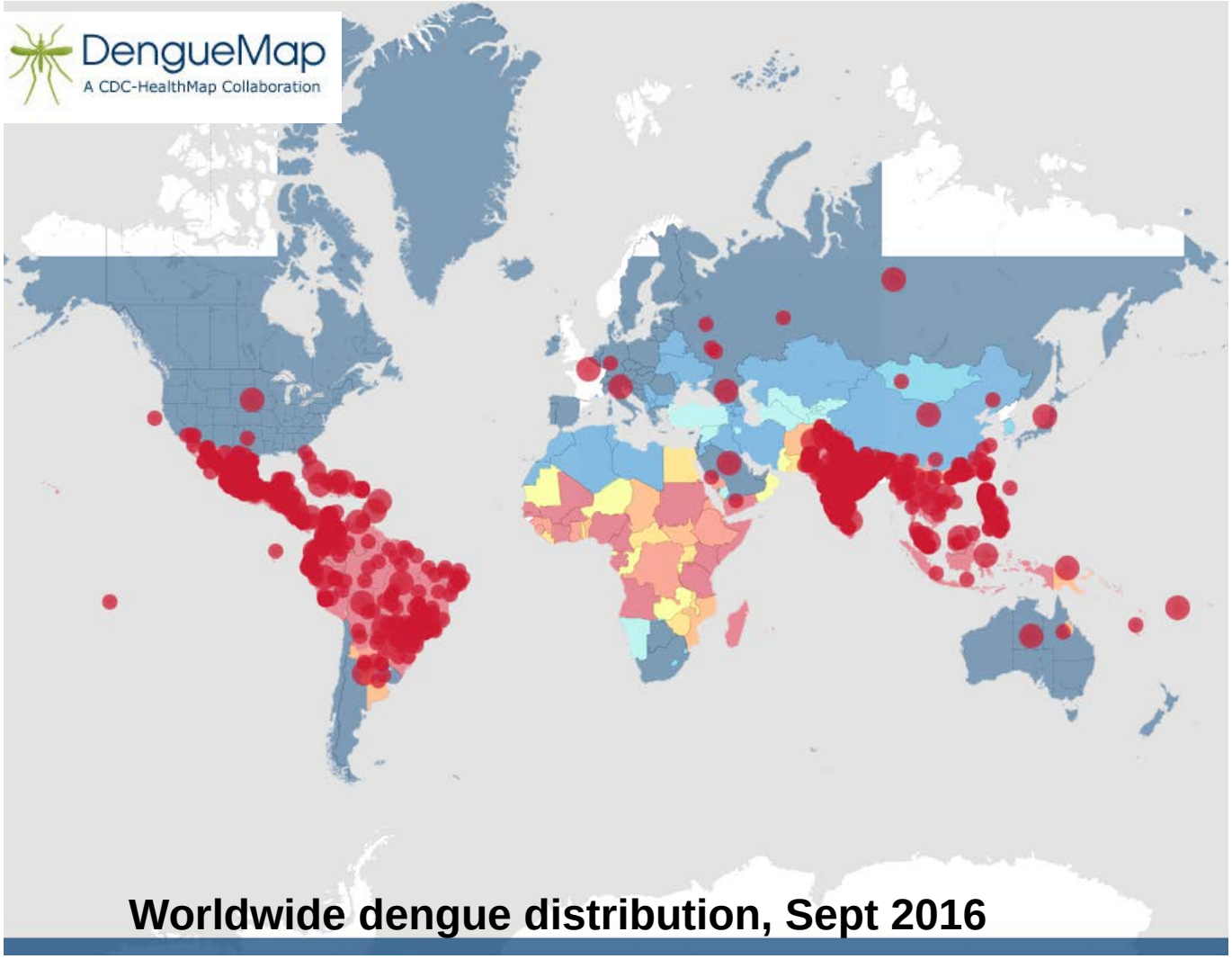
Onset of illness has ranged between 9/11/15 – 1/8/16.




Distribution of Aedes aegypti (red shaded areas) in the Americas in 1970, at the end of the mosquito eradication program, in 1997 and in 2002.

**Source PAHO/WHO**


**American countries with laboratory-confirmed hemorrhagic fever (red shaded areas), prior to 1981, from 1981 to 1997, and from 1981-2003.**




**Worldwide dengue distribution, Sept 2016**

- Chikungunya virus (CHIK)
  - Alphavirus
  - Transmitted by both *Ae. aegypti* and *Ae. albopictus*
  - Recent outbreaks in India, Italy, current outbreak in S/C America
  - High potential for introduction in other areas where vectors are present

- CHIK infection can cause a debilitating illness, most often characterized by fever, headache, fatigue, nausea, vomiting, muscle pain, rash, and joint pain. About 10% of symptomatic individuals experience long term sequelae.

# Chikungunya virus

- The term ‘chikungunya’ is Swahili for ‘that which bends up.
- Most infected individuals have symptoms
- IIP 1-12 days, typically 3-7 days
- Highest risk for infecting bloodfeeding mosquito during first week of symptoms

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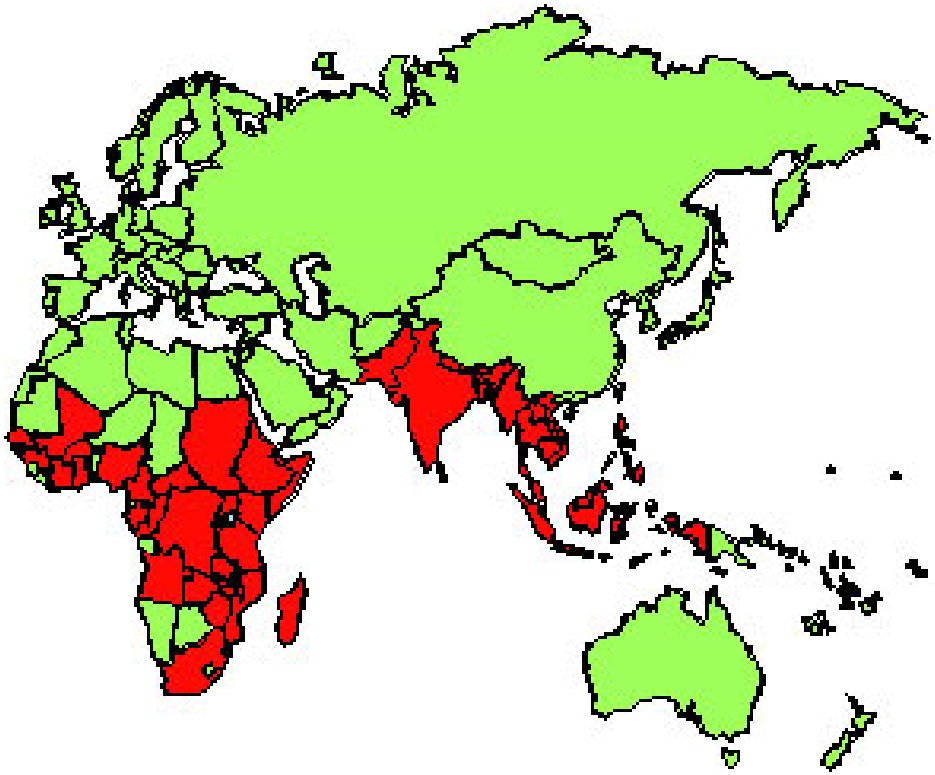
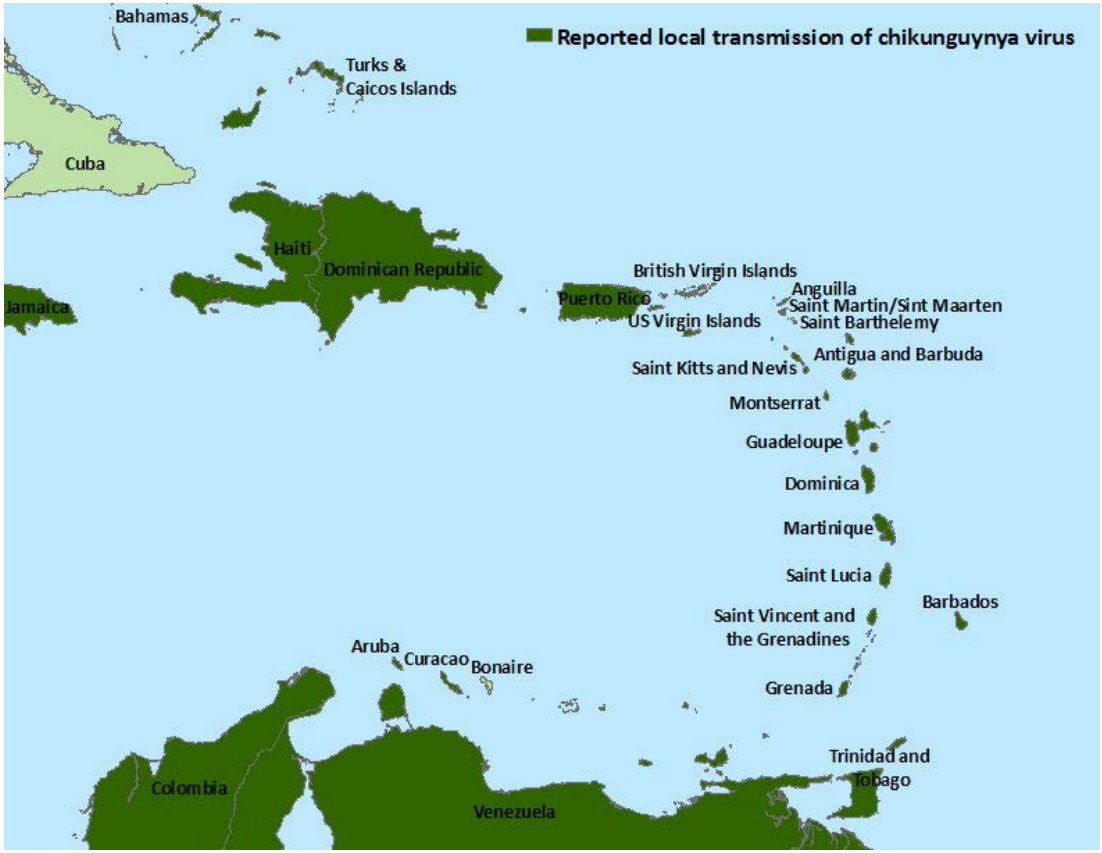
  - IIP 1-12 days, typically 3-7 days
  - Highest risk for infecting bloodfeeding mosquito during first week of symptoms



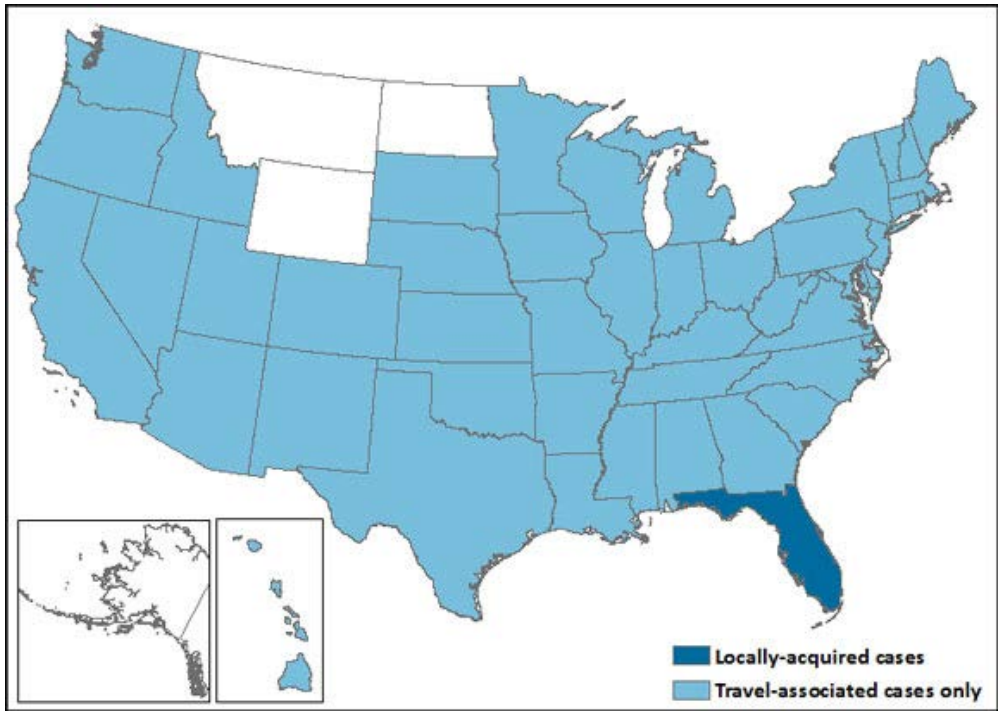
**Cases of chikungunya fever (between 1952-2006)**


**Area of Italy with 2007 outbreak of CHIKV**

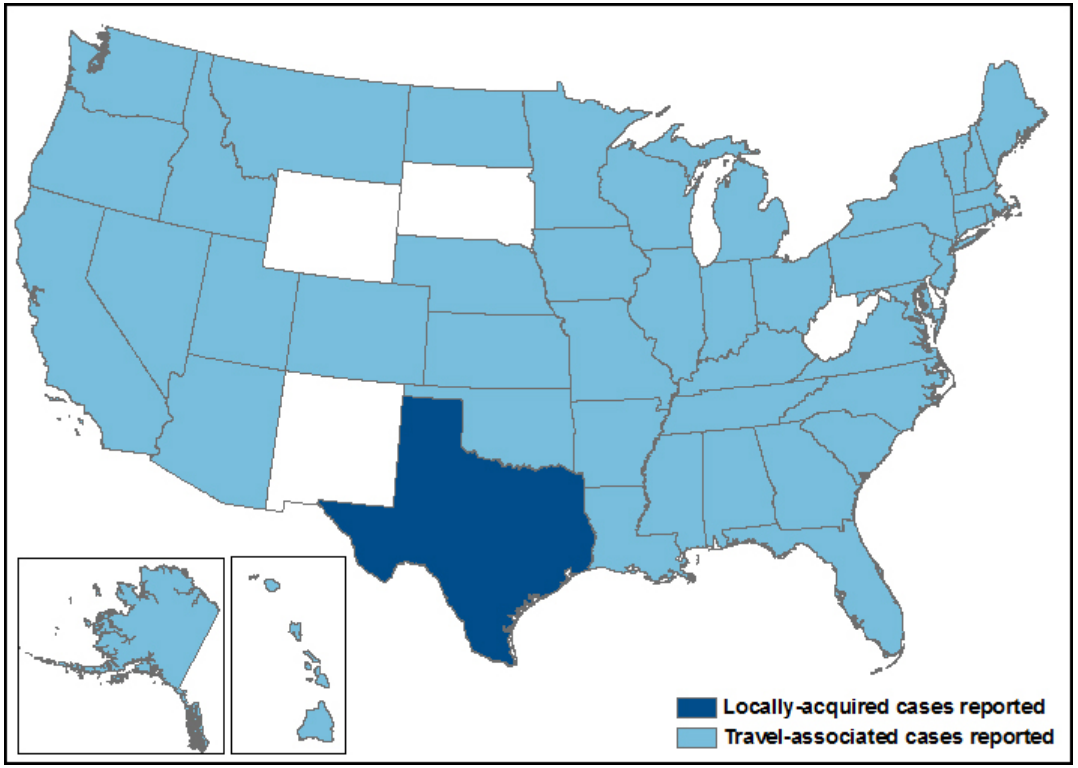
In late 2013, the first local transmission of chikungunya virus in the Americas was reported in some Caribbean countries and territories.



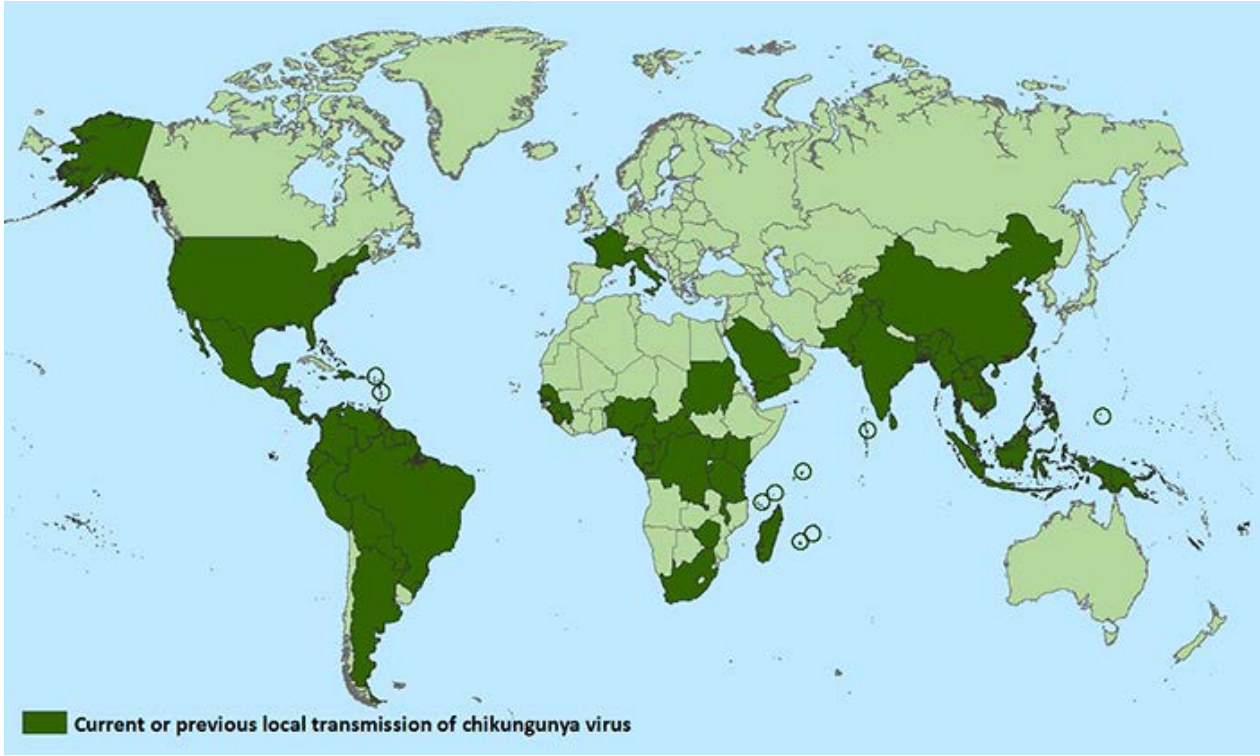

Countries and territories in the Caribbean where chikungunya cases have been reported* *(as of January 13, 2015)*




Chikungunya virus disease cases reported by state – United States, 2014




Chikungunya virus disease cases reported by state – United States, 2015




Countries and territories where chikungunya cases have been reported* *(as of April 22, 2016)*

# Summary of Important Mosquito-Borne Viruses

- ***Eastern Equine Encephalitis virus (EEEV)***
- ***Lacrosse Encephalitis virus (LACV)***
- ***St. Louis Encephalitis virus (SLEV)***
- ***West Nile virus - in US since 1999***
- **Dengue virus (DENV) – recent in South Florida, South Texas and Hawaii**
- **Chikungunya virus (CHIKV) - South Florida, South Texas**
- **Zika virus (ZIKV) – South Florida, South Texas *(next lecture)***
- **Japanese Encephalitis virus (JEV)**
- **Rift Valley Fever virus (RVFV) - see text**
- **Yellow Fever virus (YFV)**
- **Venezuelan Equine Encephalitis virus (VEEV) see text**

**Occur regularly in the US.** **Occur occasionally in the US.** **Not currently in the US.**

# Summary

- Important arboviruses and their vectors
- Prevention/control
- Ongoing threat of introduction

What is the next most likely introduction?

The Disease Daily About Authors DD on Take Part Outbreak Rese

# Mayaro Virus: The Next Alphavirus to Strike?

Nov 18, 2016 | Jackie Sheridan | Outbreak News

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HealthMap About Projects Mobile Disease Daily