Emerging Issues in Vector-Borne Diseases: Arboviruses

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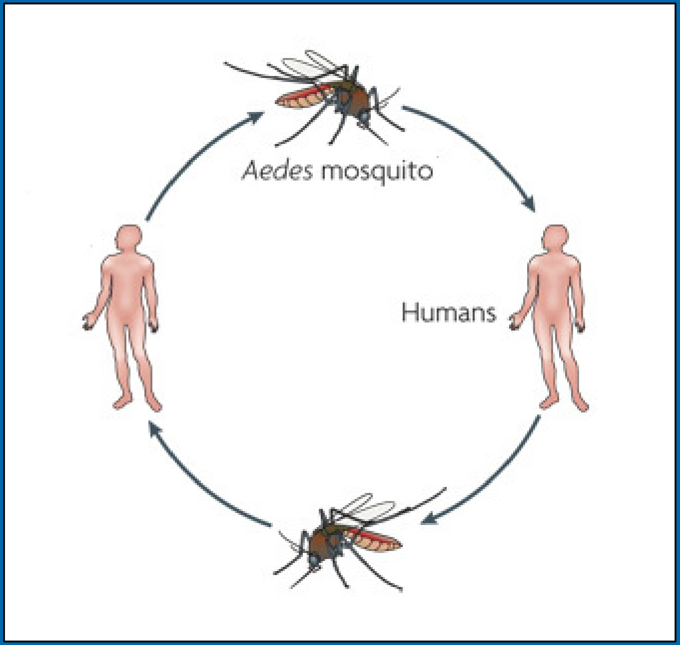
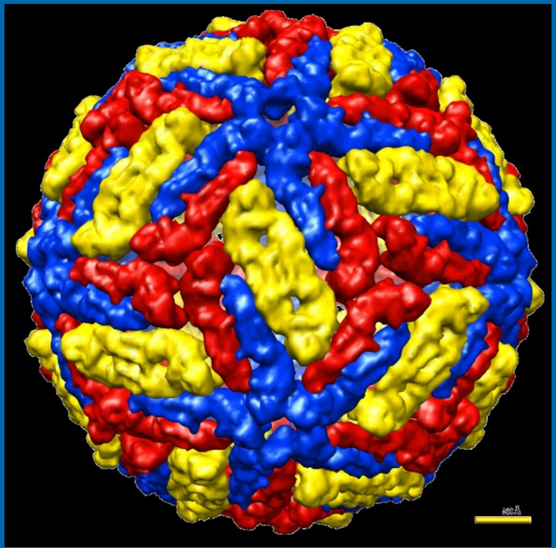
Arthropod Vectors

Dengue and Chikungunya

- Epidemic Transmission
  - Human-Mosquito-Human
- Dengue: Flavivirus
- CHIKv: Alphavirus
- Peridomestic Transmission:
  - *Aedes* mosquitoes
    - *Aedes aegypti*
    - *Aedes albopictus*



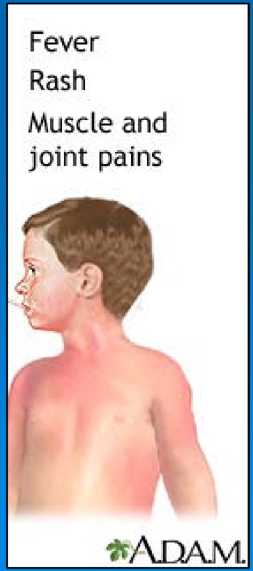
Dengue


West Nile virus only. PDB 1K4R from Kuhn et al. (2002) Cell 108: 717-725. Rendered with UCSF Chimera. images © 2012 JY Sgro; UW-Madison.

- Dengue virus (DENv)
- Flavivirus
- Various closely related viruses
  - DENv1, DENv2, DENv3, DENv4
- Infection with 1 serotype gives type-specific protective immunity
- Subsequent infections with different serotypes increases risk for severe disease

Dengue Virus

- Causes dengue and dengue hemorrhagic fever
- 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

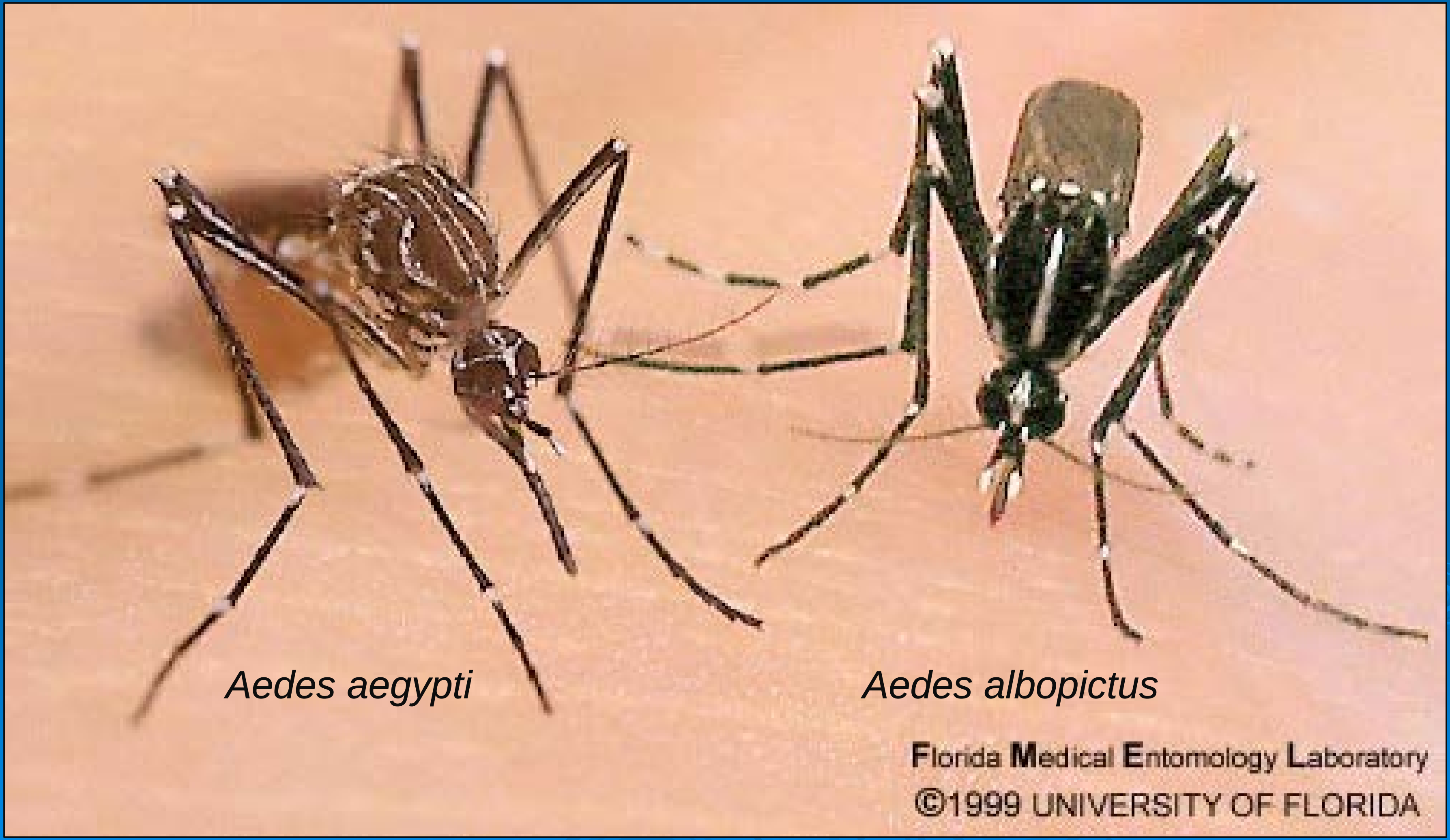


Credit: WHO/TDR/STI/Hatz

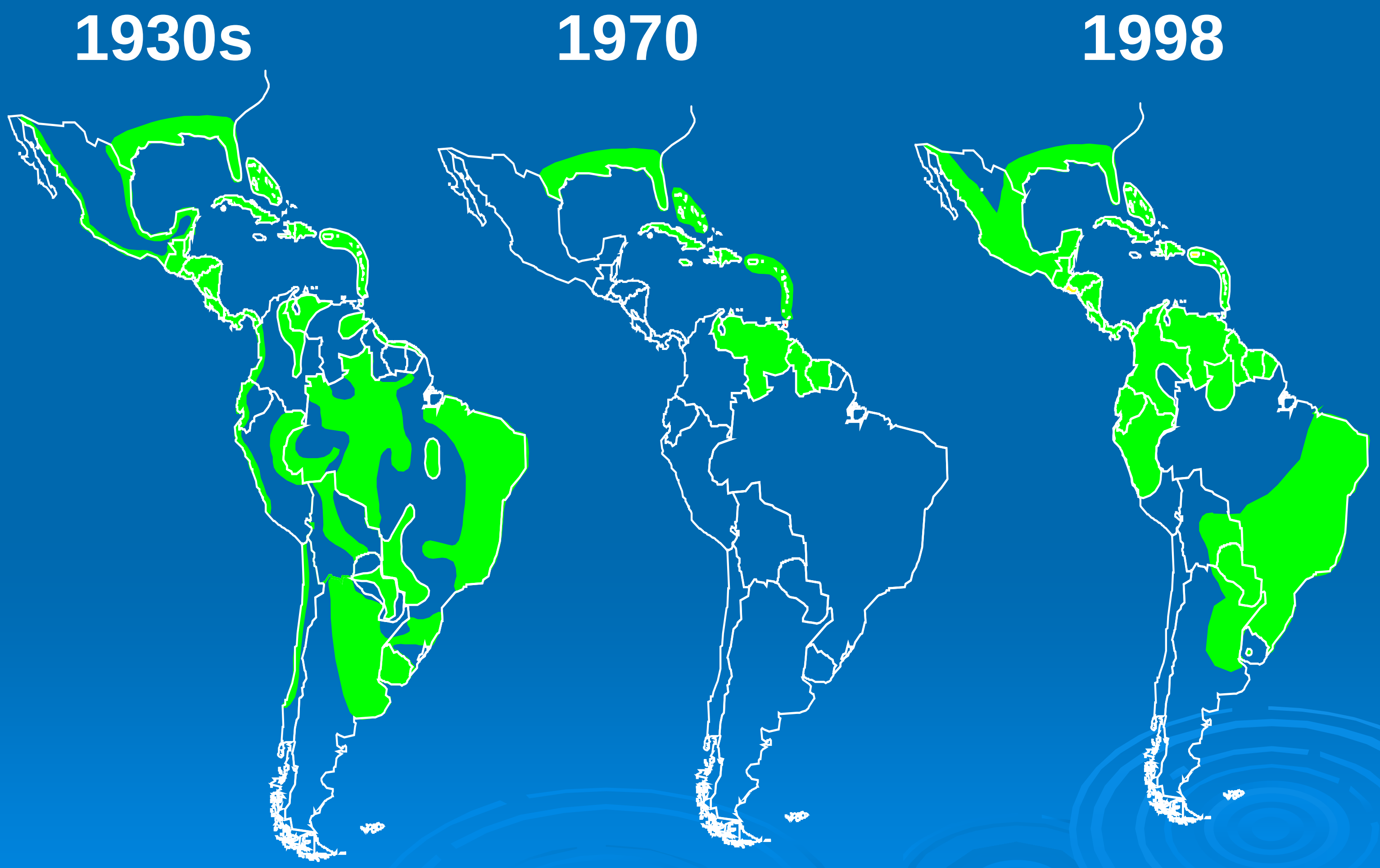
Dengue Symptoms

- Dengue Fever: high fever, severe headache, severe pain behind the eyes, joint pain, muscle and bone pain, rash, and mild bleeding (e.g., nose or gums bleed, easy bruising).
- Severe Dengue (DHF/DSS): persistent vomiting, severe abdominal pain, internal bleeding, difficulty breathing, failure of the circulatory system and shock, followed by death

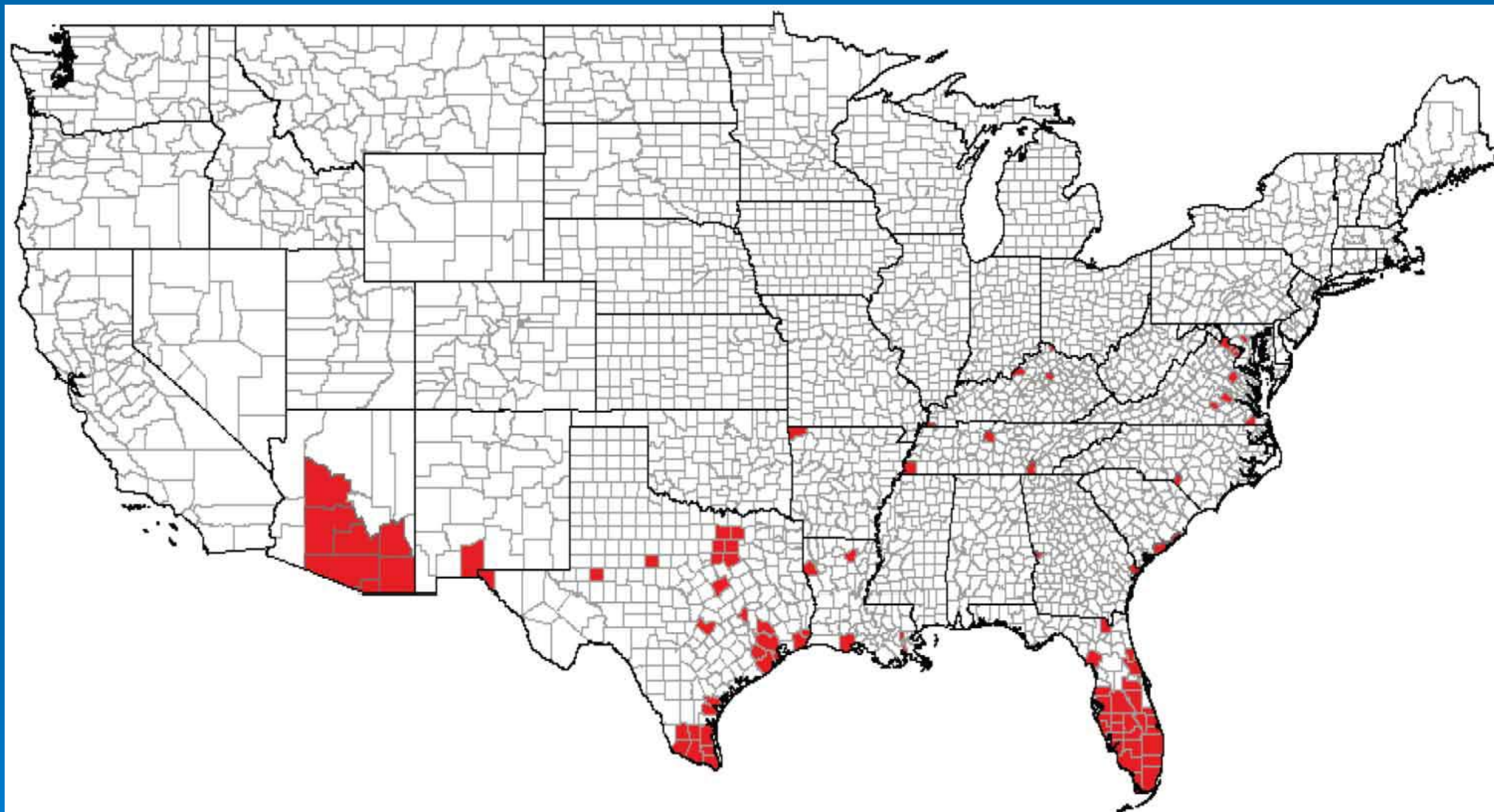
Principle Vectors



Reinfestation by *Aedes aegypti*

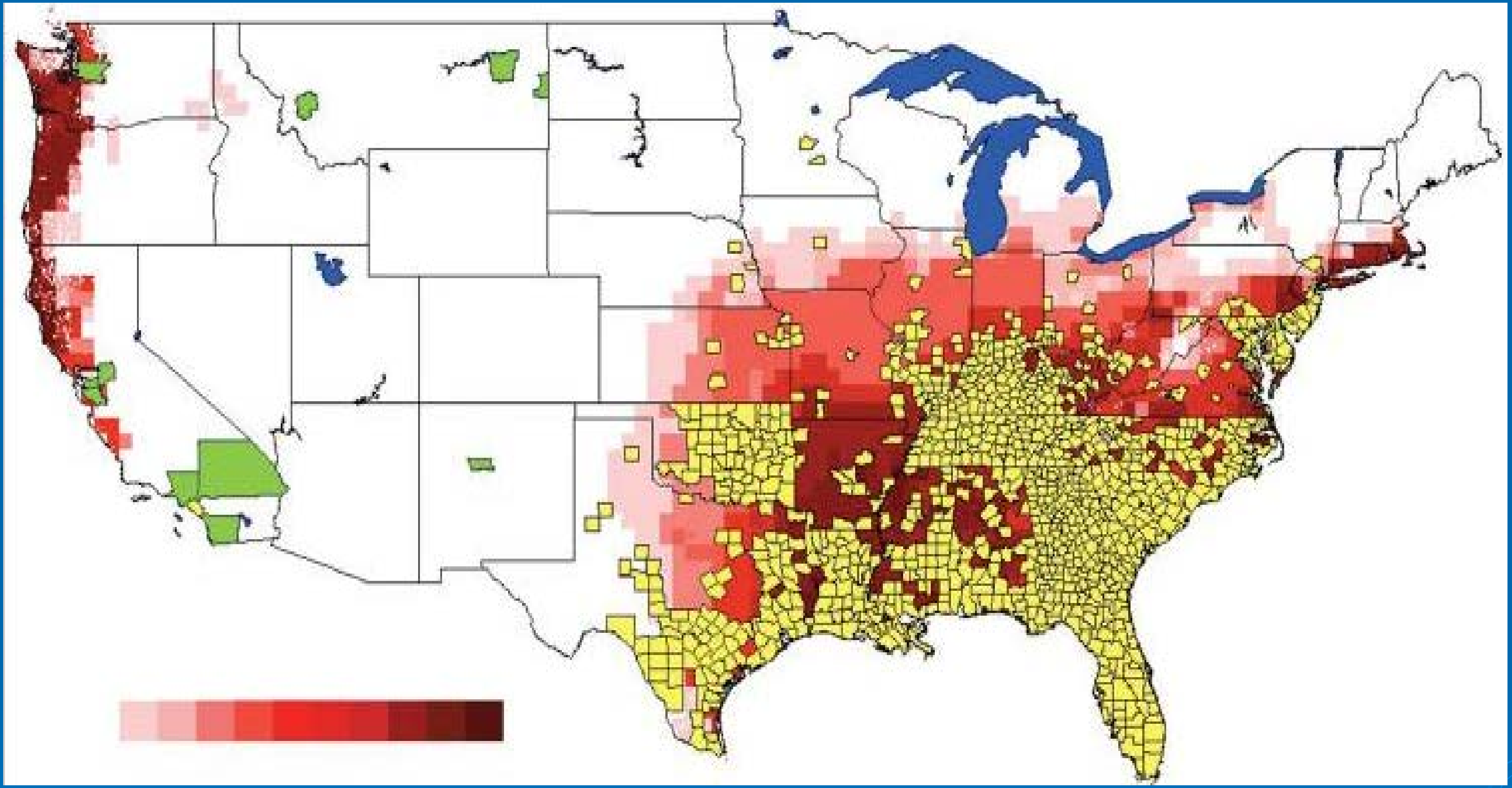


Reported *Aedes aegypti* distribution (1986-2010)



Counties in the continental United States with collection records of *Ae. aegypti* from 1986 to 2010 (shaded red), based on information from a database for invasive mosquito species curated by C. G. Moore of Colorado State University. This database includes data from the Centers for Disease Control and Prevention ArboNet initiative, as well as reports from state and local public health and vector control programs, university researchers, and others.

Reported and Predicted *Aedes albopictus* distribution



Predicted distribution maps and actual spread of *Ae. albopictus* in the lower 48 states. The predicted distribution areas (red) and the documented spread (yellow) of *Ae. albopictus* through the year 2001 are shown. One of the two prediction maps for the US is shown. Differences between the two consisted largely of one of the ten models used to create the prediction map that predicted a broader Texas distribution. Counties colored green are those in which introduction has occurred but not establishment.

Vector Borne Zoonotic Dis. 2007; 7(1): 76–85.

Main dengue vectors

Aedes aegypti

African treehole mosquito
Closely associated with people
Does not depend on the presence of vegetation
Indoor / outdoor (resting, biting, ovipositing)
Urban/suburban/rural areas
Greater resistance to desiccation (eggs)
Main dengue vector worldwide

Aedes albopictus

Asian treehole mosquito
Less dependent on people
Depends on tall vegetation
Outdoor mosquito
Suburban/rural areas
Main dengue vector in some areas / secondary
Greater cold hardiness
Better competitor in larval stage

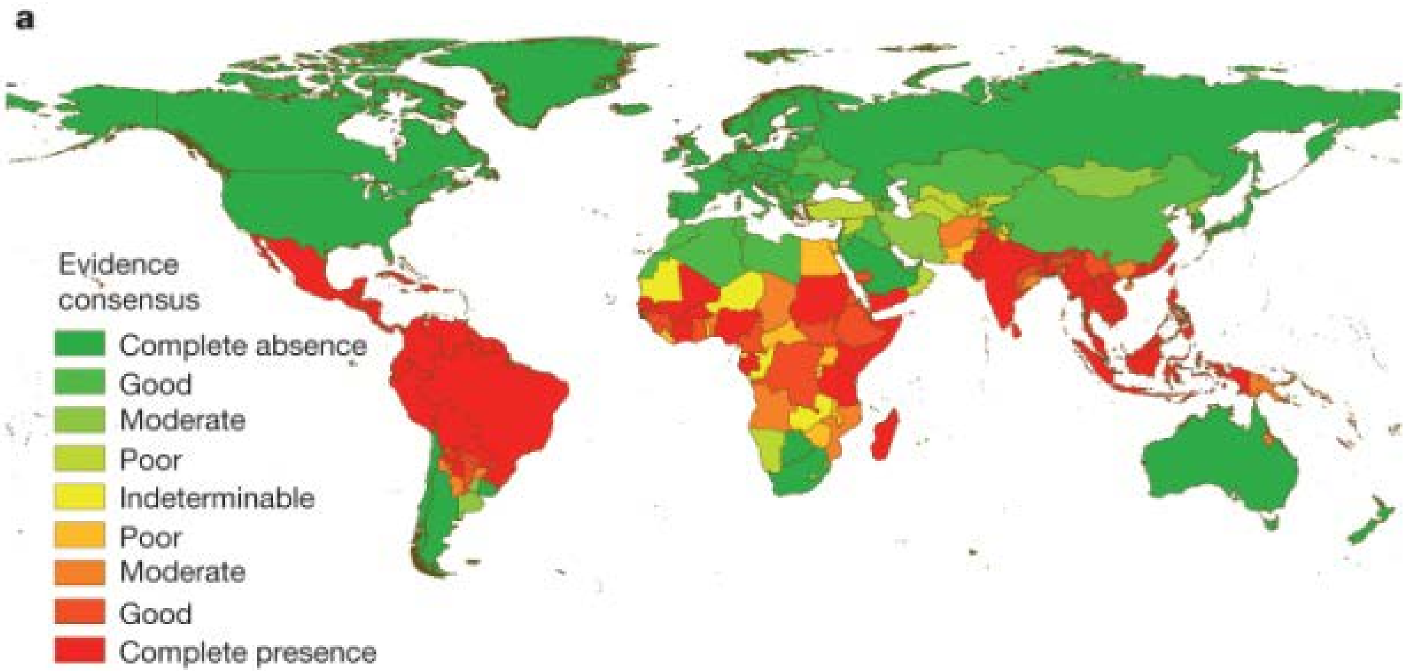
R. Barerra (CDC): AMCA Webinar 2014

Epidemiology

- Globally, most important arbovirus
- There are 390 million dengue infections per year, of which 96 million present some level of disease severity

- Mortality due to dengue can be <1%

Global evidence consensus, risk and burden of dengue in 2010.

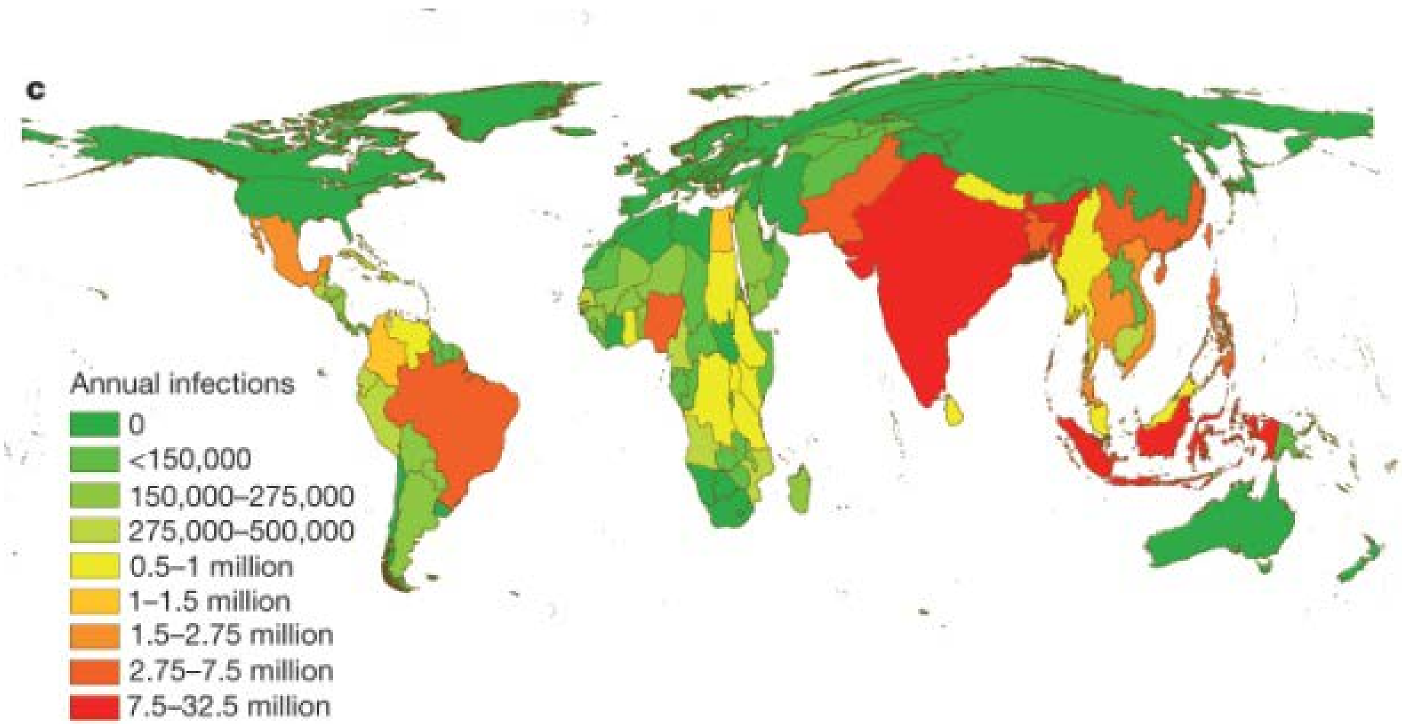


National and subnational evidence consensus on complete absence (green) through to complete presence (red) of dengue

nature

S Bhatt *et al. Nature* **000**, 1-4 (2013) doi:10.1038/nature12060

Global evidence consensus, risk and burden of dengue in 2010.



Cartogram of the annual number of infections for all ages as a proportion of national or subnational (China) geographical area

S Bhatt *et al. Nature* **000**, 1-4 (2013) doi:10.1038/nature12060

nature

Dengue in the USA

a. Endemic / epidemic dengue
   i. *Aedes aegypti* is present: **Puerto Rico, US Virgin Islands, and American Samoa**

b. Non-endemic – Risk for dengue emergence / re-emergence
   i. *Aedes aegypti* / *Ae. albopictus* are present: Southern areas of **Florida, Texas**, Arizona, New Mexico, California
   ii. *Aedes albopictus* is present: Guam, Mariana Islands, and **Hawaii**

c. Non-endemic – Lower risk areas
   i. *Aedes albopictus* is present: South Atlantic (Florida, Georgia, South Carolina, North Carolina, Virginia, West Virginia, Maryland, Delaware, Washington DC), Middle Atlantic (Pennsylvania, New Jersey, Connecticut, **New York**), East South Central (Mississippi, Alabama, Tennessee, Kentucky), West South Central (Louisiana, Oklahoma, Arkansas), and East North Central (Illinois, Indiana, Ohio)

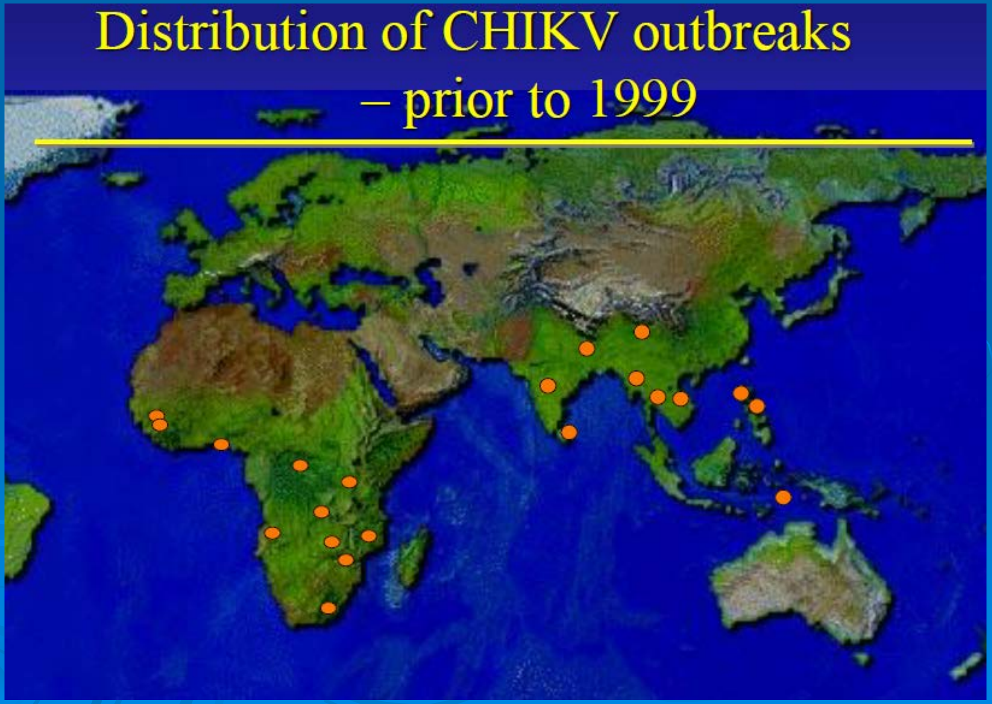
d. No dengue vectors - Risk for dengue vectors invasions but their establishment is unlikely
   i. Pacific (Alaska, Washington, Oregon), Mountain (Montana, Idaho, Wyoming, Nevada, Utah, Colorado), West North Central (North Dakota, South Dakota, Minnesota, Nebraska, Iowa, Kansas, Missouri), and East North Central (Wisconsin, Michigan)

In bold: recent autochthonous dengue transmission

R. Barerra (CDC): AMCA Webinar 2014

Chikungunya Virus (CHIKv)

- Togoviridae, Alphavirus
- Infection likely provides life-long immunity
- Multiple virus strains with different epidemic potentials



CHIKv

- Most infections are symptomatic (76-97%)
- Chikungunya virus infection can cause a debilitating illness, most often characterized by fever, headache, fatigue, nausea, vomiting, muscle pain, rash, and joint pain (similar to dengue)
- Chikungunya virus infection is thought to confer life-long immunity

CHIKv

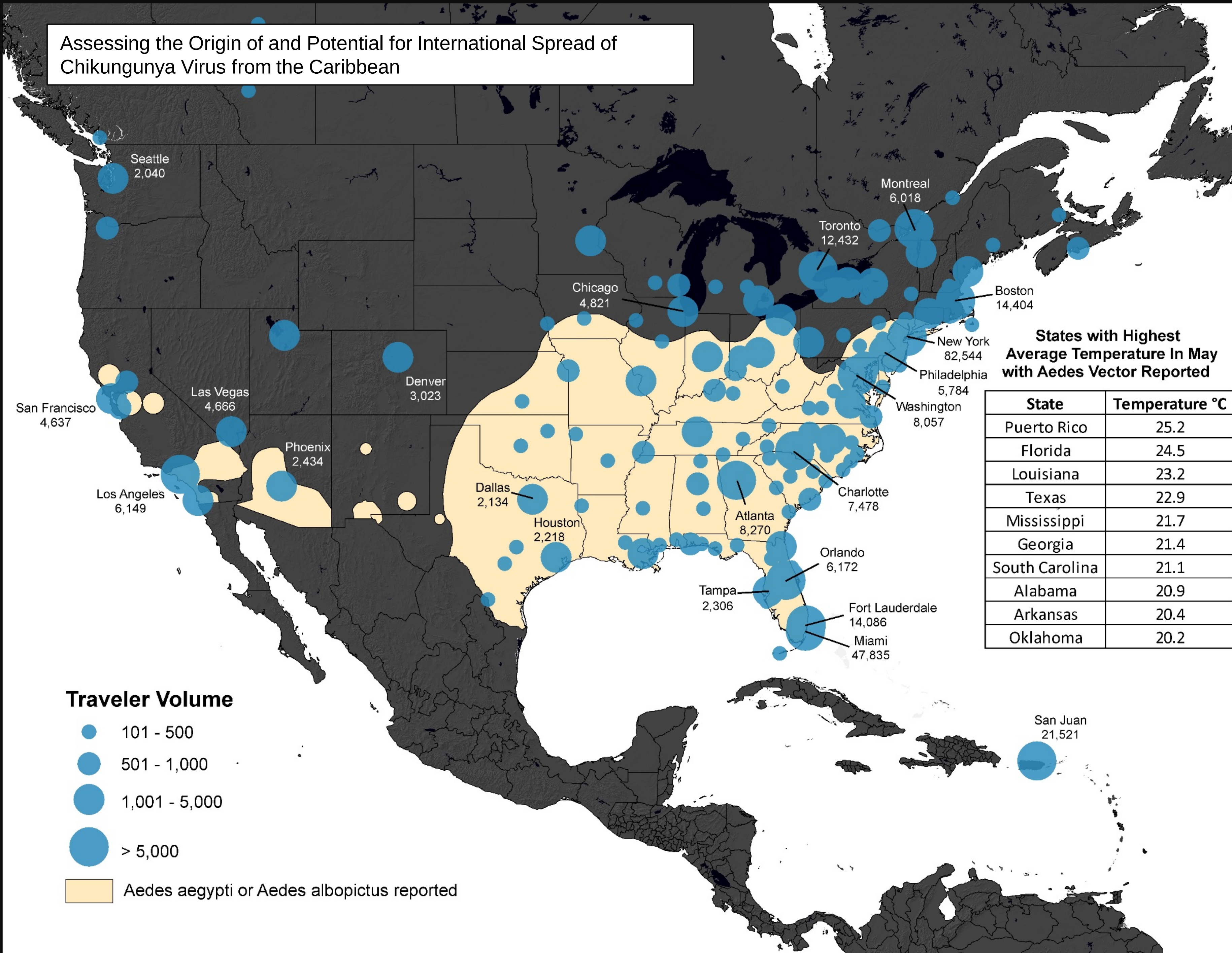
- Fatalities related to chikungunya virus are rare
- There is no vaccine or specific antiviral treatment currently available for chikungunya or dengue fever

No Vaccine or Therapies: Prevention is the Key!

Rapid Spread in Caribbean

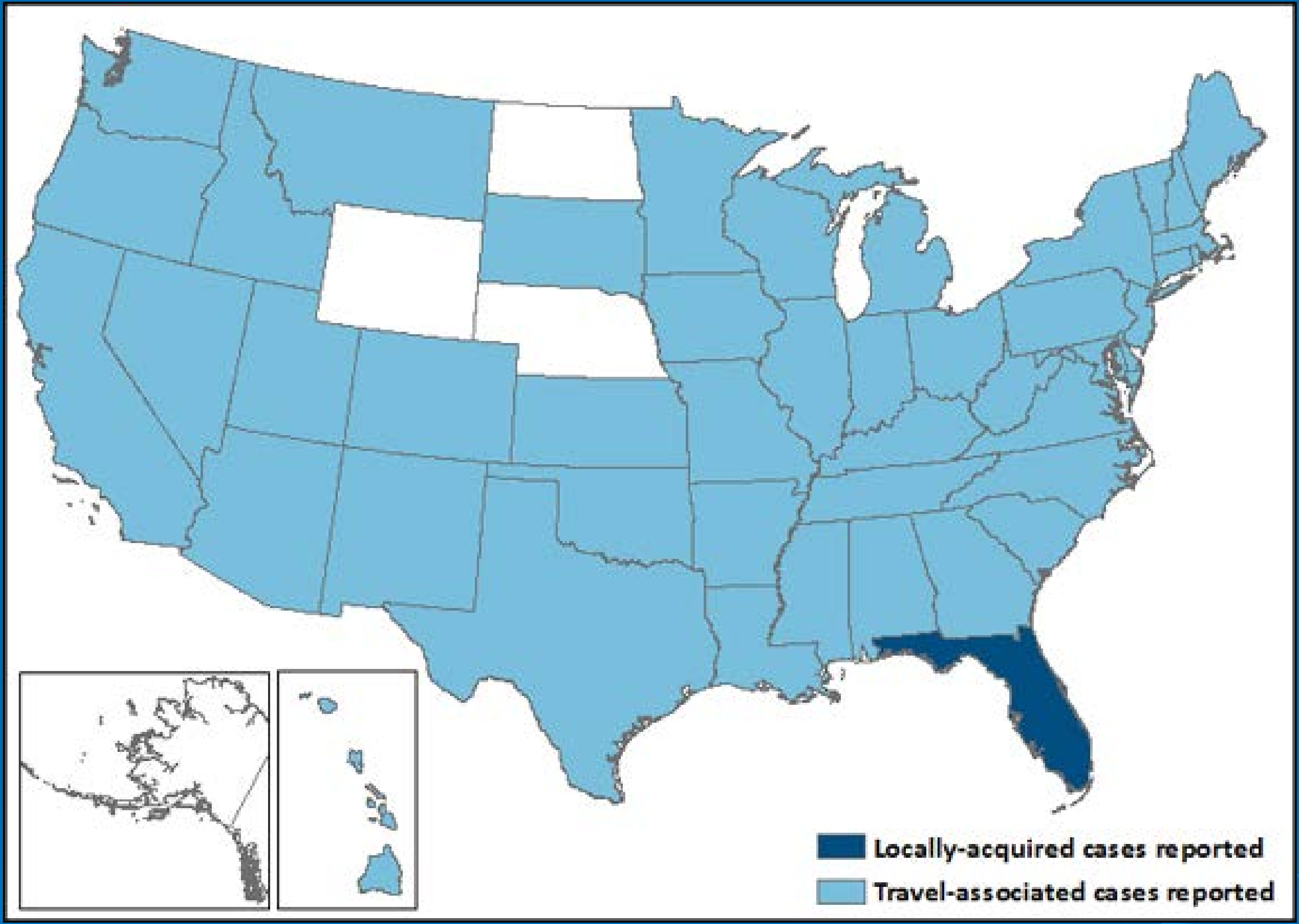
- Completely immunologically naïve population
- Social factors
- Environmental/ecological conditions
- Presence of both known epidemic vectors
- Insufficient/unavailable public health response
- High viremias/ long duration of viremia

Assessing the Origin of and Potential for International Spread of Chikungunya Virus from the Caribbean

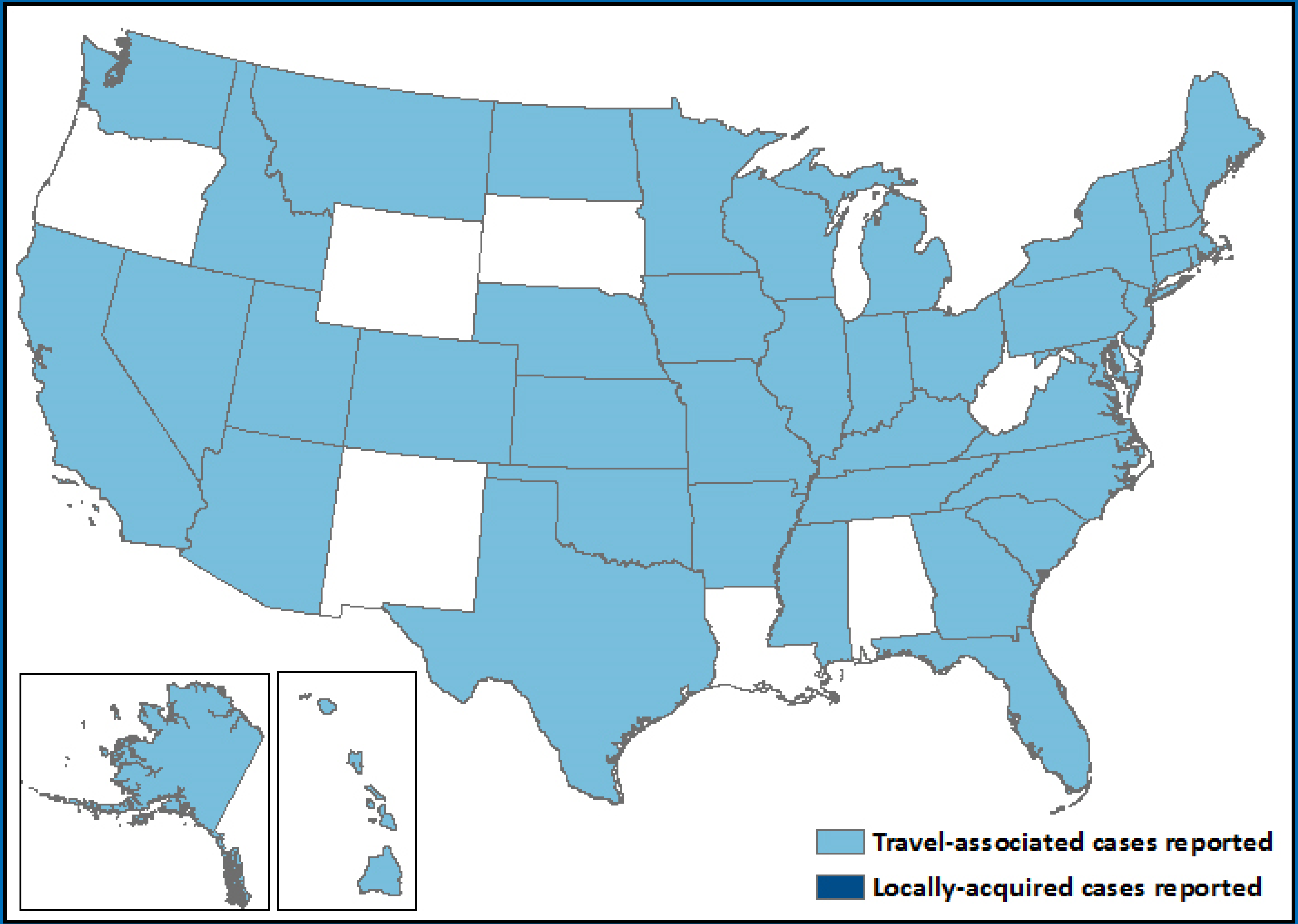


States with Highest Average Temperature In May with Aedes Vector Reported

State	Temperature °C
Puerto Rico	25.2
Florida	24.5
Louisiana	23.2
Texas	22.9
Mississippi	21.7
Georgia	21.4
South Carolina	21.1
Alabama	20.9
Arkansas	20.4
Oklahoma	20.2



States reporting chikungunya virus disease cases – United States, 2014
CDC



States reporting chikungunya virus disease cases – United States, 2015
(as of November 17, 2015)
CDC

Emerging Issues in Vector-Borne Diseases: La Crosse Encephalitis

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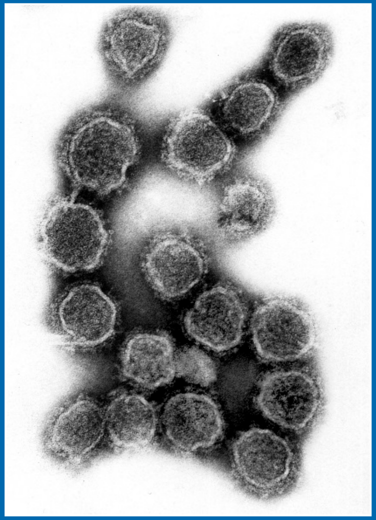
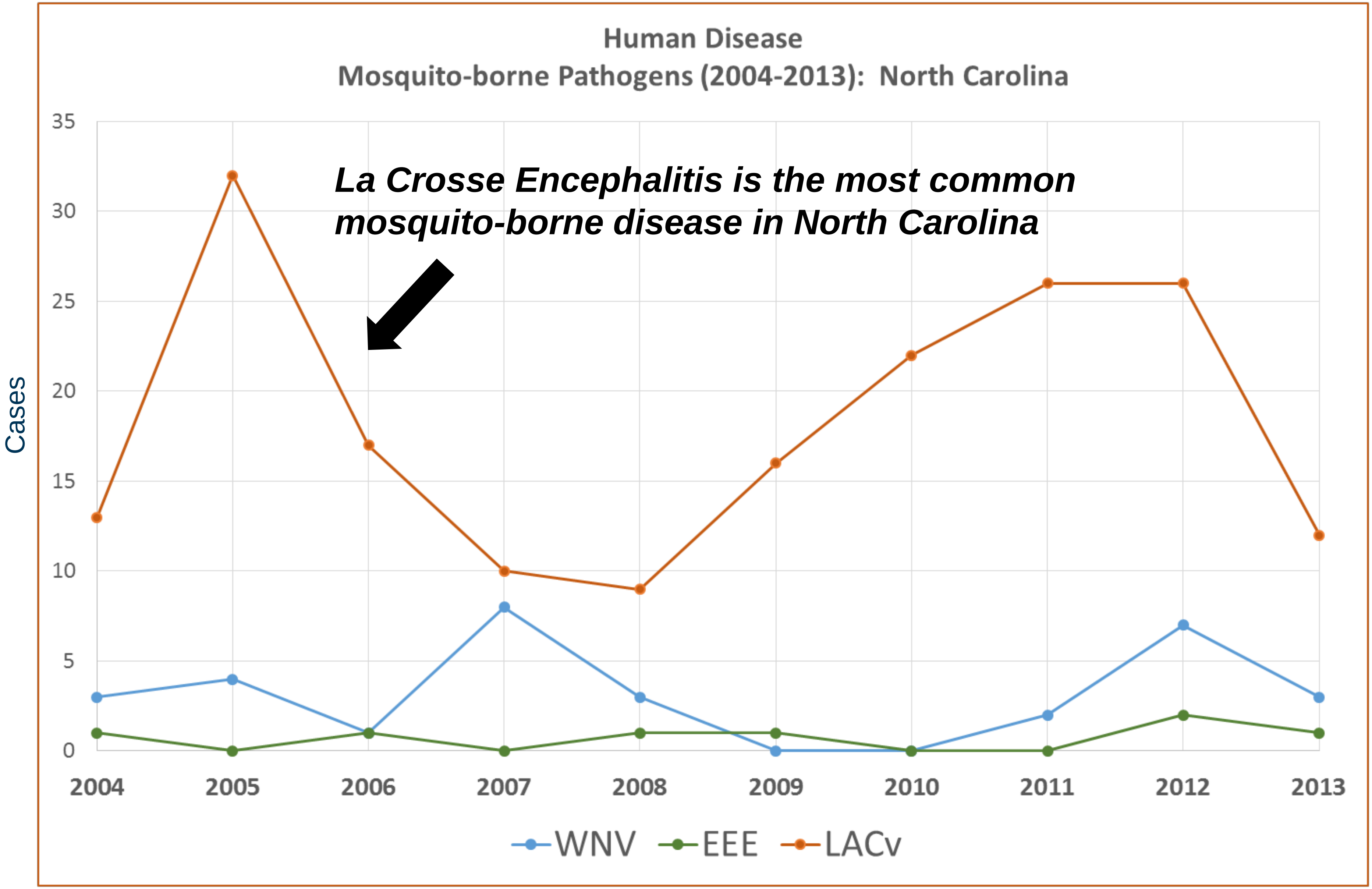
La Crosse Virus (LACv)

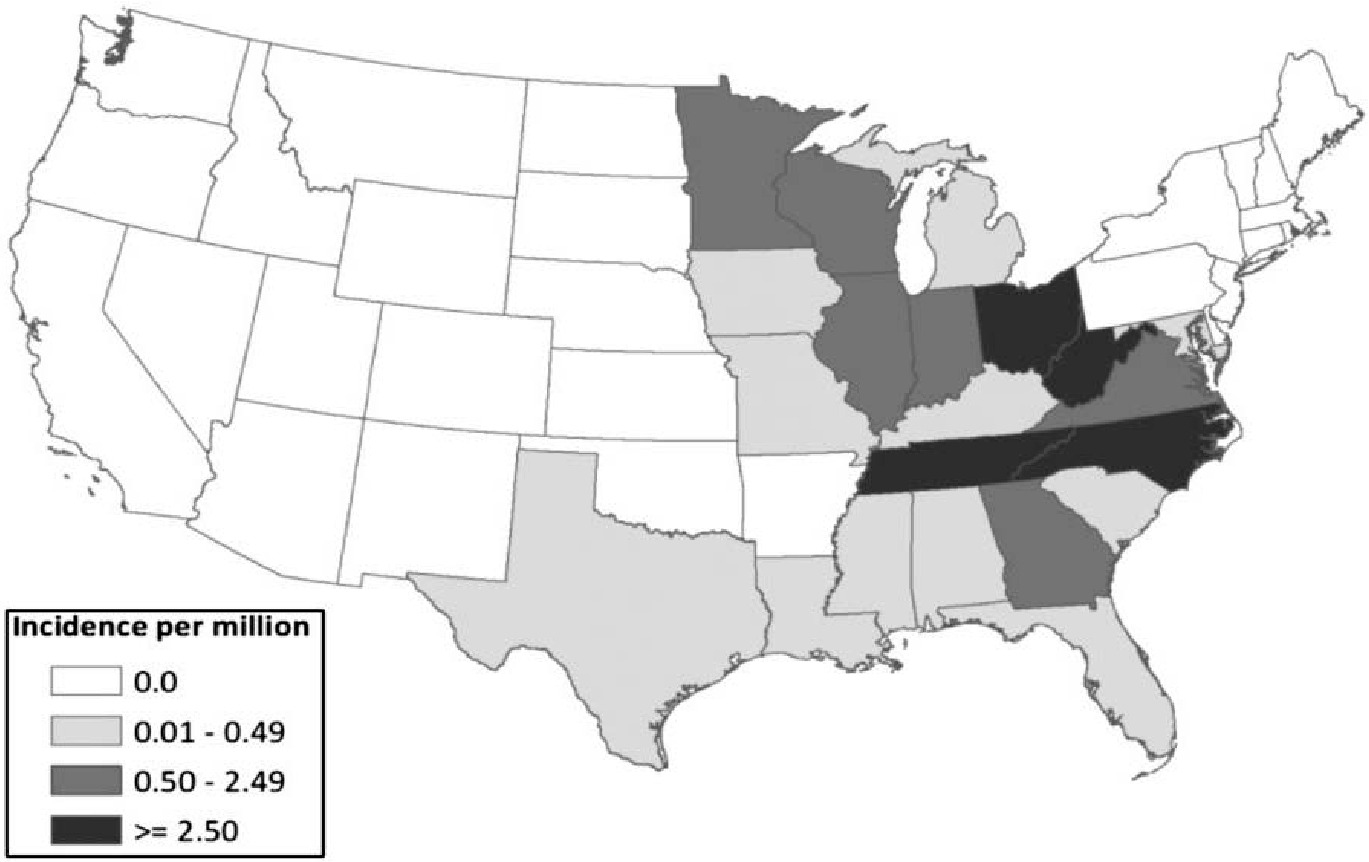
- Isolated in 1960's in La Crosse, Wisconsin from a fatal case (4 y/o girl)
- Only acquired through the bite of a mosquito
  - Eastern-tree hole mosquito (principle vector)
- LACV is the most common arboviral cause of pediatric encephalitis in the US





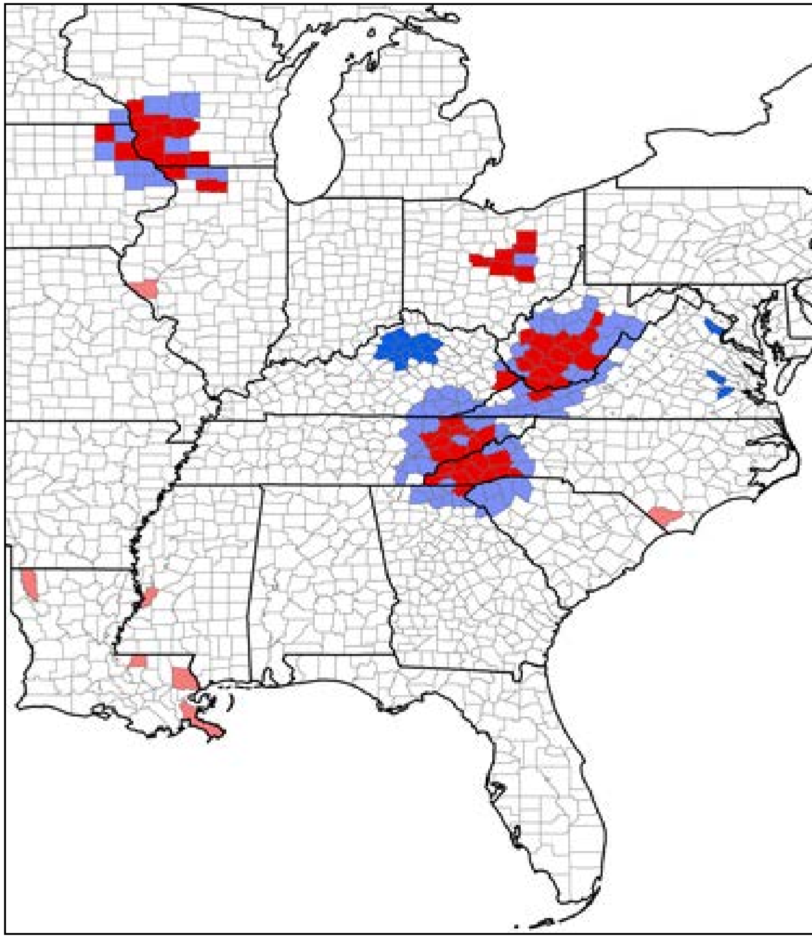
CDC/ArboNET/USGS

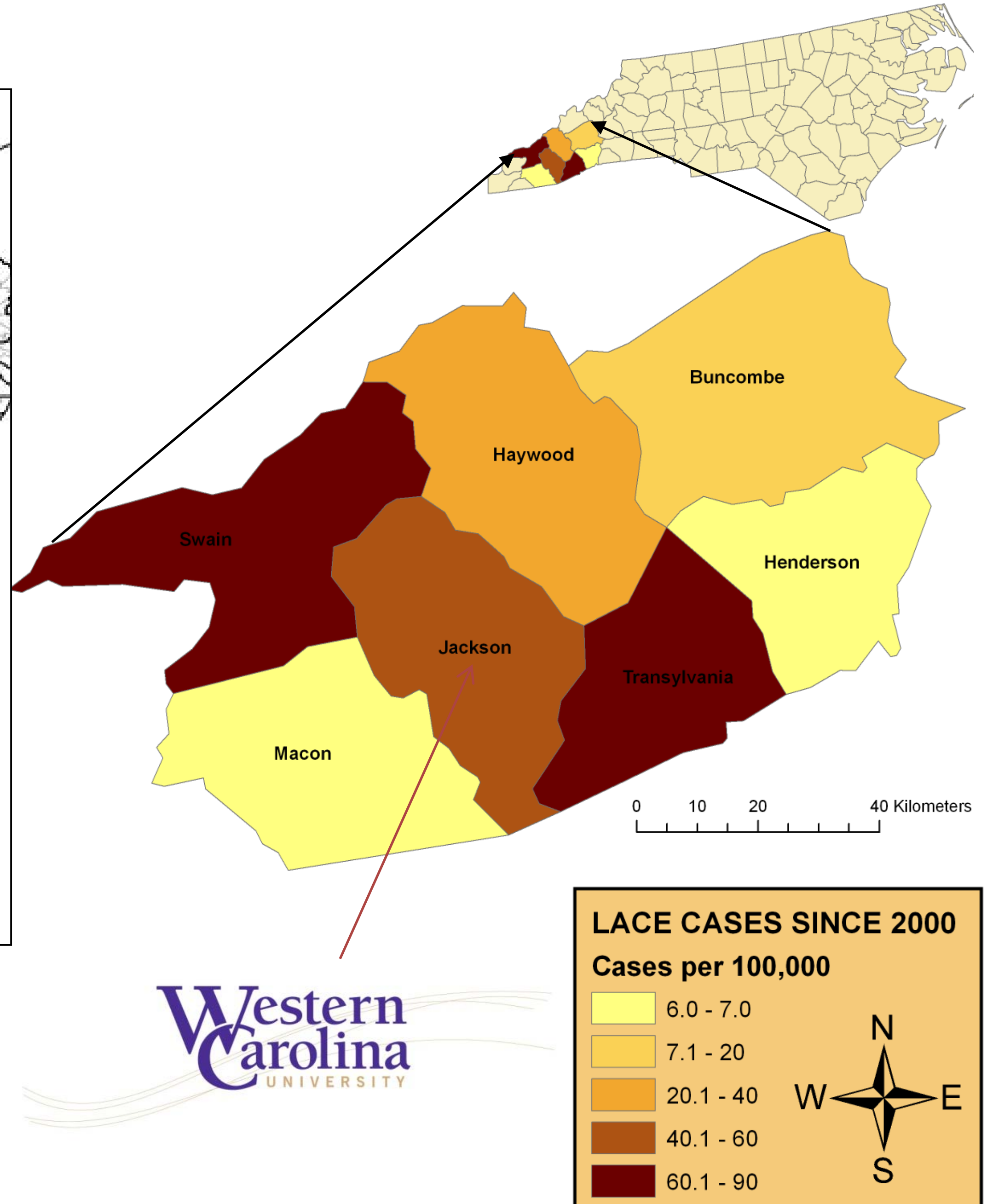
LACE (2003-2012)



Although LACE was historically found throughout the Midwest, burden has shifted to Appalachian region: 81% reported from Ohio, West Virginia, North Carolina, and Tennessee

(Gaensbauer et al., 2014)

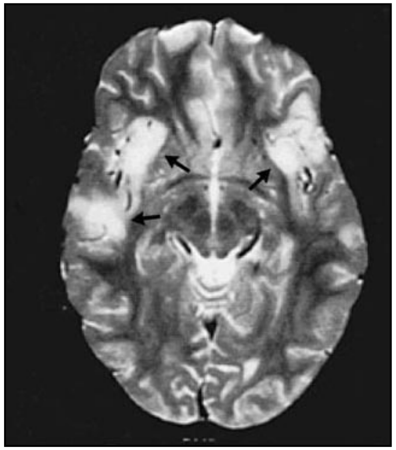




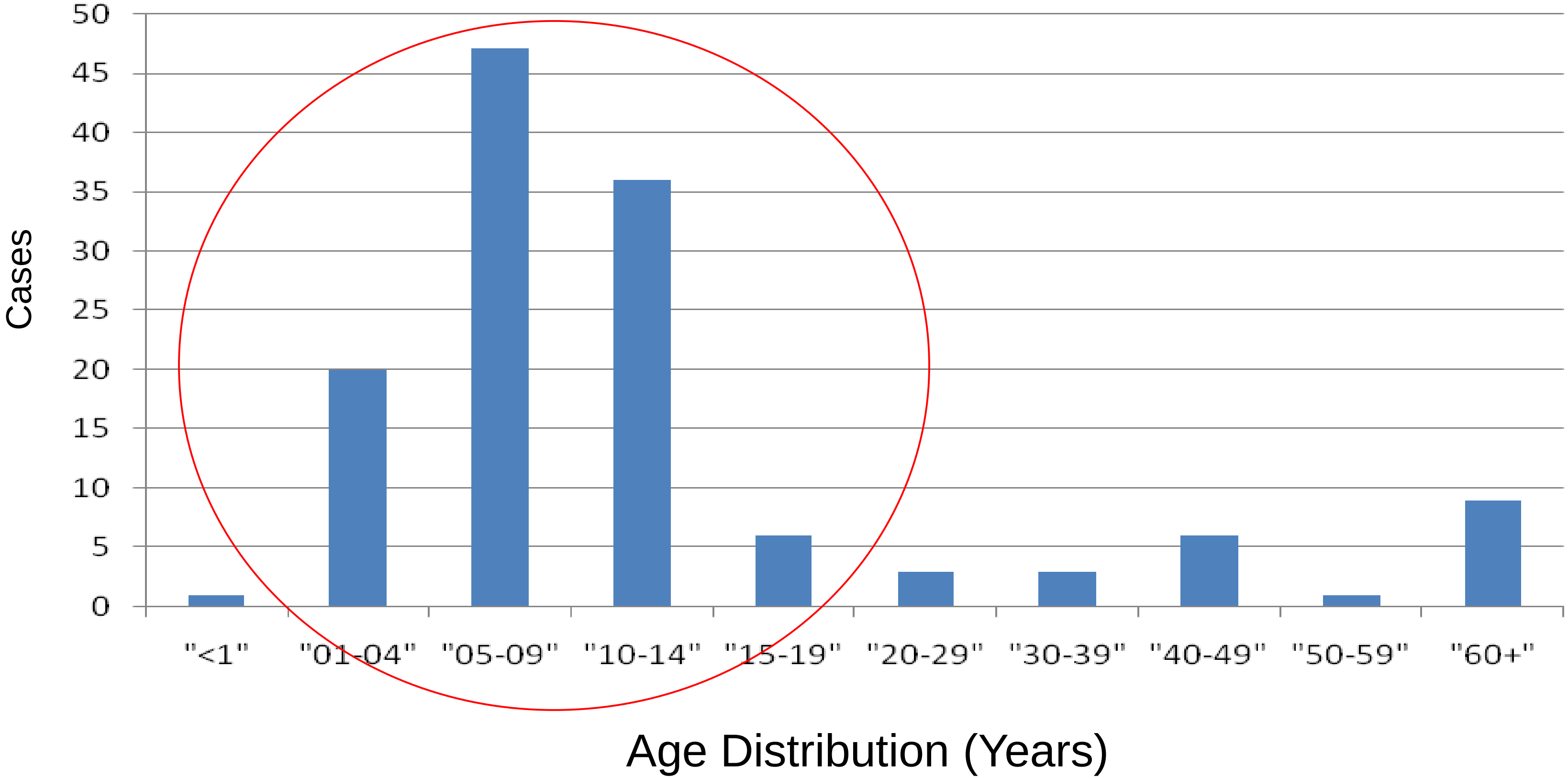
Haddow AD and Odoi A, The incidence risk, clustering, and clinical presentation of La Crosse virus infections in the eastern United States, 2003-2007. *PLoS One*. 2009 Jul 3;4(7):e6145.

Western Carolina UNIVERSITY

La Crosse Encephalitis

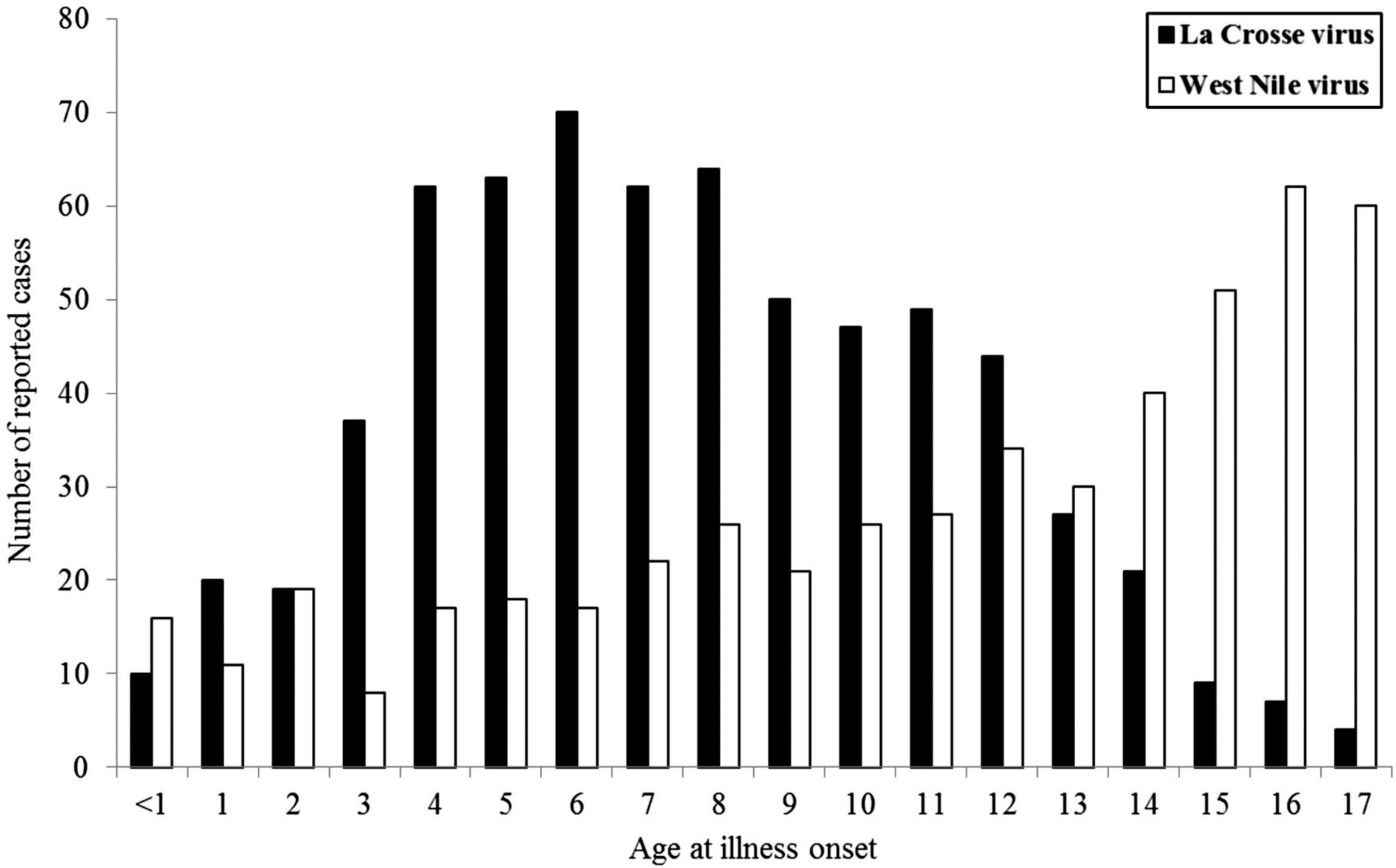


Illness is seen primarily in pediatrics



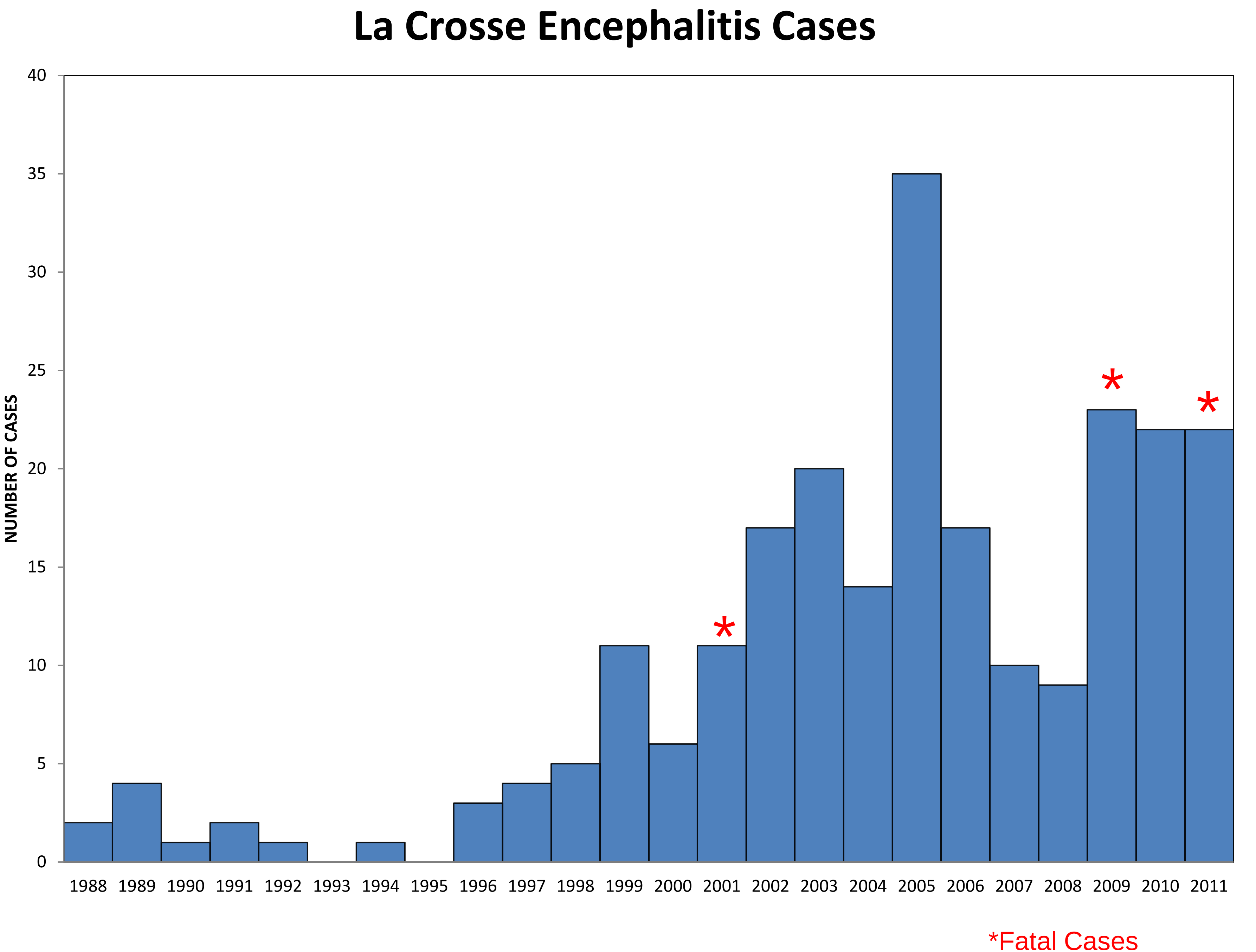
1998-2005 (NC)

Number of reported pediatric neuroinvasive arboviral disease cases due to La Crosse and West Nile viruses, by age at illness onset: United States, 2003–2012.

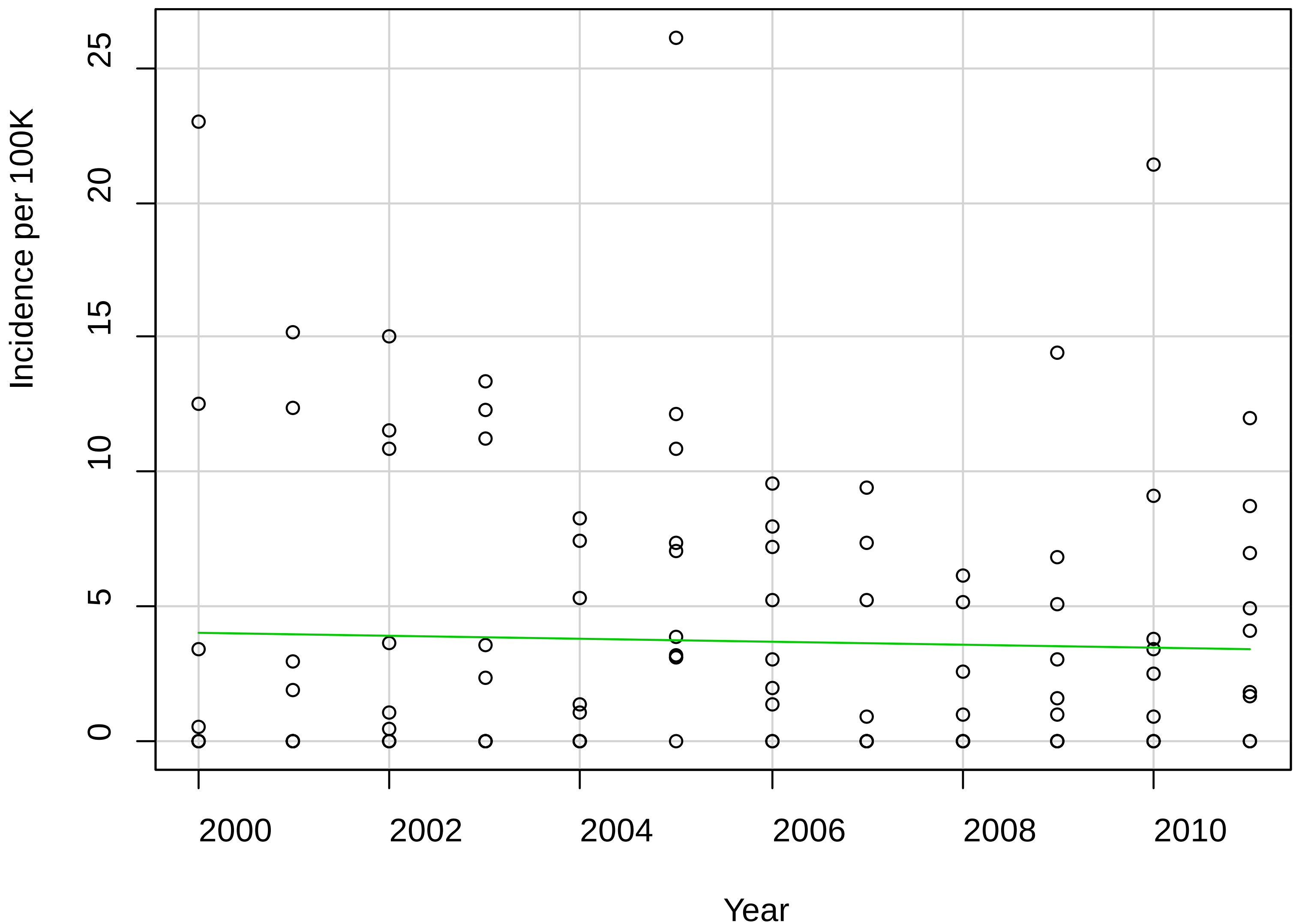


James T. Gaensbauer et al. Pediatrics 2014;134:e642-e650

PEDIATRICS

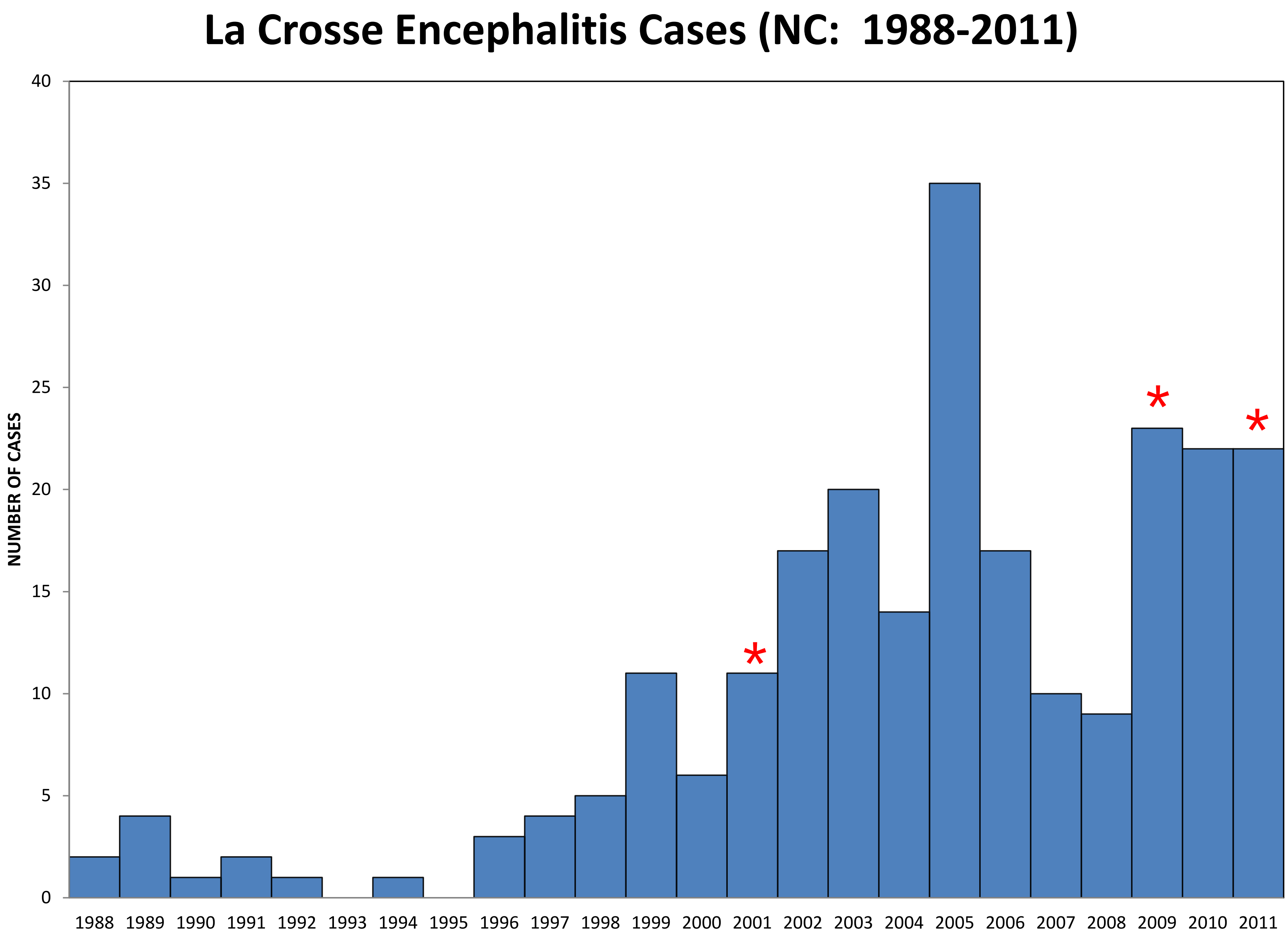

La Crosse Encephalitis Cases
NUMBER OF CASES
0
5
10
15
20
25
30
35
40
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
*
*
*
*Fatal Cases

Annual Incidence per 100K (Western NC Counties)



Pearson's *r : -0.039*

95% CI: -0.21 – 0.14)


La Crosse Encephalitis Cases (NC: 1988-2011)
NUMBER OF CASES
0
5
10
15
20
25
30
35
40
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
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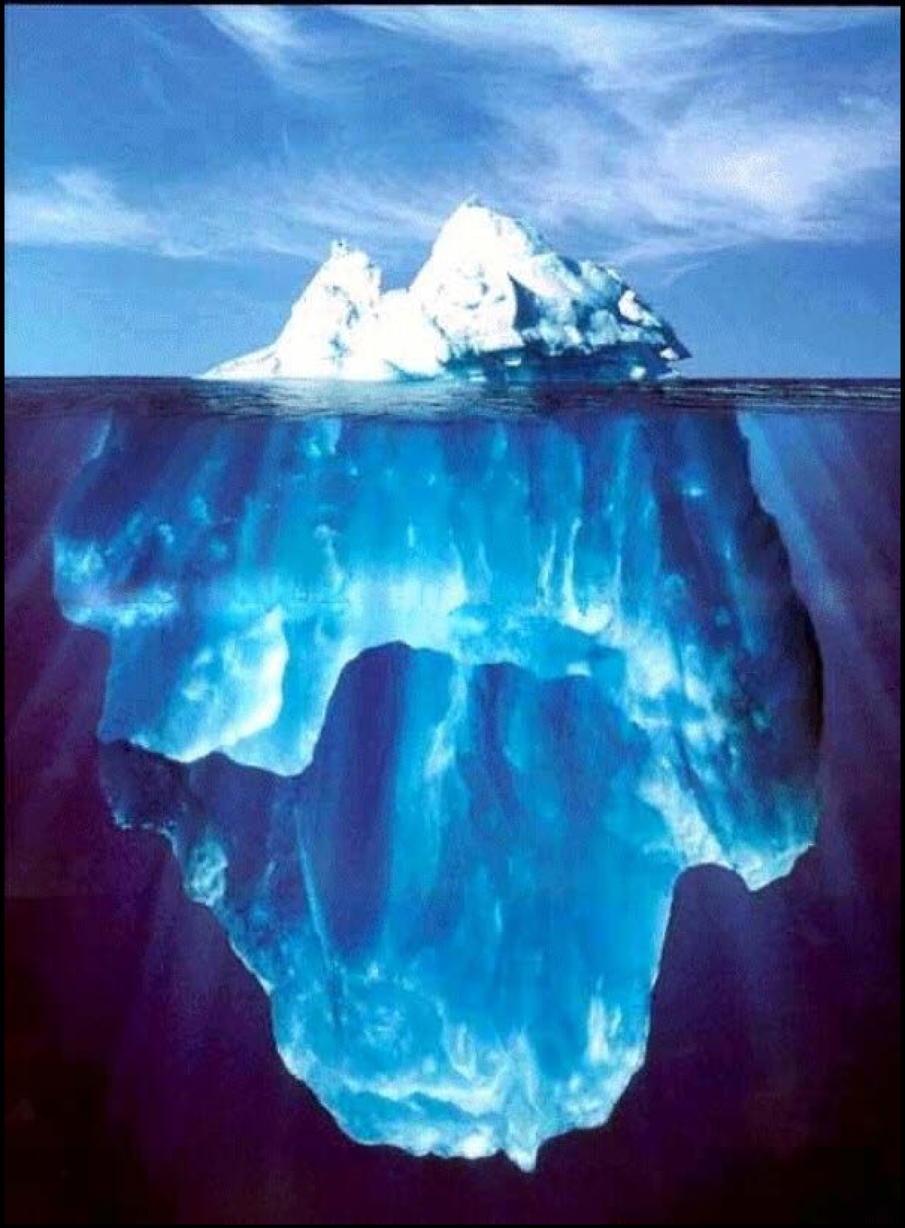
*
*

“Tip of the Iceberg” Phenomenon

Tip of the Iceberg: 1 recognized LACE case

“Tip of the Iceberg” Phenomenon



Iceberg: est. 100-300 individuals exposed to LACV

Prevalence of La Crosse virus antibody in blood serum or Nobuto strip samples collected in western North Carolina*

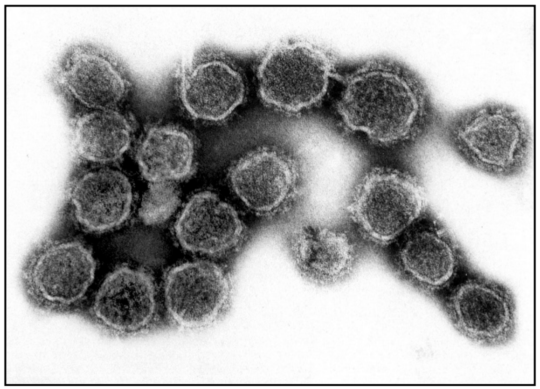
Location	n	% positive per location	Overall % positive
Cherokee Indian Reservation	311	20.6	6.8
Macon County	36	8.3	0.3
Swain County	175	8.0	1.5
Jackson County	225	4.9	1.2
Haywood County	162	2.5	0.4
Eight additional counties	32	3.0	0.1

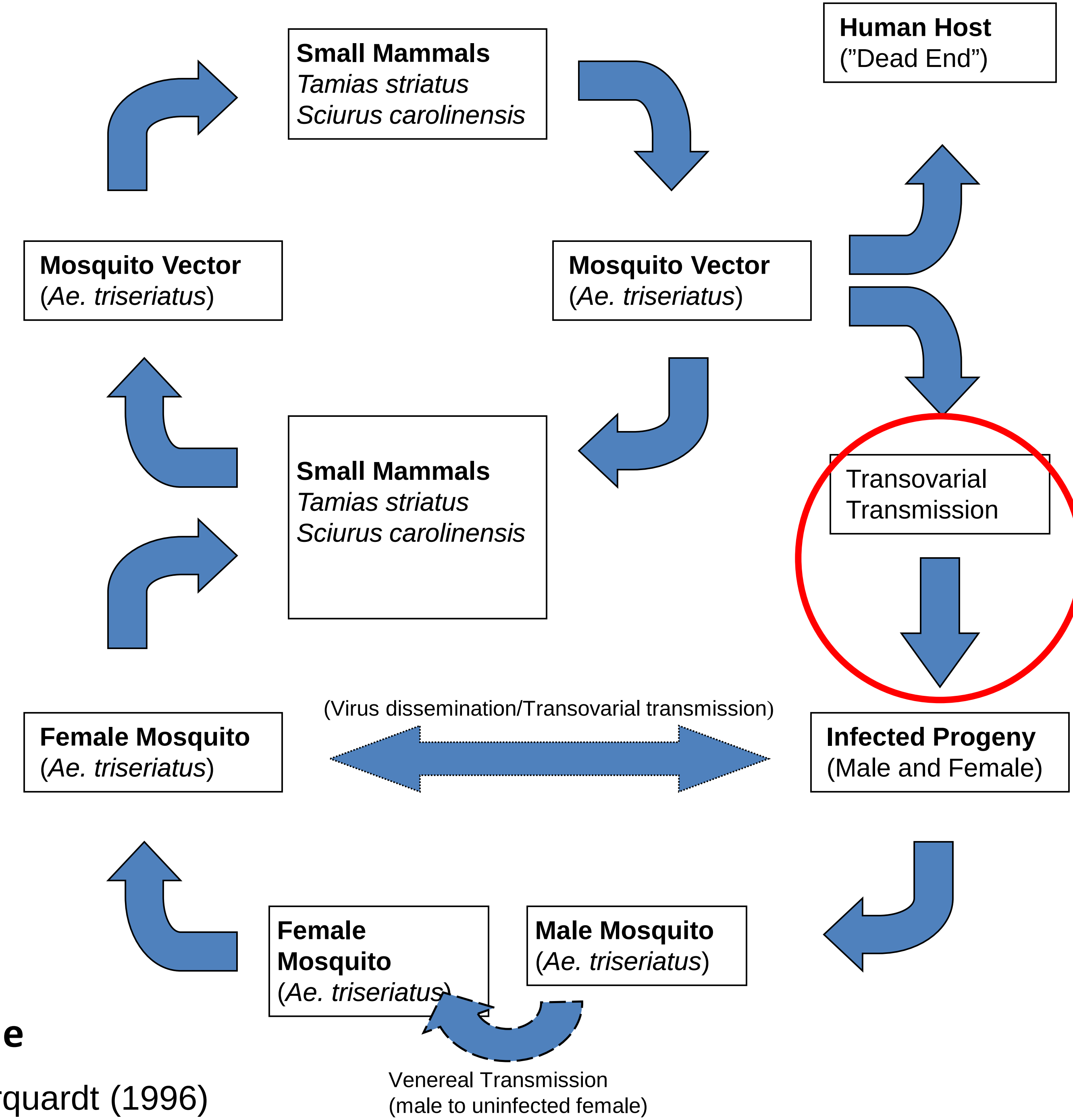
* The county of origin for 66 samples collected off the reservation was missing.

Szumlas et al. 1996

Aedes triseriatus

Photo Credit: CDC: J.Gathany (2002)





La Crosse Virus Cycle

Adapted from Beaty and Marquardt (1996)

INVASIVES: Secondary/Suspect Vectors

Aedes albopictus: Asian Tiger mosquito
Competent in lab
Found infected in nature

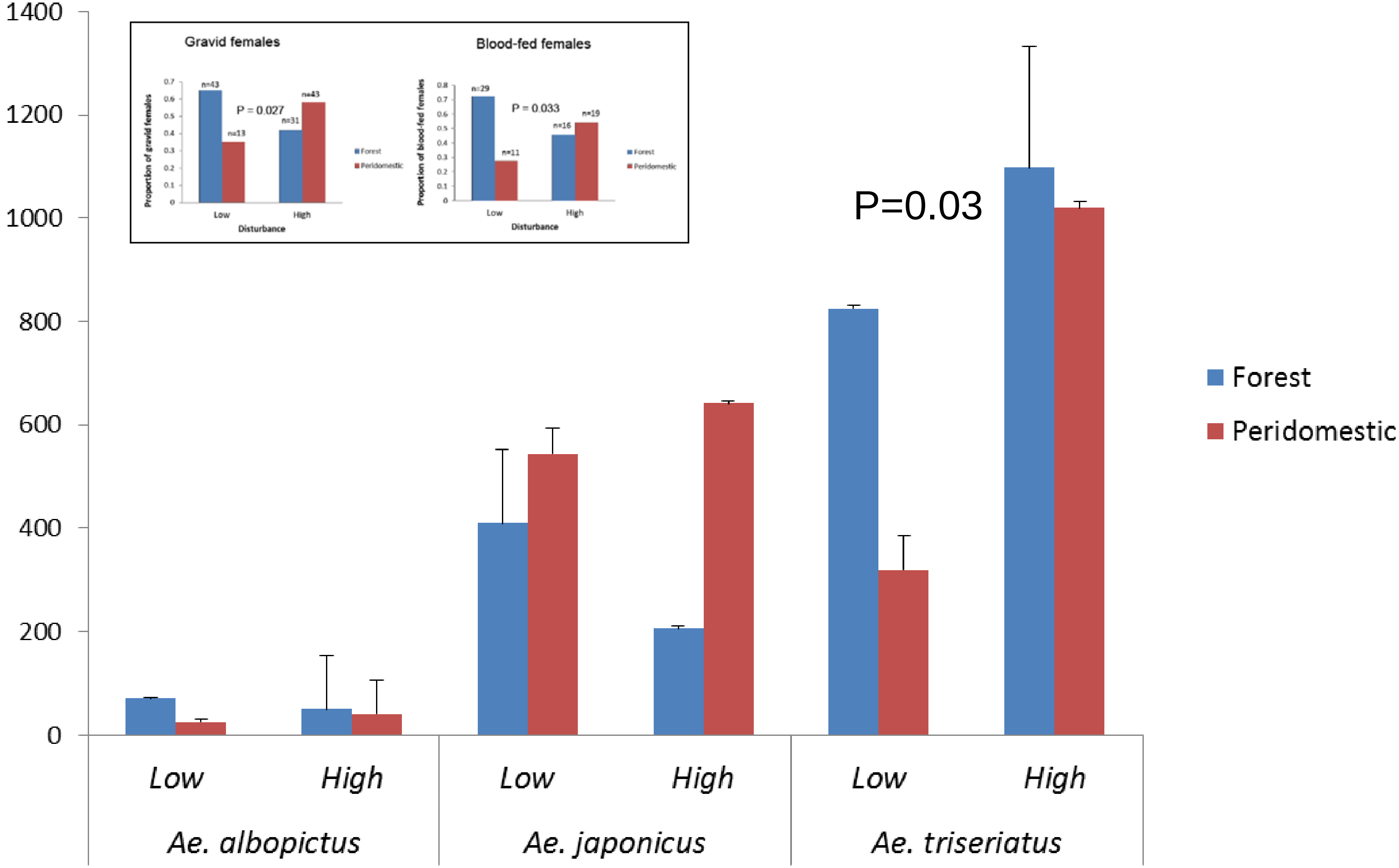
Aedes japonicus: Asian Bush mosquito
Competent in lab
Found infected in nature

MIR for *Ae. japonicus* (0.63) were lower than *Ae. triseriatus* (2.72) and *Ae. albopictus* (3.01) (Westby et al., 2015)

Treeholes

LACE Case Residence

Peridomestic Artificial Containers Increase the abundance of *Aedes triseriatus*



Tamini et al, In Prep

Prevention: Source Reduction

- Source Reduction
  - “Tip and Toss” containers holding water
  - Solid Waste Management
  - Remember “cryptic” habitats
    - Check Rain Gutters
  - Tree-hole Management



Prevention: Personal

- Apply Repellents According to the Label
  - CDC Recommends EPA Registered Repellents*
  - DEET, picaridin, IR3535, and some oil of lemon eucalyptus products
- Long Sleeves and Pants (As Appropriate)
- Avoid contact at “peak” hours

*EPA registration means that EPA does not expect the product to cause adverse effects to human health or the environment when used according to the label.`

QUESTIONS?

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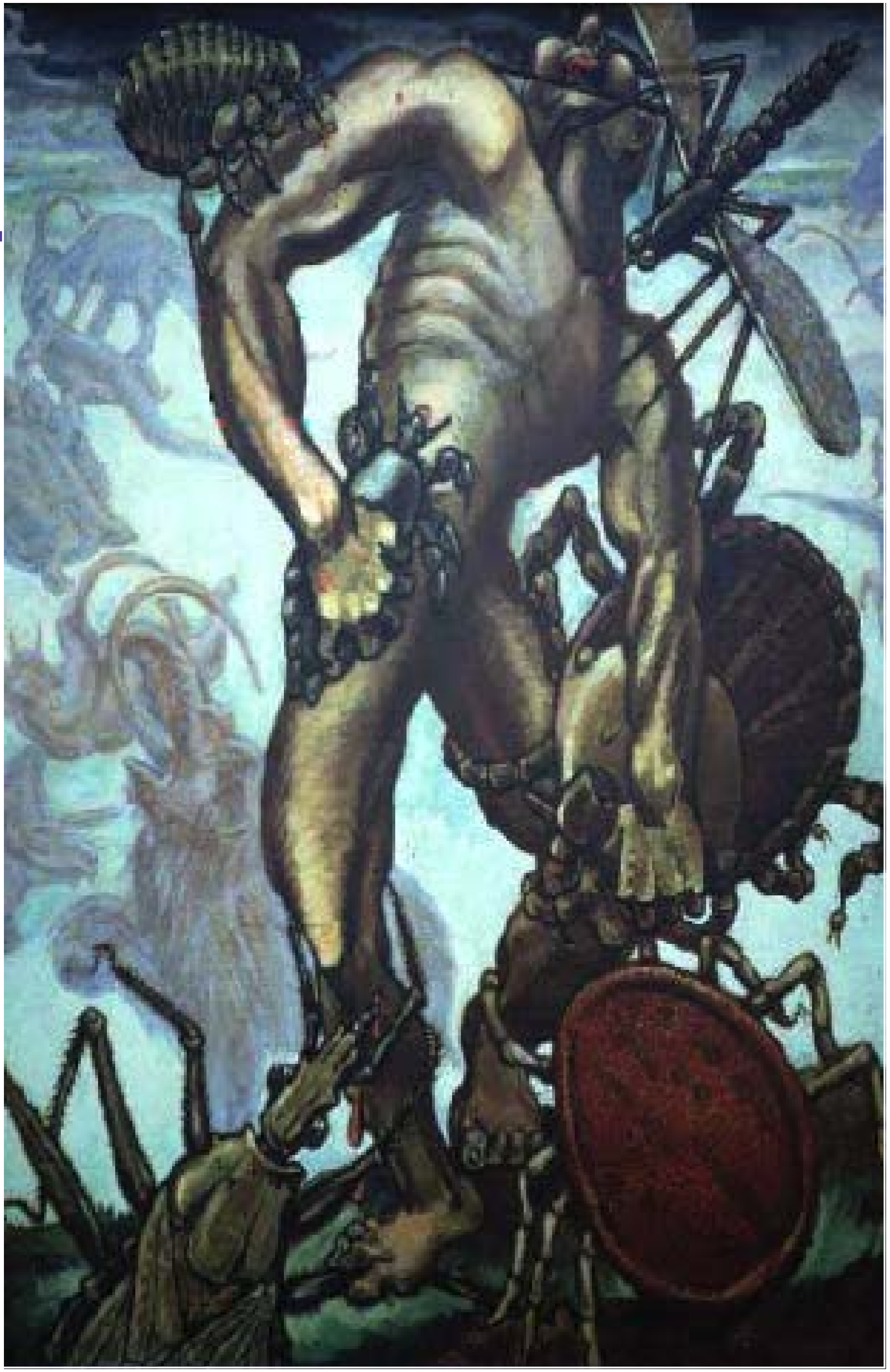


Trapping Methods for LACv Vectors

- CDC light traps (baited)
  - Physiologically biased
  - Battery-powered
- BG-Sentinel
  - Physiologically biased
  - Battery-powered
- Nasci aspirator
  - Limitations: energy and time intensive strategy
- <u>All have limited utility for surveillance & are ineffective for control</u>

CDC Autocidal Gravid Ovitrap

CDC-AGO:

Designed by the CDC for Dengue

Vector: *Ae. aegypti*

-Hay infusion: Microbial Cues

-Lure gravid females

-Affordable, low maintenance

Study Aims (M. Henry)

- 1. Determine the efficacy of AGO for LACv vector surveillance
- 2. Compare attractiveness of a White Oak (WO) infusion versus hay infusion

Abbreviated Methods

- AGOs (n=36) deployed in a balanced, randomized block design at 6 peridomestic sites for 5 weeks (630 trap days per infusion type)
- 6 traps (3 replicates per infusion type) per block
- Sites in LACE endemic area
- Mosquitoes removed 2X weekly

Block 1 Block 2 Block 3 Block 4 Block 5 Block 6

Assign subjects to groups

Each column shows the assignments for a block. For example, the third column for the second row (not counting headings) shows the group assignment of the second subject of the third block.

Subject #	Block 1	Block 2	Block 3	Block 4	Block 5	Block 6
1	A	B	B	A	B	B
2	A	B	A	B	B	A
3	B	A	B	A	A	A
4	B	B	B	A	A	B
5	A	A	A	B	B	B
6	B	A	A	B	A	A

How it works: The random number generator is seeded with the time of day, so it works differently each time you use it. Each subject is first assigned to a group nonrandomly. Then the assignment of each subject is swapped with the group assignment of a randomly chosen subject. This should suffice, but the entire process is repeated twice to make sure it is really random. Note that you can copy and paste the values from the web page into Excel.

Infusion Type
O = Oak
H = Hay

Distance between traps = 5 meters

Methods

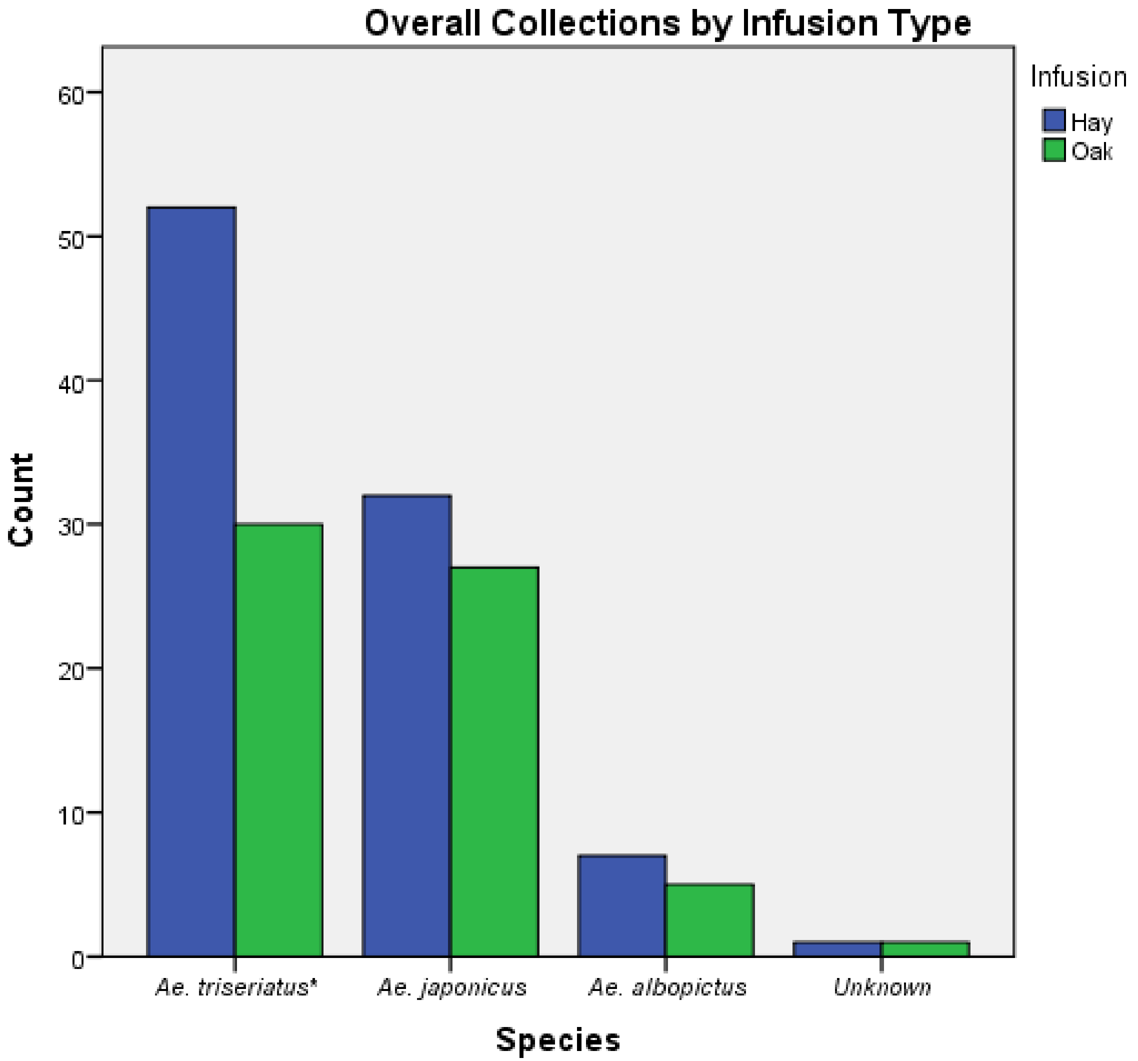
- Mosquitoes collected and processed
- Identified microscopically
- Physiological status determined (e.g., gravid)
- Unknowns -- Mol. techniques

Ae. triseriatus vs. *Ae. hendersoni* (Wilson et al., 2014)

CDC-AGO highly specific for the three targeted LACv vectors (98.7%)

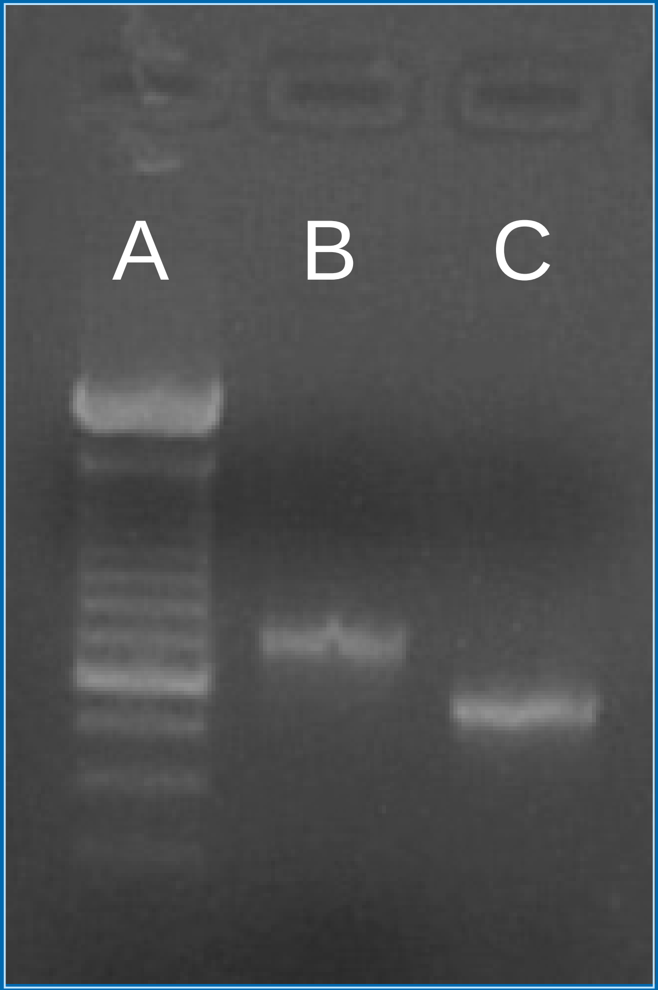
Ae. triseriatus (52.9%)
Ae. japonicus (38.1%)
Ae. albopictus (7.7%)

88% gravid



Mean yield of LACv vectors: **0.84** mosquitoes per trap per week
Lower than yield observed in Dengue control (Barrera et al, 2014) efforts
DEN AGO Study: Mean yield 1.2 mosquitoes per trap per week

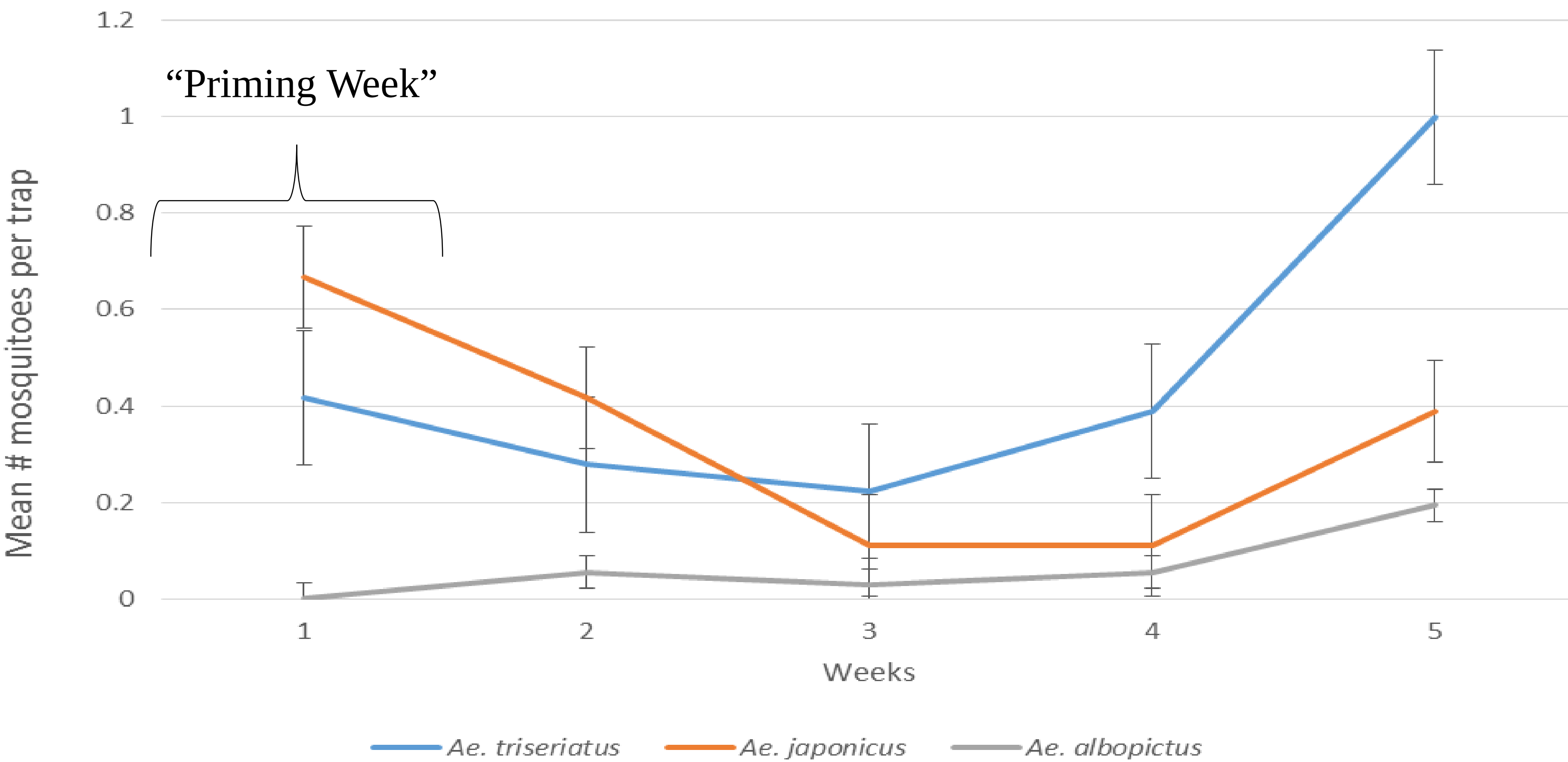
*Aedes triseriatus**

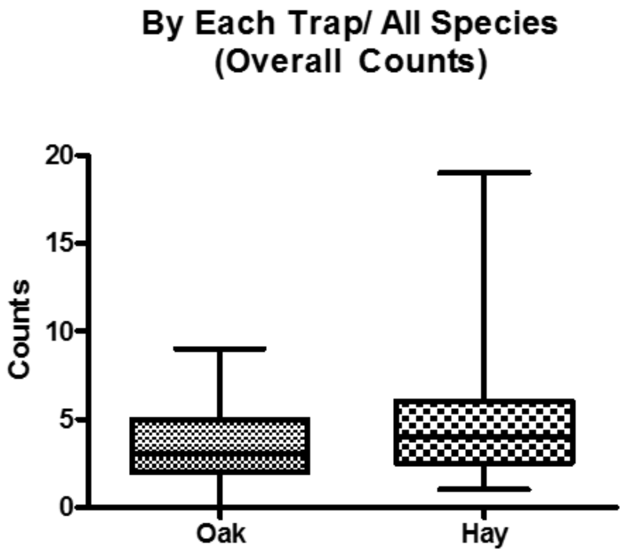


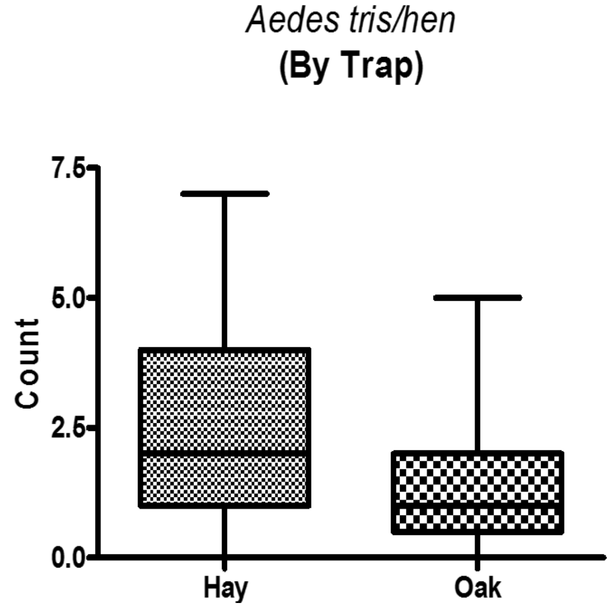
LANE	SAMPLE
A	100 bp ladder (DNA Standard)
B	Ae. triseriatus (691 bp) amplicon
C	Ae. hendersoni (550 bp) amplicon

Wilson R, Harrison R, Riles M, Wasserberg G, Byrd BD. Molecular identification of *Aedes triseriatus* and *Aedes hendersoni* by a novel duplex polymerase chain reaction assay. J Am Mosq Control Assoc. 2014 Jun;30(2):79-82.

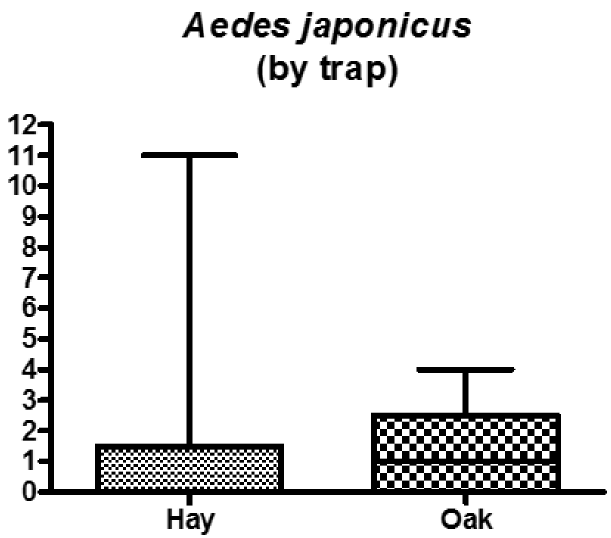
Species-Specific Mosquito Collections by Week







(p<.05)



-Hay infusion more effective for trapping *Ae. triseriatus* than the oak leaf infusion (p<.05)

-Similar infusion study, similar results using gravid trap (Sither)

-Easier method

Results/Significance:

- AGO collects targeted LACv vectors
- Results suggestive for future large-scale trials to reduce peridomestic LACv vector populations
- In this context, the AGOs may be useful as an environmental “sink”
- Ongoing studies to determine practicality of AGO
  - Does the AGO reduce proportion of gravid mosquitoes?
  - How does this influence disease risk?

QUESTIONS?

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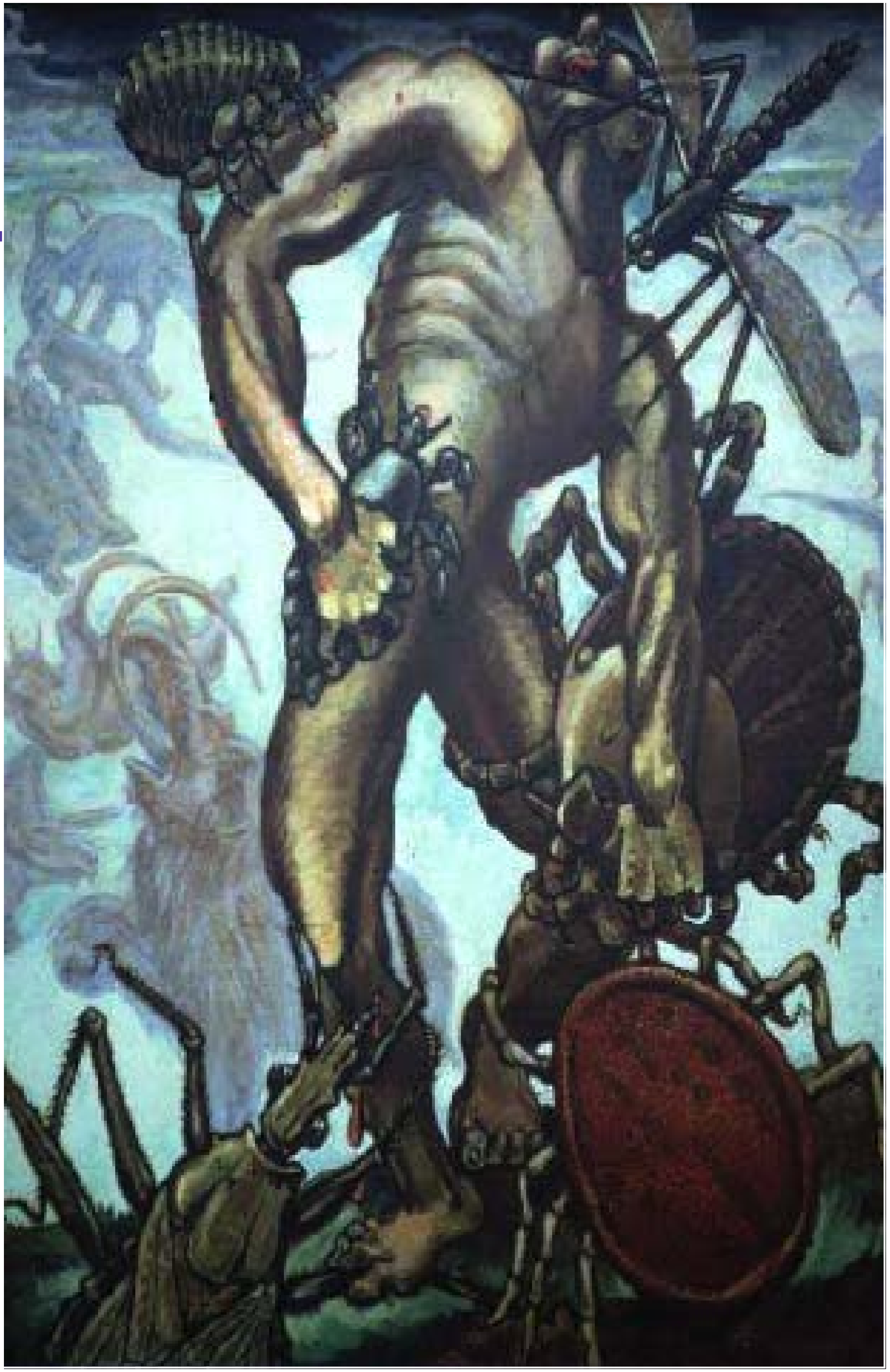
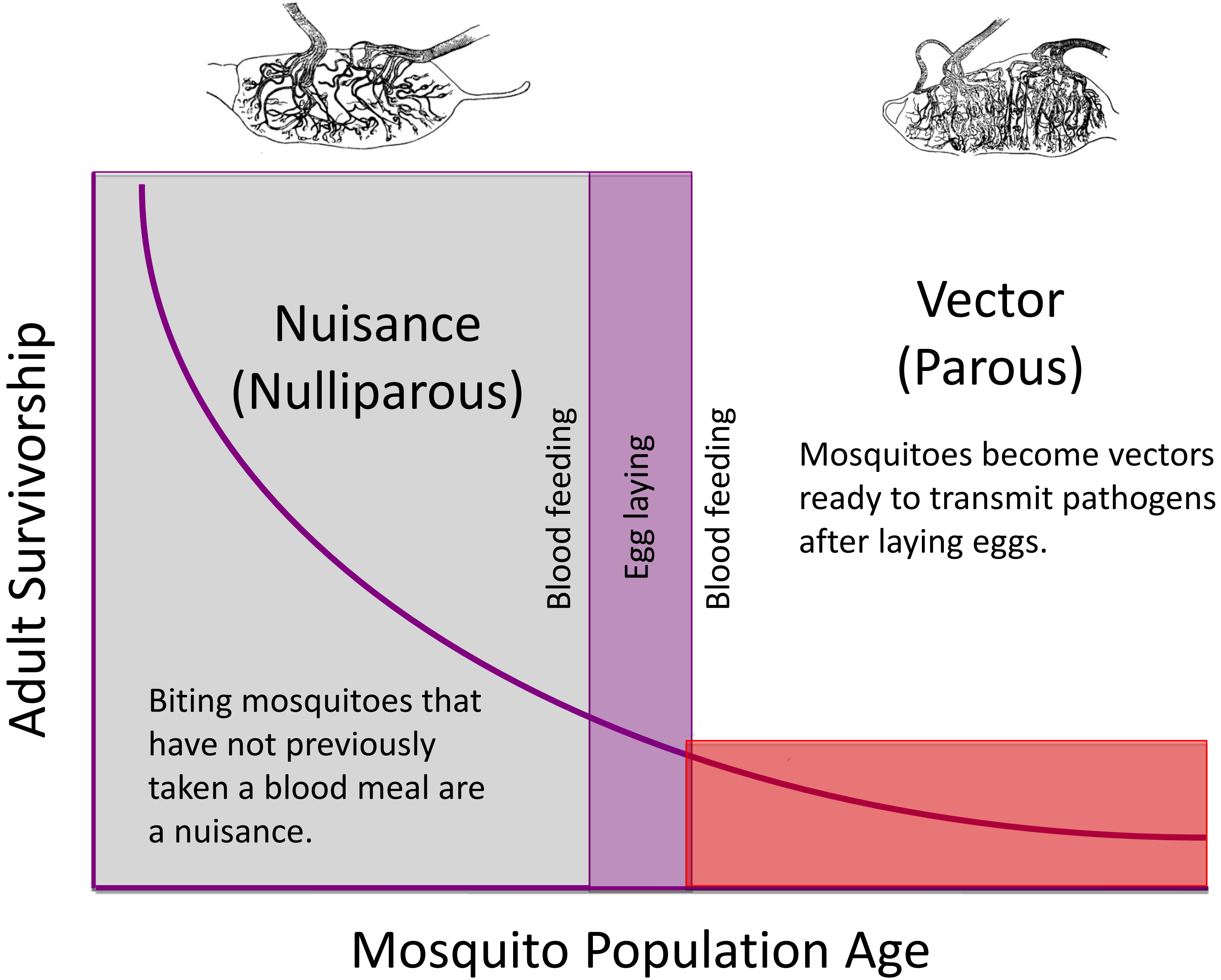
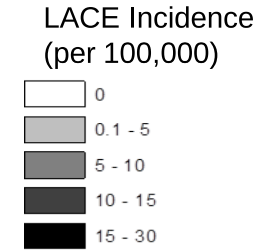
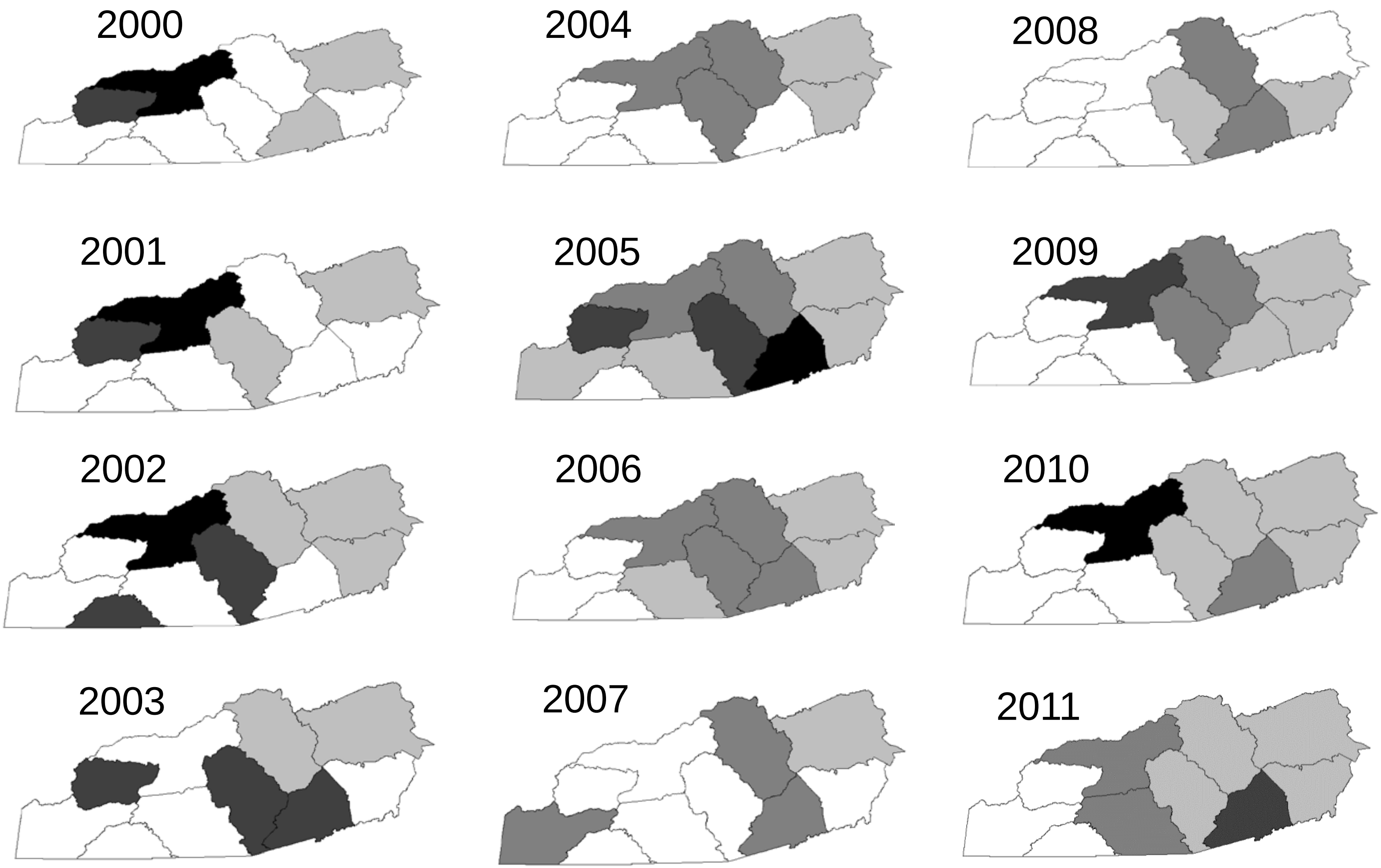


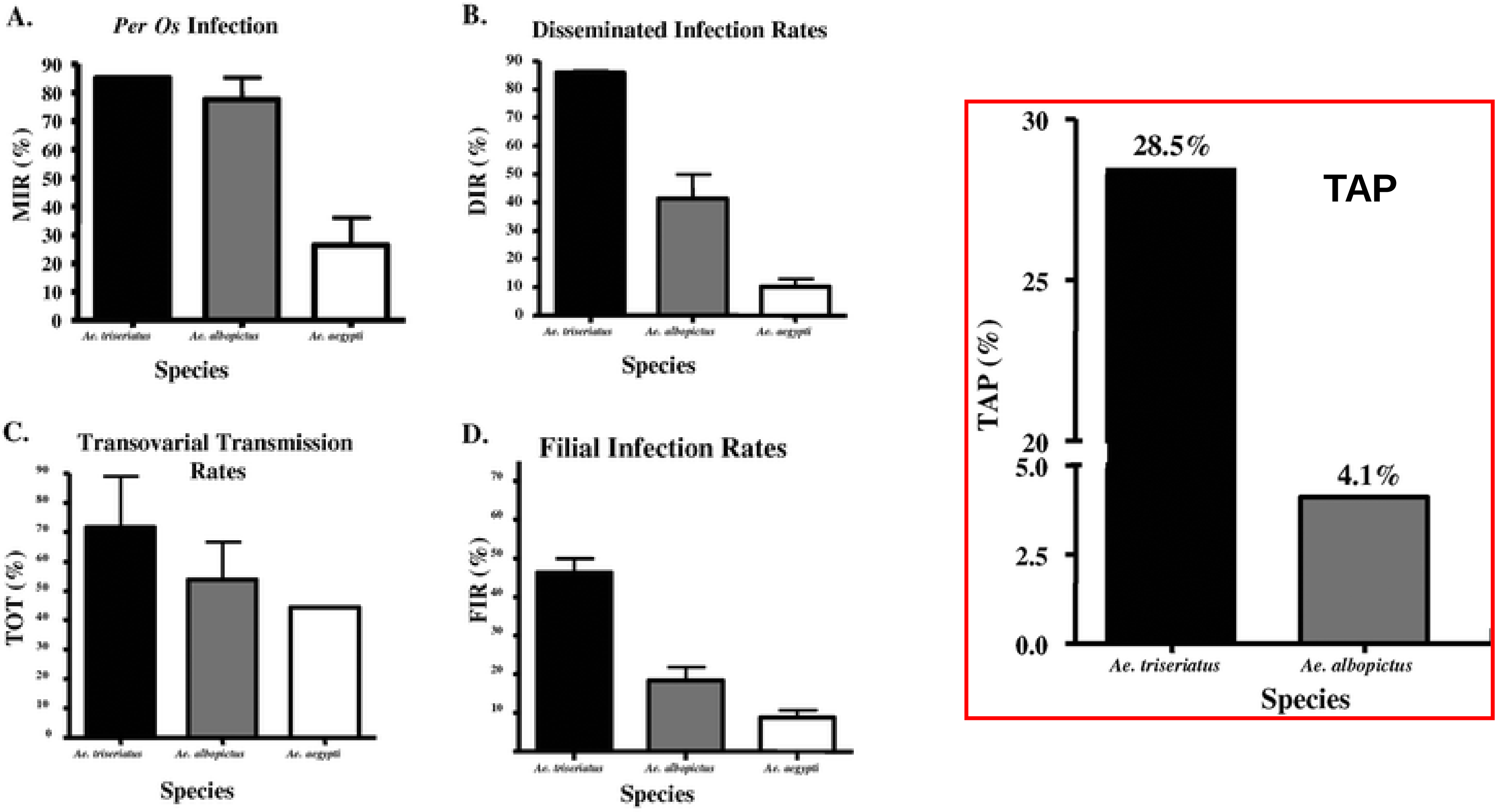

Nuisance
(Nulliparous)
Vector
(Parous)
Blood feeding
Egg laying
Blood feeding
Mosquitoes become vectors ready to transmit pathogens after laying eggs.
Biting mosquitoes that have not previously taken a blood meal are a nuisance.
Adult Survivorship
Mosquito Population Age

Annual Incidence per 100K





Transmission Amplification Potential



Hughes MT et al. Comparative potential of *Aedes triseriatus*, *Aedes albopictus*, and *Aedes aegypti* (Diptera: Culicidae) to transovarially transmit La Crosse virus. J Med Entomol. 2006 Jul;43(4):757-61.

Larval Indices

- House Index

$$HI = \frac{\text{\# of positive houses}}{\text{Total \# of houses surveyed}}$$

After effective control operations the HI=0

Larval Indices

- Breteau Index

$$BI = \frac{\text{\# of positive containers}}{\text{100 houses surveyed}}$$

Risk of dengue transmission when BI>5
Emergency vector control when BI>50

Larval Indices

- Container Index

$$CI = \frac{\text{\# of positive containers}}{\text{Total \# of containers survey}}$$

After effective control operations the CI=0

Unknowns?

- Secondary Morphological Characters
- rDNA ITS2 size