



What You Need to Know About Zika Virus

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Disclosures

I have no relevant financial relationships to disclose for this presentation.

Some Good News

- Zika is not the first emerging infectious disease the blood community has faced
 - *Treponema pallidum* recognized in the early 1900s, with subsequent donor serology testing
 - Hepatitis B recognized in the 1960, with donor HBsAg testing available in the 1970s
 - AIDS epidemic in the 1980s leading to the discovery of HIV, with donor testing available the same year

TEAM AWESOME,



WE GOT THIS!

Approach to Emerging Infectious Disease in the Blood Collection Community



- Donor deferrals
 - Education
 - Risk assessment screening with the DHQ
- Limited physical exam
- Deferral registries
- Laboratory testing including serology and NAT testing
- Pathogen reduction

Lessons From West Nile Virus

- First large scale arboviral threat to the US blood supply
- August 2002: WNV infection acquired by organ donation, due to WNV-infected blood given to organ donor
- Investigational screening test for blood donors available within 7 months of the November 2002 consensus workshop
- WNV has since become endemic in the US

Other Arboviruses

- Chikungunya: Puerto Rico, Caribbean and Latin America
- Dengue: Hawaii, Florida, Texas, Puerto Rico
- Hawaii and Florida have voluntarily suspended collection during local outbreaks
- Puerto Rico quarantines units, followed by post donation follow up for symptoms of infection
- It is thought the modest and slow response addressing the transfusion risk of chikungunya and dengue reflects a general sense of the limited health impact in the continental US

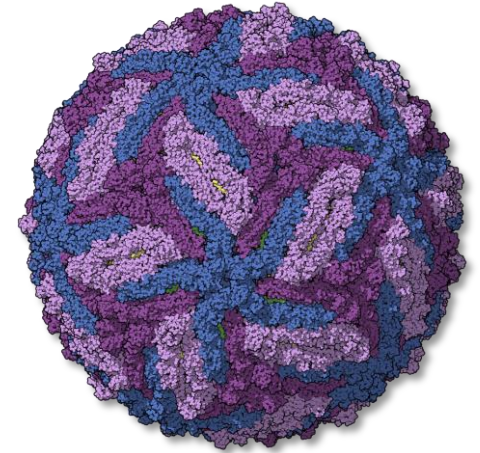
Zika Virus

- More like WNV than chikungunya and dengue with regard to transfusion risk
- Rapid and dramatic spread of the virus
- Association with serious clinical complications has raised public concern

Objectives

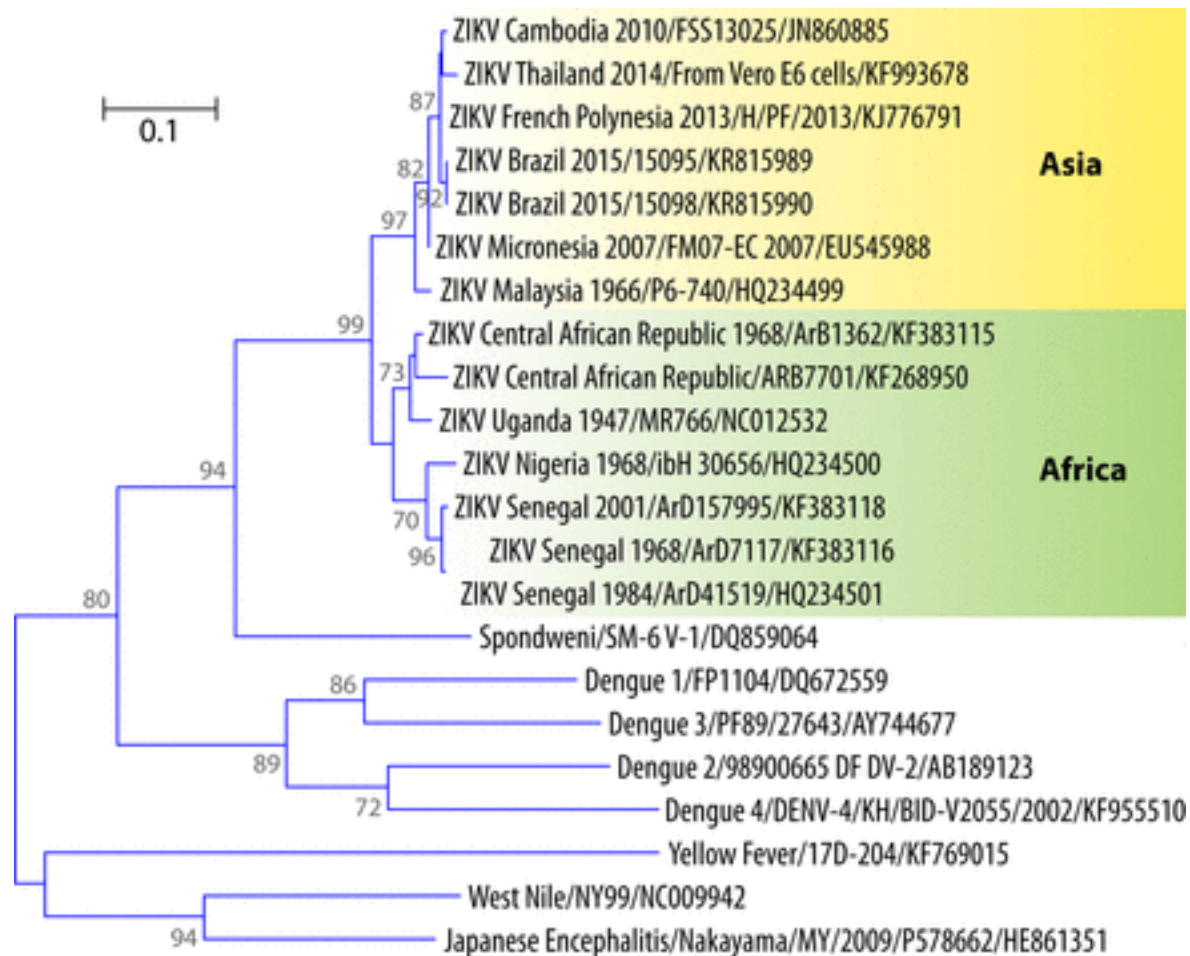
- History and epidemiology
- Modes of transmission
- Clinical presentation & complications
- Diagnostic testing (for symptomatic patients)
- Future directions in Zika research
- Zika and blood safety

Zika Virus (ZIKV)

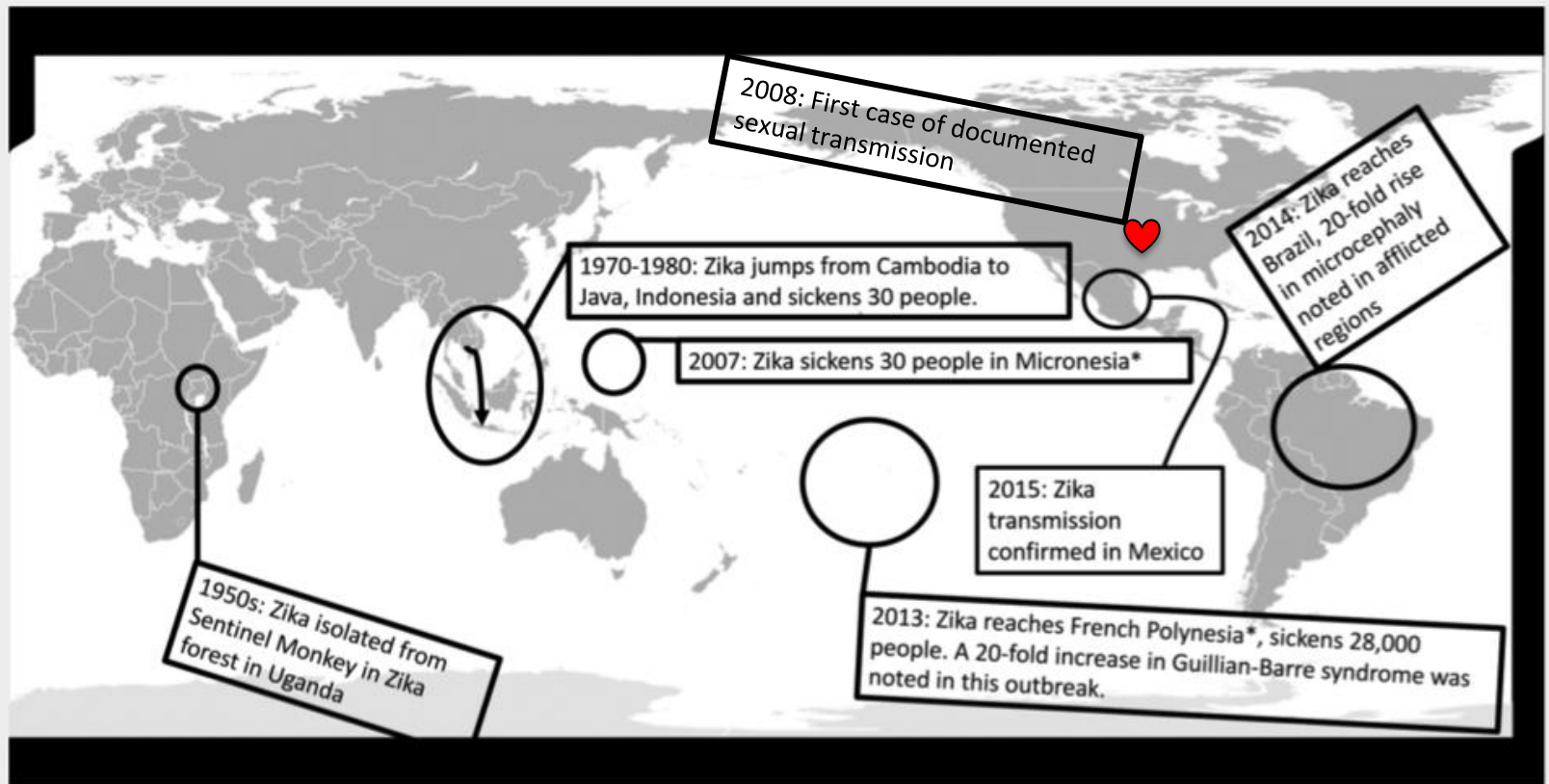


- Arbovirus (arthropod borne)
- Member of the *Flavivirus* genus and *Flaviviridae* family
 - Includes yellow fever virus, West Nile virus, dengue virus
 - Enveloped, icosahedral with a non-segmented, single-stranded, positive-sense RNA genome
 - Two distinct lineages
 - African
 - Asian

Zika Virus Lineages



A Brief History Of Zika Virus



Simplified timeline of Zika outbreaks, in relation to geographic area. Asterisks denote approximate locations. Map image credit: Lokal_Profil, via Wikimedia commons. License info: Public domain. Image modified to show timeline of Zika transmission by Joe Ballenger

Why now? Why us?

- Climate change
- Reduction in insecticide use based on concern about human toxicity
- Urbanization in tropical regions
- Large susceptible population in the Americas with no pre-existing exposure or immunity

Mosquito Vectors

Key to Aedes

Scutum with lyre-shaped white markings----- *Aedes aegypti*

Scutum with a long median longitudinal white stripe extending from anterior margin to about level of wing root----- *Aedes albopictus*



Aedes aegypti

Aedes albopictus

Lyre

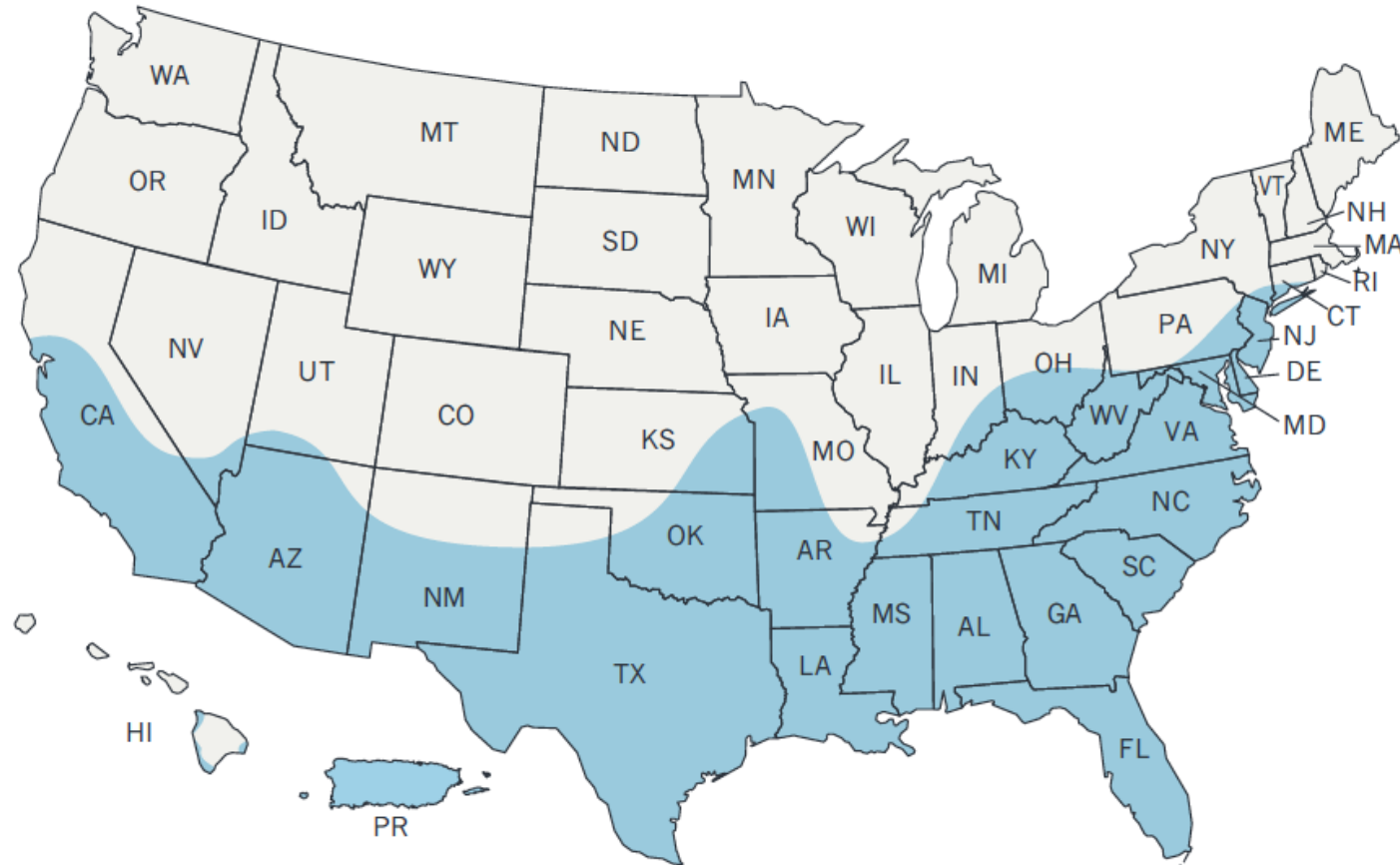
Mosquito Vectors

- *Aedes aegypti* & *Aedes albopictus*
 - Same mosquitos that spread dengue and chikungunya
- “Aggressive daytime biters” per the CDC
- Lay eggs in standing water
- Live indoors and outdoors

Global Distribution of *Ae. Aegypti* and *Ae. albopictus*

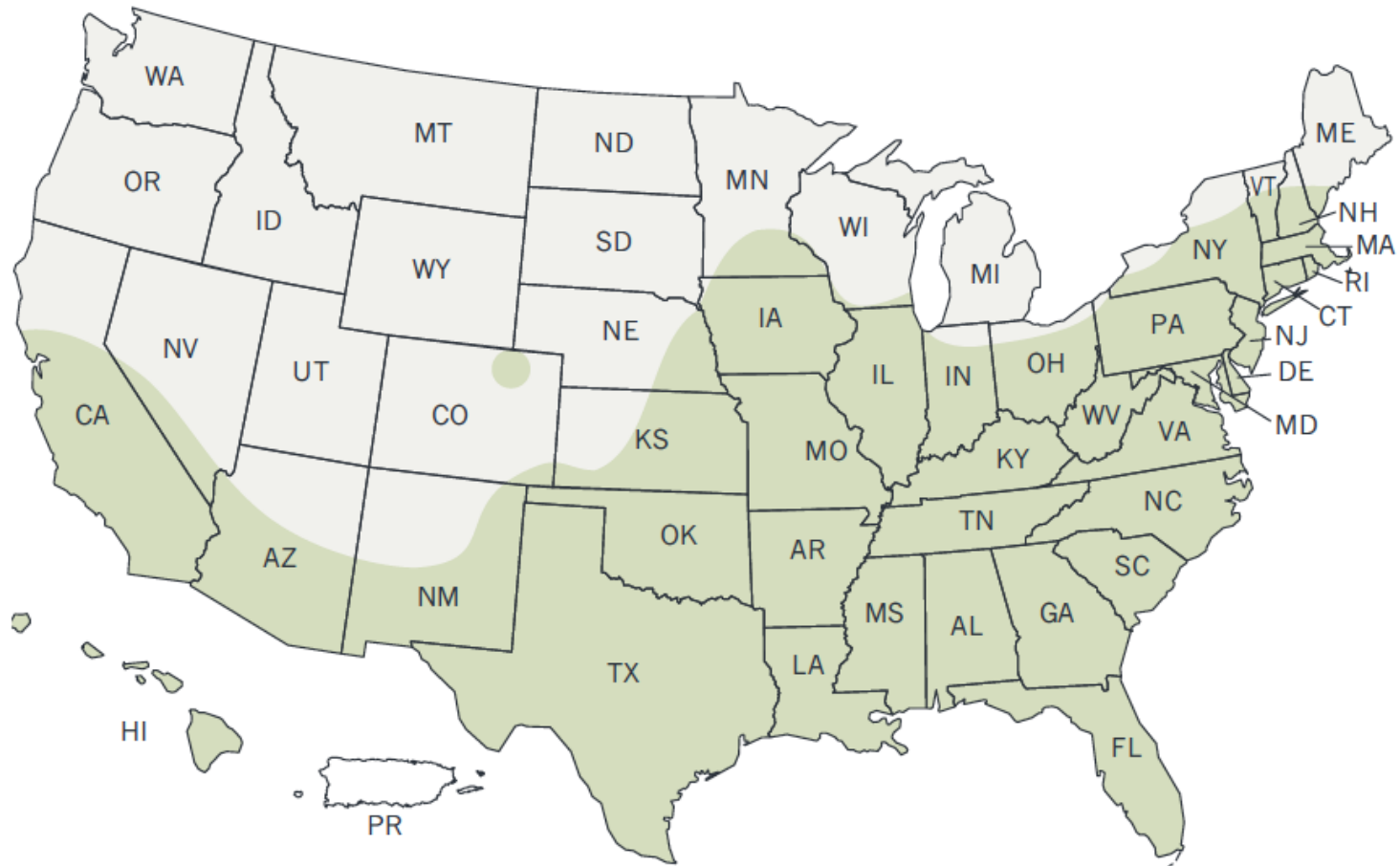


Estimated Range of *Ae. aegypti* in US



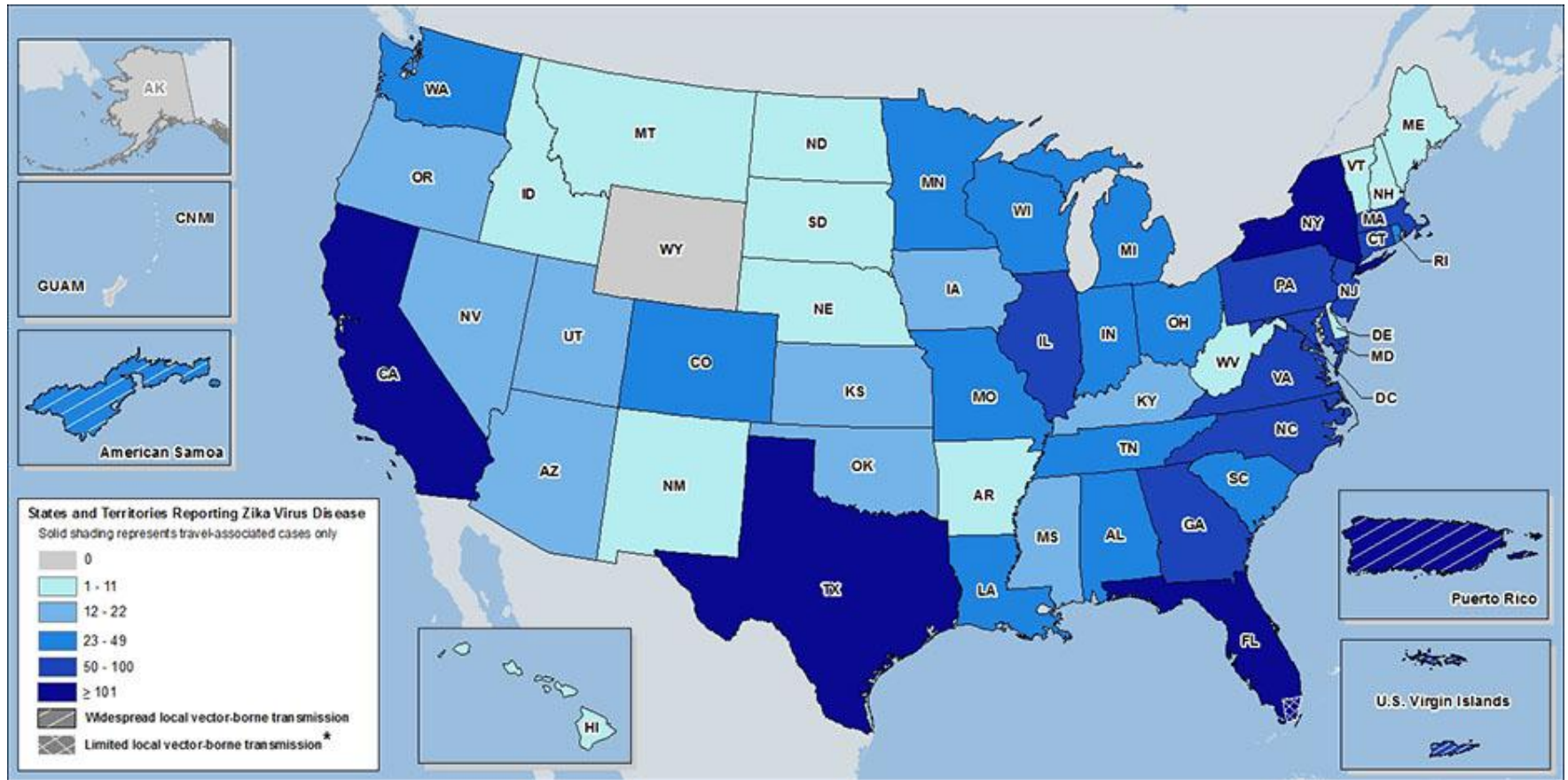
Estimated range of *Aedes albopictus* and *Aedes aegypti* in the United States, 2016. CDC, April 2016.

Estimated Range of *Ae. albopictus* in US

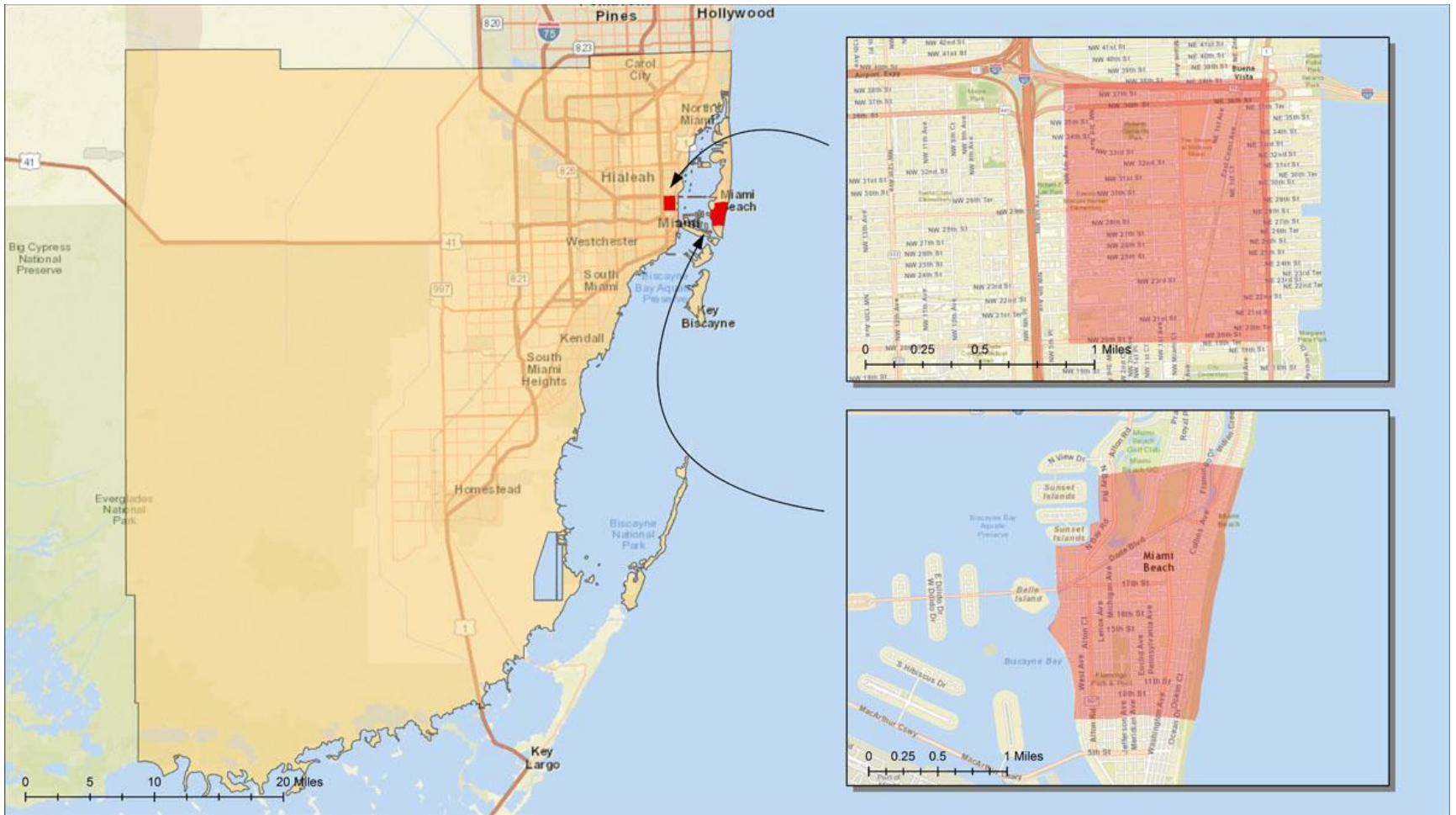


Estimated range of *Aedes albopictus* and *Aedes aegypti* in the United States, 2016. CDC, April 2016.

Zika Cases Reported in the US



Areas of Local Transmission in the US



Sexual Transmission of Zika

- Male to female
- Male to male
- Female to male

- ZIKV RNA detected up to 6 months in semen
- ZIKV RNA detected up to 11 days in vaginal fluid; may persist longer

Deckart DT et al. Male-to-male Sexual Transmission of Zika Virus—Texas, January 2016. *MMWR Morb Mortal Wkly Rep.* 2016; 65(14):372-4.

Davidson A, et al. Suspected Female-to-Male Sexual Transmission of Zika Virus- New York City, 2016. *MMWR Morb Mortal Wkly Rep.* 2016; 65(28):716-7.

Vertical Transmission; Mother to Child

- ZIKV-RNA+ has been well documented in mothers' blood, placenta and amniotic fluid and fetuses (including replicating virus isolated from brain tissue) suffering from microcephaly
- Animal studies in mice demonstrate vertical transmission with marked effect on fetal brain development



Oliveira AS, Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound Obstet Gynecol* 2016;47:6-7.

Martines RB, et al. Notes from the field: evidence of Zika virus infection in brain and placental tissues from two congenitally infected newborns and two fetal losses—Brazil, 2015. *MMWR Morb Mortal Wkly Rep* 2016;65:159-60.

Wu, KY et al. Vertical transmission of Zika virus targeting the radial glial cells affects cortex development of offspring mice. *Cell Research* (2016) 26:645-654.

Via Blood Transfusion

- ZIKV RNA detected in 2.8% of samples from asymptomatic blood donors during 2013-2014 French Polynesia outbreak
- ZIKV RNA detected in 1% of samples from asymptomatic donors in Puerto Rico in 2016
- Multiple case reports of probable transfusion transmitted Zika in **Brazil**



Motta et al. Evidence for transmission of Zika virus by platelet transfusion. N Engl J Med.
Barjas-Castro, ML et al. Probable transfusion-transmitted Zika virus in Brazil. Transfusion, 56: 1684-1688.

Other Possibilities

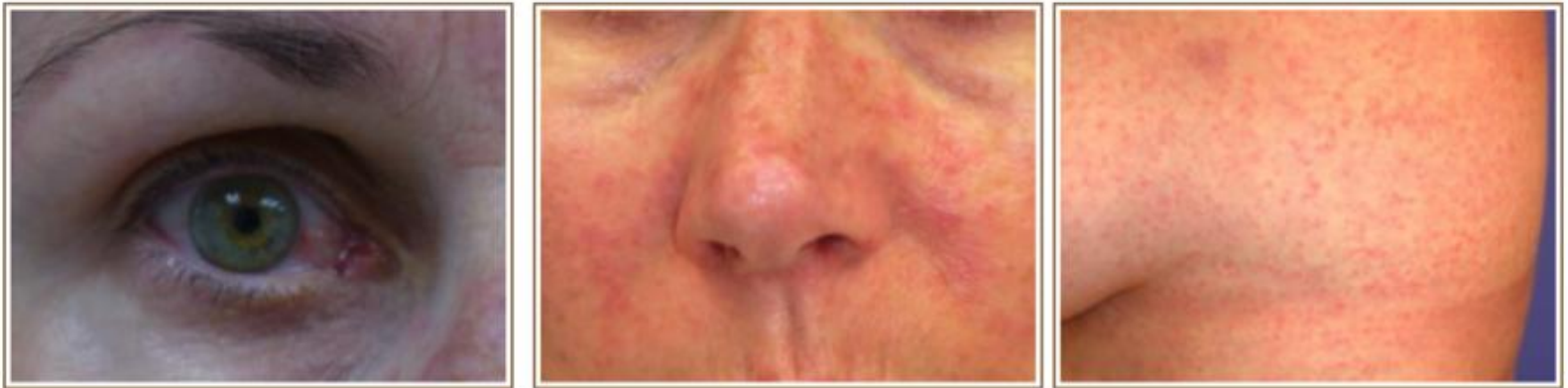
- Infectious ZIKV-RNA has been isolated from urine, breast milk, and saliva.
- Persistence of West Nile Virus and Dengue in solid organs with transmission through transplantation has been documented and raises serious concern for the same possibility with Zika



Clinical Presentation

- Fever
- Joint pain (affecting small joints of hands and feet)
- Conjunctivitis (red, painful eyes)
- Rash

Zika virus infection



Clinical Presentation

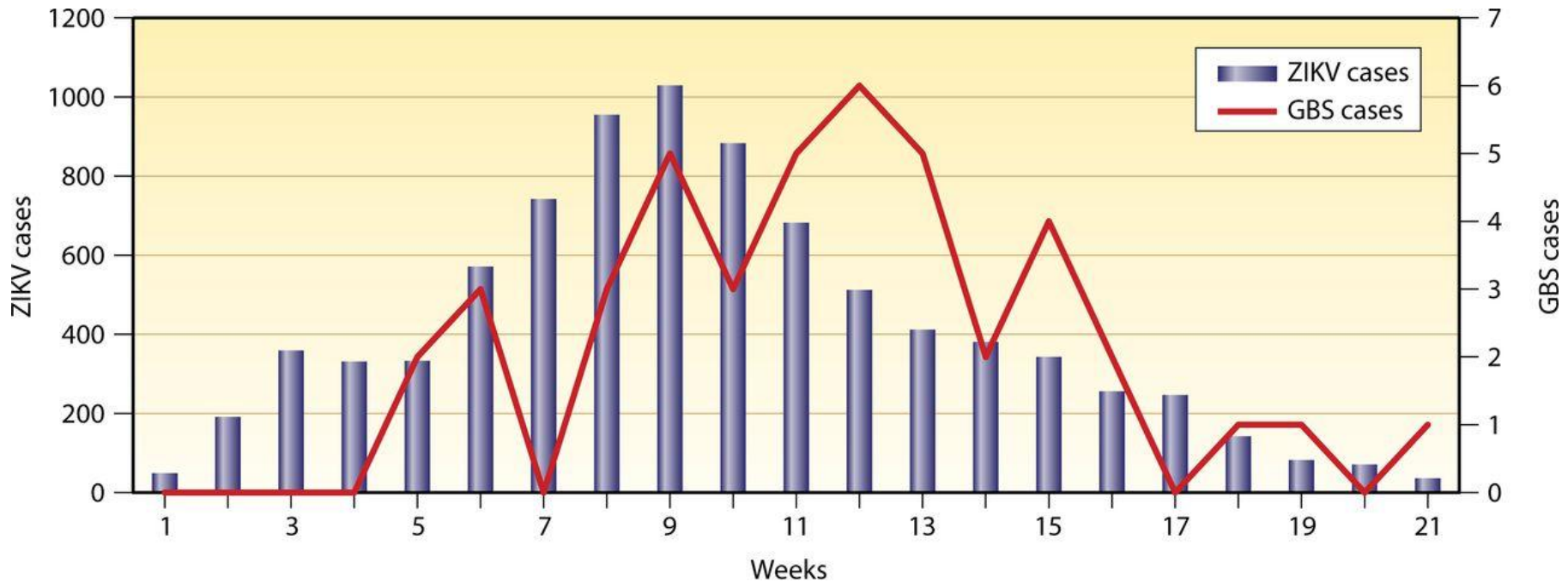
- 80% of infected individuals are asymptomatic
- Usually mild course, with symptoms lasting a few days to a week
- Complications include Guillane-Barré Syndrome and birth defects
- High viral loads (up to 8.1×10^6 copies/mL) are detected during the viremic phase of Zika infection, which can last anywhere from a few days to two weeks

Guillane-Barré Syndrome

- Ascending weakness of the arms and legs
- In severe cases, may affect the muscles that control breathing, requiring patient to be placed on a ventilator
- Caused by the patient's immune system attacking their nervous system; usually occurs after an infection
- Currently affects 3,000 to 6,000 people in the US annually



Temporal Association of Guillane-Barre Cases and Zika Cases in Micronesia 2007



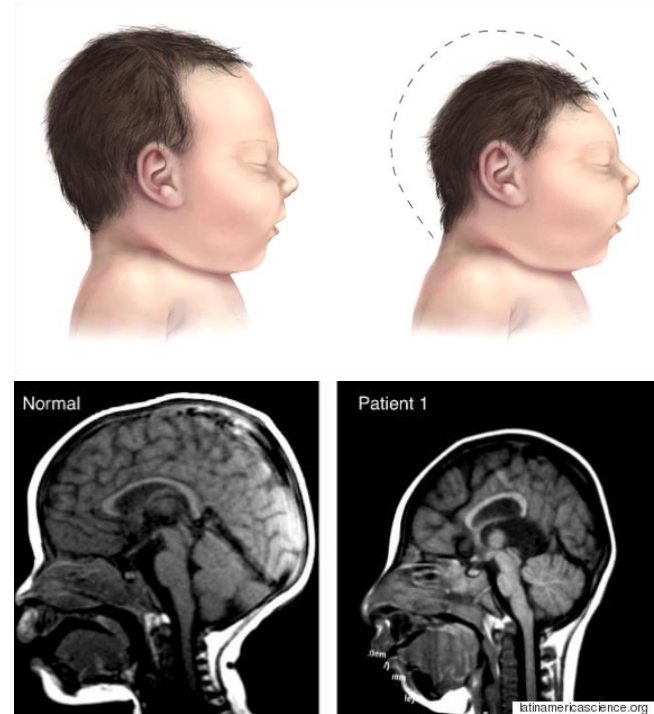
Zika in Pregnancy

- Zika may be transmitted from mother to fetus
- The CDC has concluded Zika virus causes microcephaly and other severe fetal brain defects
 - Analysis published in the New England Journal of Medicine in April 2016.



Zika and Birth Defects

- Microcephaly is a birth defect where the baby's head is smaller than expected compared to other babies
- Microcephaly is associated with a smaller brain and abnormal neural development
- Other severe fetal brain defects linked to Zika include eye defects, hearing loss, impaired growth



The CDC on Zika and Pregnancy

What we know

- Zika virus can be passed from a pregnant woman to her fetus
- Infection during pregnancy can cause certain birth defects
- There is no vaccine to prevent or medicine to treat Zika

What we do not know

- If there's a safe time during your pregnancy to travel to an area with Zika
- How likely it is that Zika infection will affect your pregnancy
- If your baby will have birth defects if you are infected while pregnant

Rasnussen SA, et al. Zika Virus and Birth Defects— Reviewing the Evidence for Causality. *New England Journal of Medicine*, 2016; 374:1981-1987.

Maritines RB, et al. Notes from the field: evidence of Zika virus infection in brain and placental tissues from two congenitally infected newborns and two fetal losses—Brazil, 2015. *MMWR Morb Mortal Wkly Rep* 2016;65:159-60.

Zika Treatment

- Supportive care
 - Oral rehydration
 - Acetaminophen (Tylenol)
- No FDA approved treatments exist
- The FDA states it is not aware of any specific treatments in development for Zika at this time.
- No FDA approved vaccine exists. Several vaccines are currently in development.



Diagnostic Tests for Zika

- Available under FDA emergency use authorization
 - Zika MAC-ELISA (CDC)
 - Trioplex rRT-PCR (CDC)
 - Zika Virus RNA Qualitative Real-Time RT-PCR (Focus Diagnostics, Inc.)
 - RealStar Zika Virus RT-PCR Kit U.S. (Altona Diagnostics GmbH)
 - Aptima Zika Virus assay (Hologic, Inc.)
 - Viracor-IBT Laboratories, Inc.'s Zika Virus Real-time RT-PCR Test (Viracor-IBT)
 - VERSANT® Zika RNA 1.0 Assay (kPCR) Kit (Siemens Healthcare Diagnostics Inc.)
 - xMAP® MultiFLEX Zika RNA Assay (Luminex Corporation)
 - ZIKV Detect IgM Capture ELISA (InBios International, Inc.)
 - LightMix® rRT-PCR Test (Roche Molecular Systems, Inc.)

Special Considerations for Serologic Testing

- Areas endemic for Zika are also endemic for Dengue virus
- Zika and Dengue are very closely related
- Existing Dengue antibodies may cross react as anti-Zika antibodies both in vivo and in vitro
 - In vivo: may blunt Zika-specific IgM and IgG seroconversion
 - In vitro: may lead to false positive Zika IgM or IgG detection
- All serology testing should be confirmed by neutralization assays, which are only performed in a limited number of specialized labs

WHO & CDC Recommendations for Diagnostic Testing

- Serology not recommended
- NAT assays that are more specific are recommended
 - Caveat that these assays are only sensitive if performed in the acute phase of infection

FDA Zika Virus Reference Materials

- NAT-based testing is the most sensitive method to detect acute Zika infection
- Sensitivity and specificity may vary greatly across assays
- EUA Zika tests MUST assess the sensitivity and specificity of their assay with an FDA-recommended reference material
- Reference material includes RNA from two current Zika Virus strains in human plasma and three controls for blind testing

Accepted Specimen Types

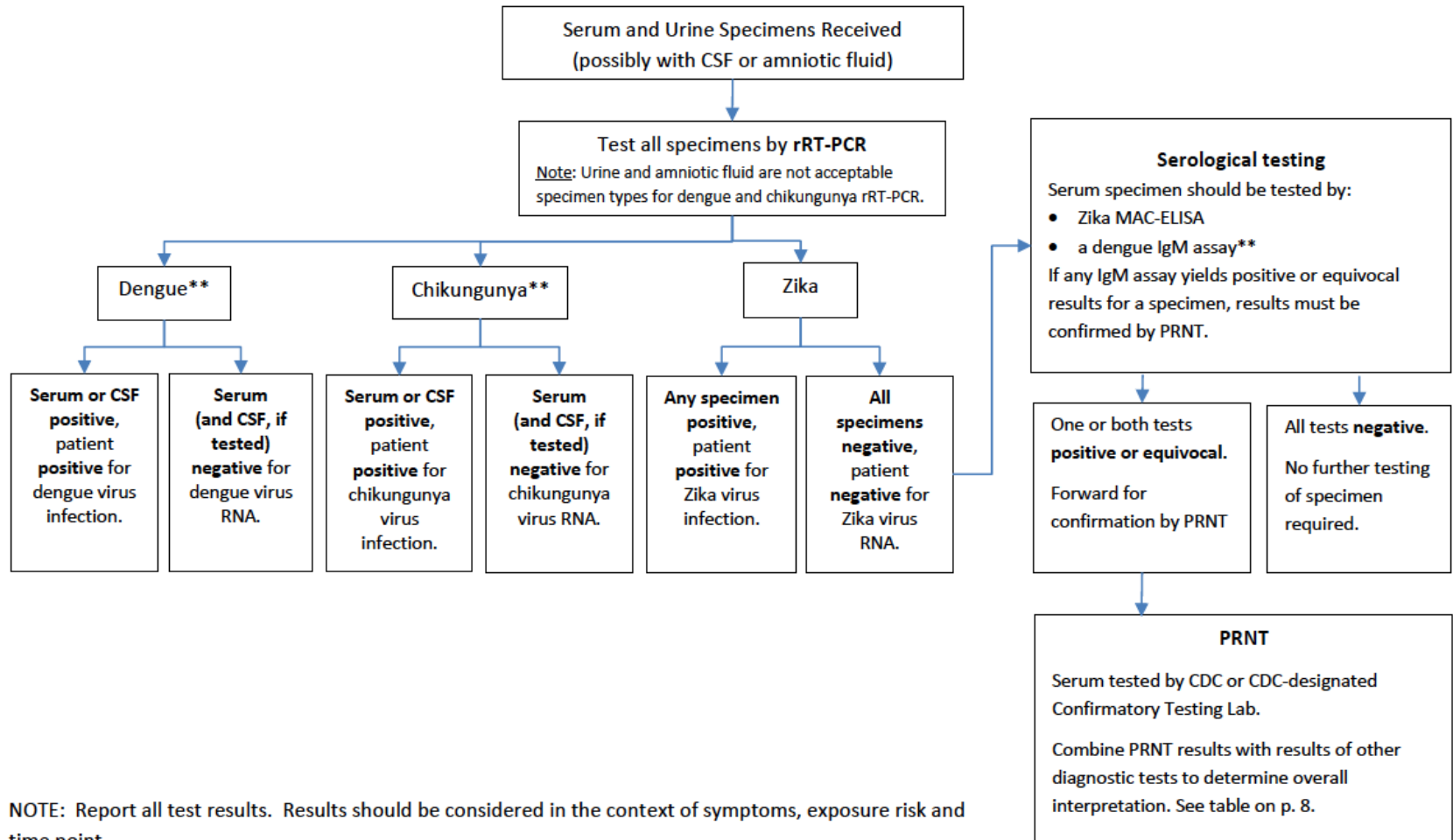
- Serum
 - PCR based or molecular method
 - Acute, up to 5 days after onset of symptoms
 - Does NOT detect infection if > 5 days after onset of symptoms!!
 - IgM
 - subacute, persists ~12 weeks
- Urine
 - PCR based or molecular method
 - acute, up to 20 days after onset of symptoms
 - Urine testing is more sensitive in early infection (56% sensitivity in 0 – 5 day serum specimens versus 95% sensitivity in urine; 0% sensitivity in serum in 6 – 10 day period versus 89% sensitivity in urine)
- *Of note, Zika RNA is detected in saliva almost as well as urine, and much better than serum. Saliva is not an accepted specimen type for currently available tests in the US.*

Who Should Get Tested?

- Symptomatic individuals who have lived in or recently traveled to a Zika area
- All pregnant women should get assessed for Zika exposure

2016 Zika Response: Algorithm for U.S. Testing of Symptomatic Individuals*

Specimens Collected <14 days Following Symptom Onset



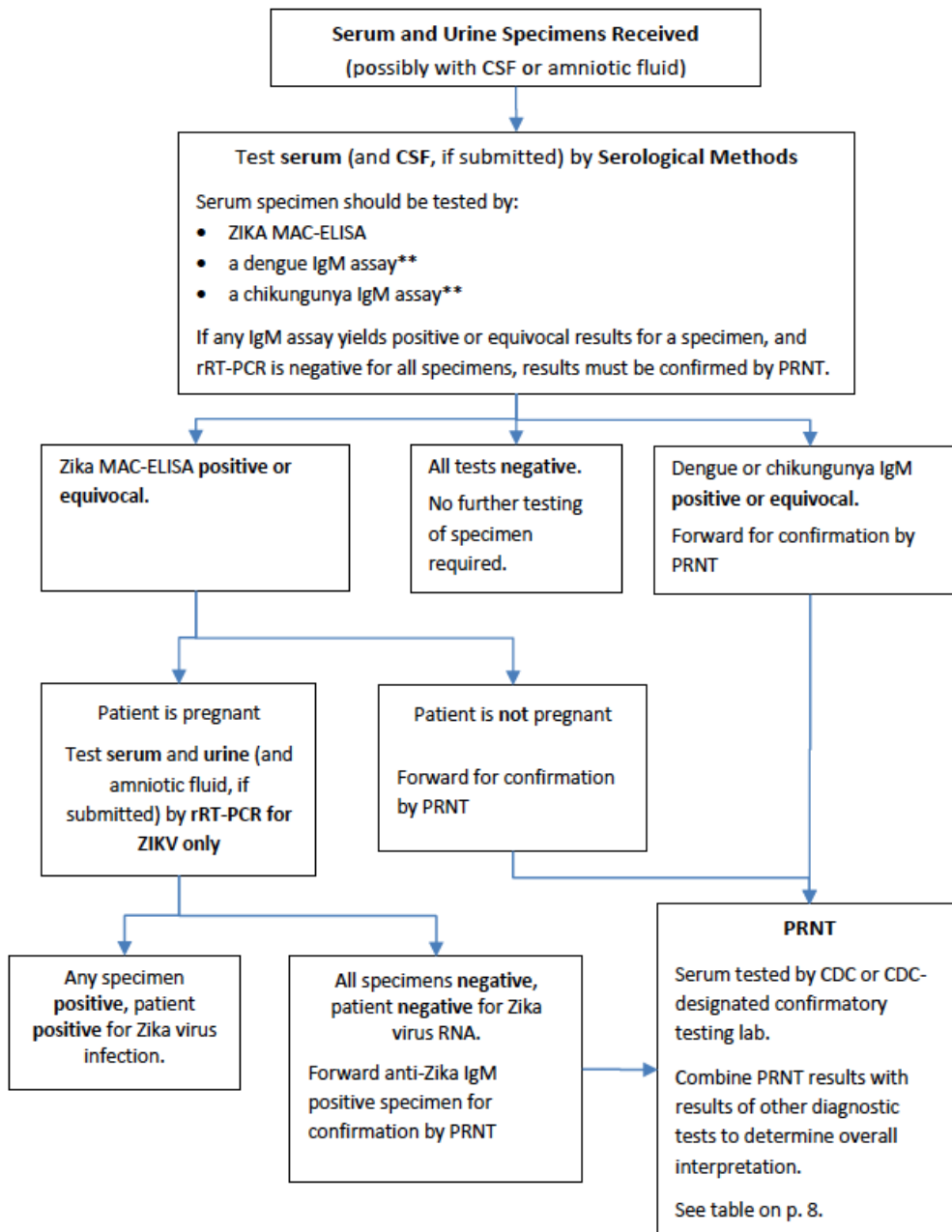
NOTE: Report all test results. Results should be considered in the context of symptoms, exposure risk and time point.

*Pregnant and non-pregnant symptomatic individuals

**For CDC guidance on patient management and follow-up for dengue or chikungunya virus infection, please refer to the CDC websites listed on p. 9 of this document.

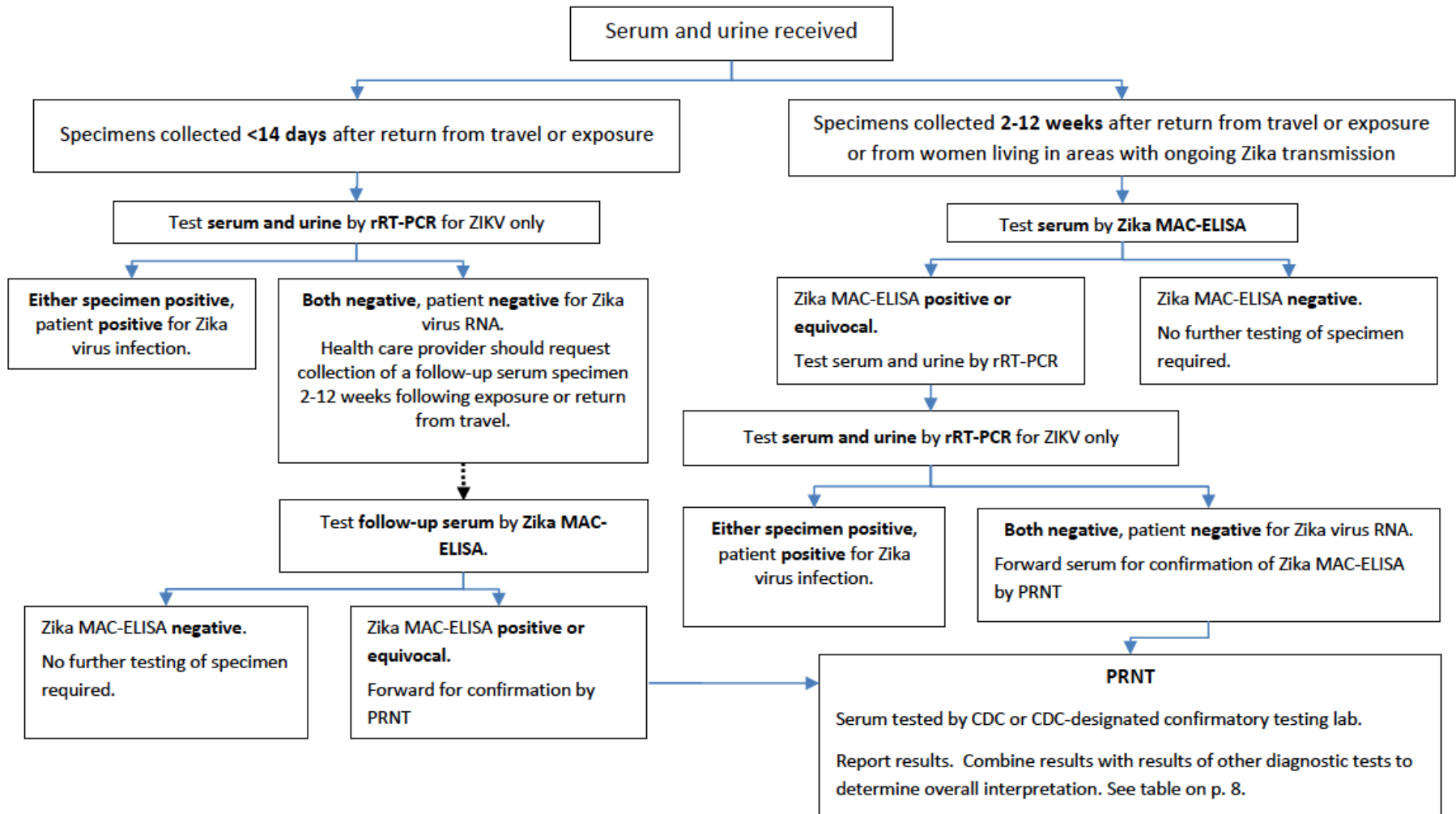
2016 Zika Response: Algorithm for U.S. Testing of Symptomatic Individuals*

Specimens Collected ≥ 14 Days Following Symptom Onset



NOTE: Report all test results. Results should be considered in the context of symptoms, exposure risk and time point.

2016 Zika Response: Algorithm for U.S. Testing of Asymptomatic Pregnant Women
 Serum and Urine from Asymptomatic Pregnant Women Meeting Epidemiologic Criteria



NOTE: Report all test results. Results should be considered in the context of exposure risk and time point.

Prevention

- Wear long sleeved shirts and long pants
- Use EPA-registered insect repellent
- Eliminate standing water in and around your home
- Repair/update septic tank if you have one
- Keep mosquitoes out of your home
- Truck mounted or aerial spraying



Investigation Products

- Genetically Engineered (GE) Mosquitoes
 - Oxitec GE Mosquitoes have been approved for a field trial in Florida to determine if the GE mosquitoes will mate with wild type mosquitoes and decrease the mosquito population
 - The field study is NOT designed to assess whether the GE mosquitoes reduce Zika transmission
 - Still remote from commercial use

Research

- National Heart Lung and Blood Institute of the NIH announced support for projects to
 - Study the risk of Zika transmission by transfusion
 - Determine Zika-related complications of transfusion
 - Expand the existing Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) to investigate epidemiology and biology of transfusion-transmitted Zika virus

Utilizing ZIKV-RNA+ Blood Donors (US)

- Units that screen positive for ZIKV-RNA in will be made available for research purposes and donors that test positive will be invited to participate in follow up studies
 - Natural history of disease
 - Clinical outcomes of infection
 - Dynamics of viral and immune system variables
 - Kinetics of viral clearance in specific body fluids
 - Build repository of longitudinal specimens

Utilizing ZIKV-RNA+ Blood Donors (Brazil)

- Three additional REDS-III studies to be launched in Brazil
 - Evaluate transfusion transmission rates
 - Evaluate clinical course in cases of transfusion transmitted Zika
 - Evaluate the rates of viremia in asymptomatic blood donors in multiple geographic locations

Transfusion Transmission Risk in Brazil

- Study led by Blood Systems Research Institute in San Francisco, CA in conjunction with the Medical School at the University of Sao Paulo in Brazil
- Study period: April – May 2016; January – June 2017
- 3500 hospitalized transfusion recipients
- Multiplex NAT assay to detect CHIKV, ZIKV, and DENV RNA
 - Post transfusion testing on all subjects
 - If positive, pre transfusion specimen and stored specimens from all donations transfused to that recipient are tested
- Prospective and retrospective symptom evaluation

Transfusion Transmission Risk in Brazil

- Study to determine the rate of ZIKV-RNA positivity in blood donors
- Testing will be performed on mini-pools including specimens from 6 donors
- Four large blood centers in REDS-III
 - Recife, Belo Horizonte, Rio, Sao Paulo



Recipient Epidemiology and Donor Evaluation Study

- NHLBI program
- REDS program begun in 1980s
 - REDS-I: Focus on domestic blood (US)
 - REDS-II: Expanded to include countries affected by AIDS epidemic
 - REDS-III: new sites in Brazil, China and South Africa
- Program to ensure safe and effective blood banking and transfusion medicine through supporting basic, translational, and clinical research
- REDS-III emphasis on adult transfusion recipient epidemiology and scientific research, in contrast to REDS-I and –II, which emphasized donor safety and availability
- Cumulative database format



Recipient Epidemiology and Donor Evaluation Study

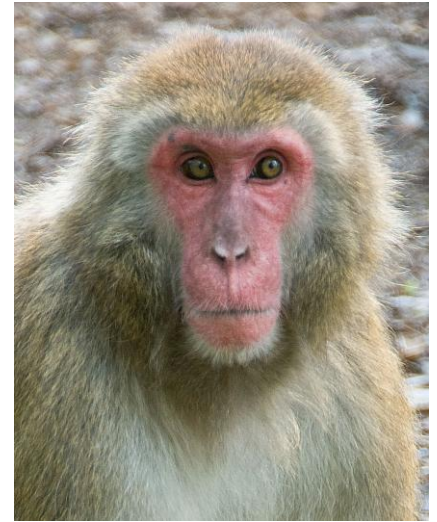
- Four US Sites:
 - Blood Center of Wisconsin
 - The Institute for Transfusion Medicine at UPMC
 - UCSF/Blood Systems Research Institute
 - Yale/American Red Cross
- Hubs participate in:
 - Studies addressing blood donors
 - Studies to optimize blood banking strategies
 - Studies addressing transfusion practices and outcomes

Transfusion Transmission Risk in Brazil

- Evaluation of rate of transfusion transmitted Zika in chronically transfused sickle cell disease patients
- Subjects from the four REDS-III sites
- Will follow positives in real time to evaluate clinical course

Other Studies in Planning

- Development of macaque model of ZIKV transmission
 - Characterize viral load and kinetics in different blood components and tissue over time in acute infection
 - Determine the minimal infectious dose required to develop transfusion-transmitted Zika infection
 - Determine the efficacy of pathogen in activation



Zika and Blood Safety

- In the face of mounting evidence, numerous agencies have issued guidance documents to decrease the risk of Zika virus through transfusion in areas without active Zika transmission
 - FDA
 - AABB
 - WHO
 - European Center for Disease Prevention and Control

February 2016:

FDA Guidance on Donor Screening

Donor Questions

- In non-endemic areas, questions are currently being used to identify donors at risk for Zika virus infection.
- Donor education material provided to instruct donors to self-defer

Donor Questions: 4 week deferrals

Areas without active transmission

- History of confirmed ZIKV
- Signs and symptoms of ZIKV infection within 2 weeks of departure from an area with active ZIKV
- Sexual contact with a man diagnosed with ZIKV or who traveled to or resided in an area with active ZIKV in the three months prior to that contact
- Traveled to an area of active ZIKV transmission

Recommendations for Areas with Active Transmission

- Obtain blood from areas of the US without active transmission
- May collect and prepare platelets and plasma locally if using FDA-approved pathogen reduction technology
- May collect blood components locally and test blood with an FDA licensed blood donor ZIKV screening test, when available.

Blood Importation

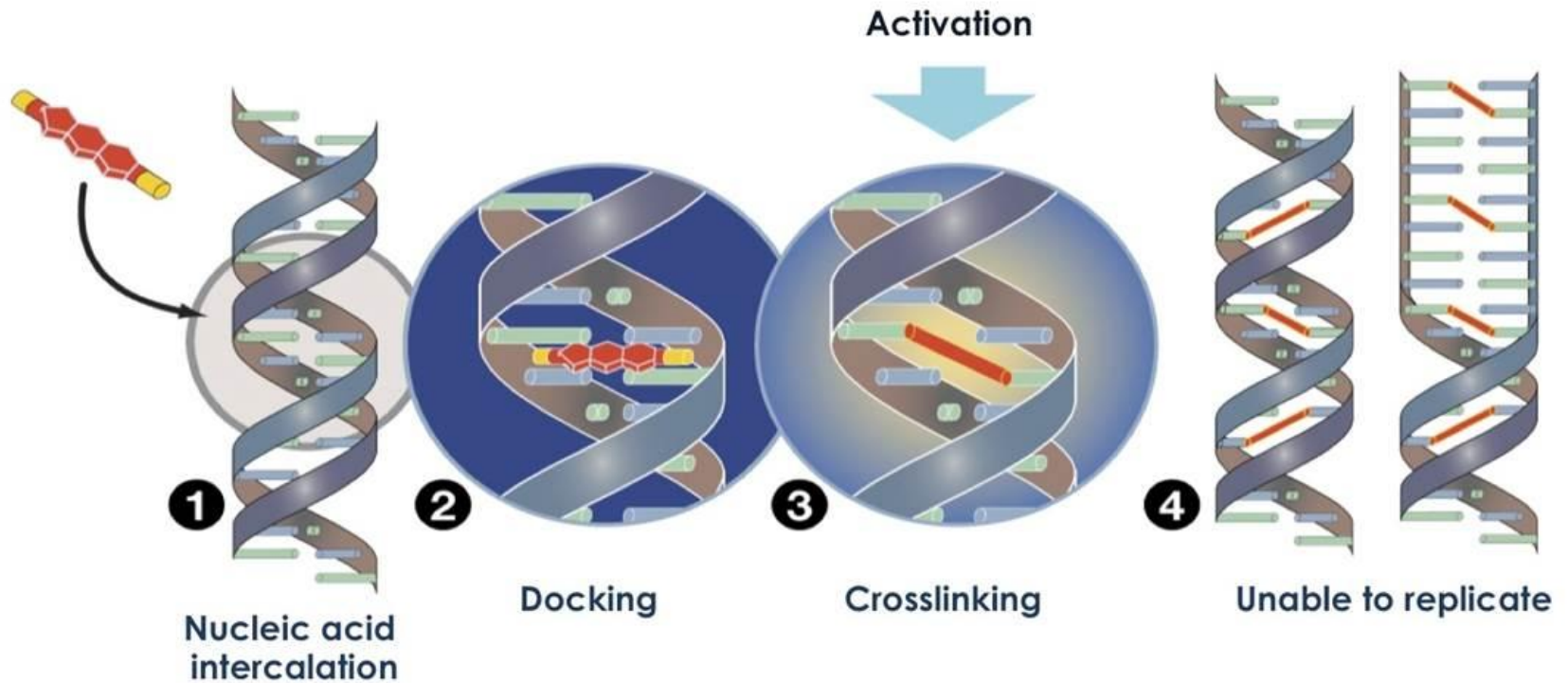
- When contained to a small geographic region, before donor testing was available, donor centers in the area would cease collection and import blood
- Not a long term solution
- Not a viable option if the virus becomes endemic in the continental US



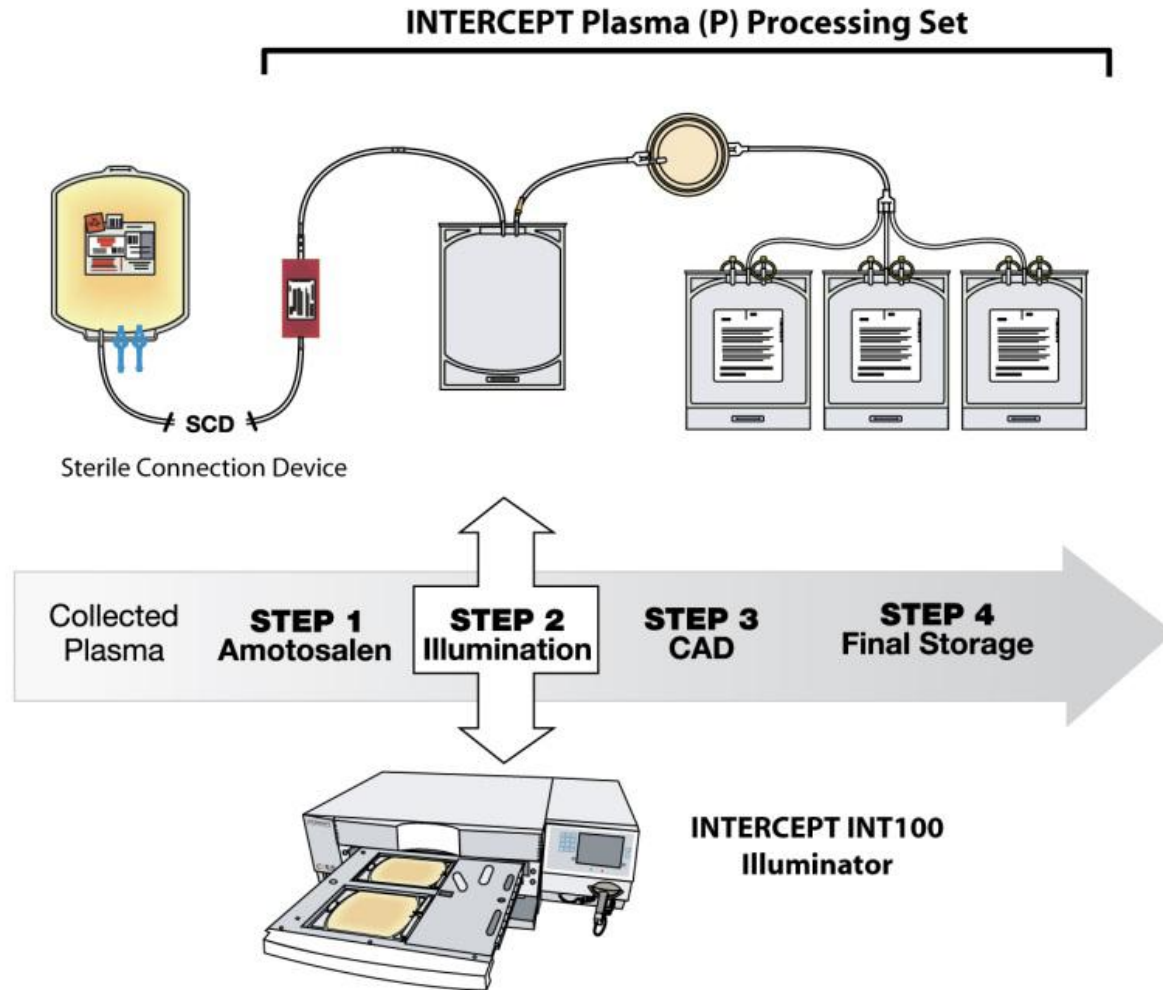
Pathogen Inactivation

- Cerus Corporation has demonstrated 6-log kill activity against Zika in plasma with the Intercept system
 - There are no alternate devices approved in the US
- It is presumed this holds for platelets as well, although it has not been directly demonstrated
- Efforts underway to develop pathogen-inactivation for RBCs

Pathogen Inactivation



Pathogen Inactivation



General Summary of Safety and Effectiveness Data for the Intercept Blood System for Plasma. (Cerus Corporation) FDA Approved December 2014.

March 2016:

FDA Guidance on HCT/P Donors

- ZIKV = relevant communicable disease agent or disease
- Living donors ineligible if
 - Diagnosis of ZIKV in past 6 months
 - Residence in or travel to area with active ZIKV in past 6 months
 - Sex within the past 6 months with a male known to have either of the above risk factors

March 2016:

FDA Guidance on HCT/P Donors

- Donors of umbilical cord blood, placenta or other gestational tissues ineligible if:
 - Diagnosis of ZIKV at any point during pregnancy
 - Residence in or travel to an area with active ZIKV at any point during pregnancy
 - Sex at any point during that pregnancy with a male with diagnosis of ZIKV in past 6 months or travel to an area with ZIKV in past six months

March 2016: FDA Guidance on HCT/P Donors

- Cadaveric donors ineligible if
 - Diagnosis of ZIKV in past 6 months

March 2016:

FDA Questions and Answers Guidance

- Clarification on recent guidances
 - Education materials instructing donors to self defer in areas without active transmission
 - Formal questions added to DHQ in areas of active transmission
- The only question added at that time for areas without active transmission was
 - History of residence in or travel to an area with active transmission of ZIKV in the past four weeks

March 30, 2016

- FDA allows use of first investigational test to screen blood donations for Zika virus
- At the time, to be used under IND for screening in areas with active mosquito transmission (Puerto Rico)
- Collection of blood in areas with local Zika transmission may resume after screening is instituted

Donor Testing for ZIKV-RNA

- Only available under IND
- Must register for clinical trial to test
 - Roche Molecular Systems, Inc. (April 3, 2016)
 - Roche cobas[®] 6800/8800
 - Qualitative NAT assay
 - Initially used in Puerto Rico
 - Hologic, Inc./Grifols (June 20, 2016)
 - Procleix Panther System
 - Procleix zika assay
 - Assay system used by ARC to screen blood for HIV, Hep B and Hep C

June 15, 2016

- FDA makes Zika virus reference material for NAT-based IVD devices available to Zika device developers
- Supports the fulfillment of an EUA condition of authorization to assess traceability
- Contains RNA from two current Zika strains

July 27, 2016

- “Advice” to blood collection establishments on non-travel related cases of Zika in Florida

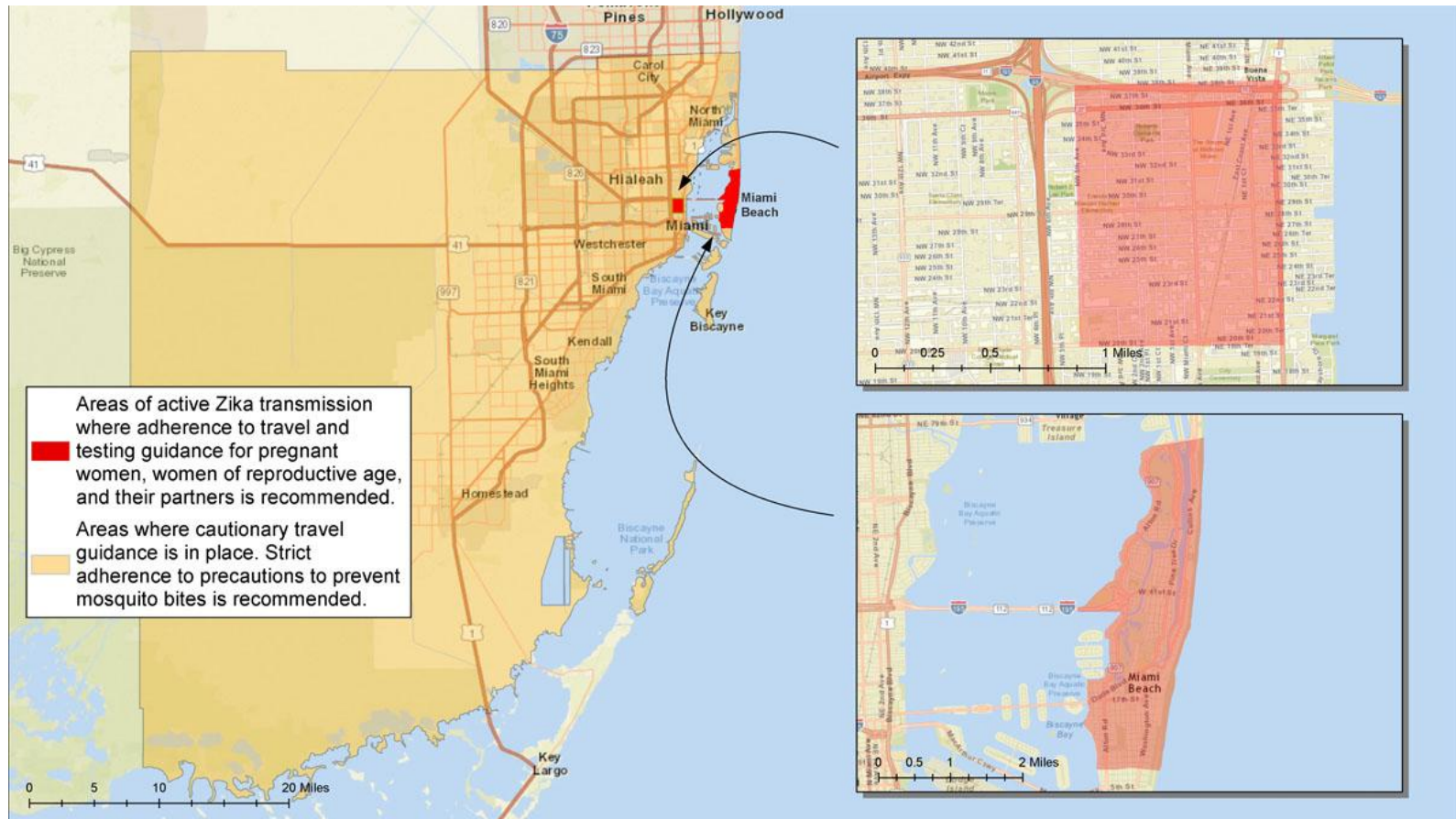


July 29, 2016:

Local Transmission of ZIKV in Florida

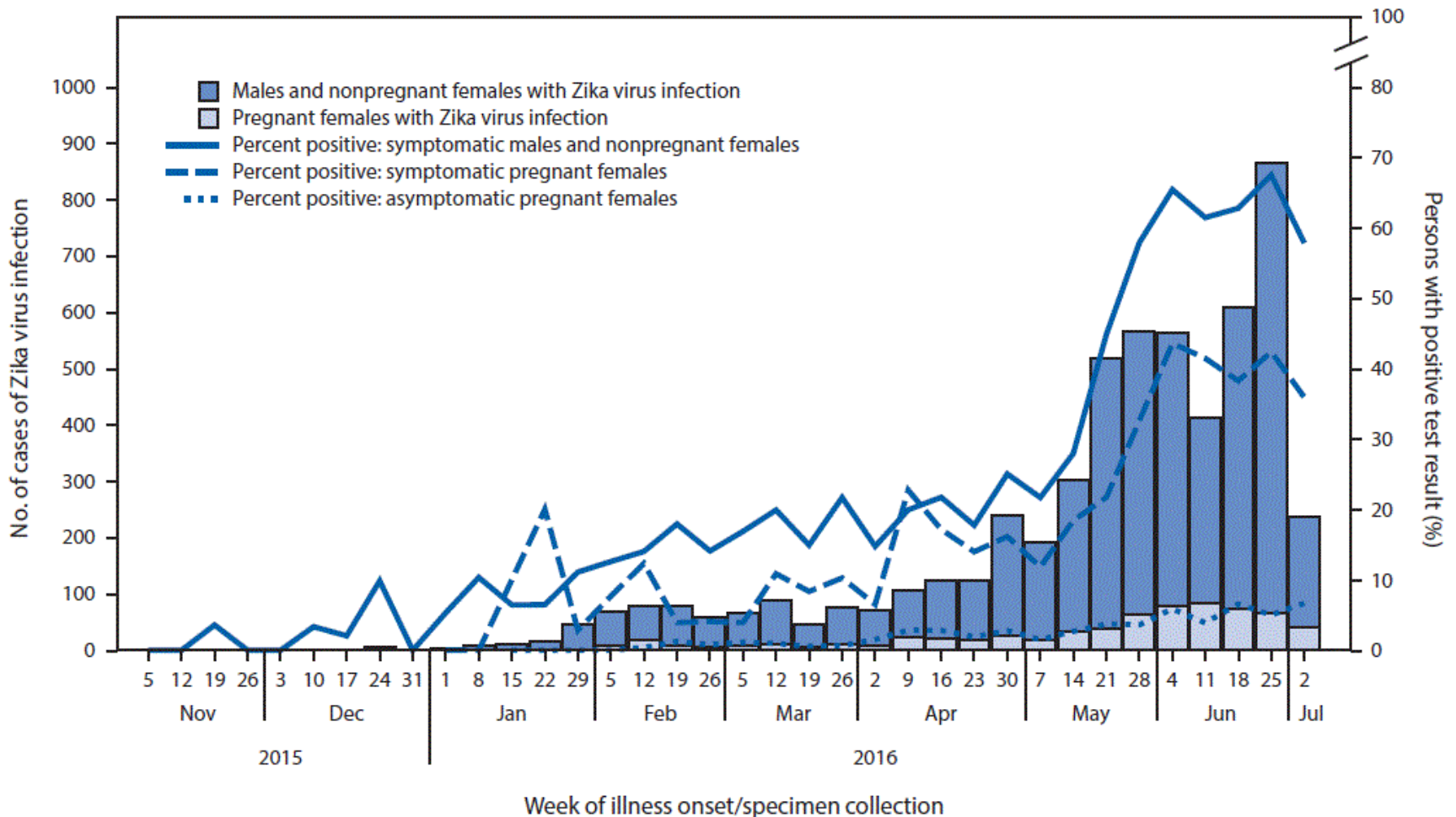
- Four cases of local mosquito-borne transmission
- Several block area (Wynwood neighborhood) of Miami, FL
- Additional cases anticipated
- Top priority to protect pregnant women
- CDC provides Florida \$8M in Zika-specific funds and \$27M discretionary emergency funding

Affected Neighborhoods in Miami, FL



August 5, 2016

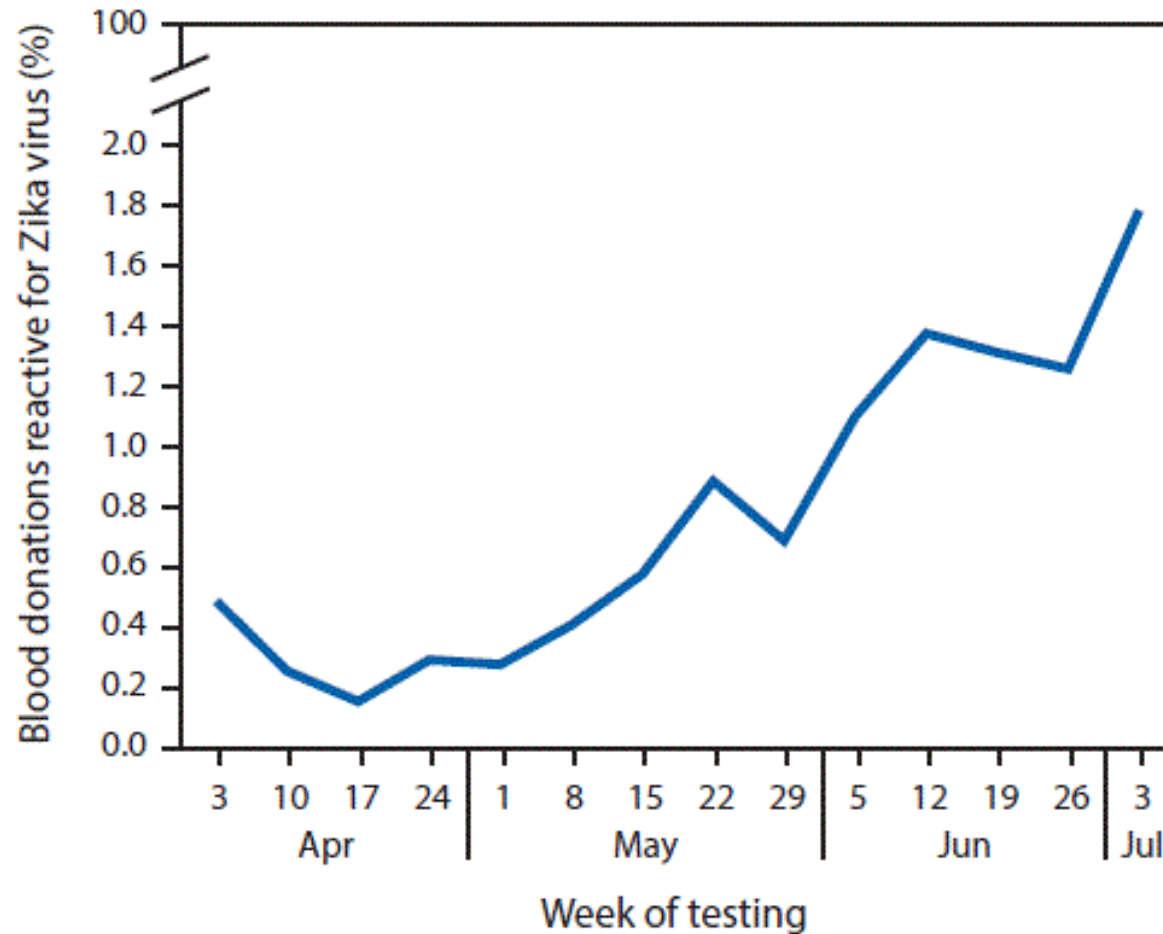
MMWR on Zika in Puerto Rico



Adams L, et al. Update: Ongoing Zika Virus Transmission—Puerto Rico, November 1, 2015- July 7, 2016. MMWR Mord Mortal Wkly Rep 2016;65:774-779.

August 5, 2016

MMWR on Zika in Puerto Rico



August 26, 2016:

Revised FDA Guidance for Reducing Zika Transmission

- Test all donations collected in the US and its territories with an investigational individual donor nucleic acid test for ZIKV **or**
- Implement pathogen reduction technology for platelets and plasma using an FDA-approved pathogen reduction device

August 26, 2016:

Revised FDA Guidance for Reducing Zika Transmission

- You may discontinue providing donor educational materials regarding ZIKV and screening donors for ZIKV risk factors
- If a donor volunteers a history of ZIKV infection, you cannot collect blood from them
 - Recommended 120 day deferral after a positive viral test or resolution of symptoms

August 26, 2016:

Revised FDA Guidance for Reducing Zika Transmission

- If ZIKV-NAT+, product may not be used
- If ZIKV-NAT+, donor is deferred 120 days from the date of reactive test or after the resolution of symptoms
- Quarantine and retrieval of in-date blood components collected from any ZIKV-NAT+ donor in 120 days prior to donation with NAT+ is recommended
 - Inform recipient's physician of any transfused products

August 26, 2016:

Revised FDA Guidance for Reducing Zika Transmission

- Labeling
 - The circular of information must include the names and results of all tests performed
 - Recommended to update circular with non-reactive ZIKV-NAT
 - Indicate whether the test was performed using an investigational or licensed test

August 26, 2016:

Revised FDA Guidance for Reducing Zika Transmission

- Areas with one or more locally acquired mosquito-borne case (Puerto Rico, Florida)
 - Immediate implementation required
 - Must cease collection until testing or pathogen inactivation can be implemented

August 26, 2016:

Revised FDA Guidance for Reducing Zika Transmission

- Areas with either proximity to areas of locally acquired mosquito-borne cases or because of other epidemiological links to Zika
 - Alabama, Arizona, California, Georgia, Hawaii, Louisiana, Mississippi, New Mexico, New York, South Carolina, Texas
 - Implement as soon as possible
 - No later than 4 weeks after the guidance

August 26, 2016:

Revised FDA Guidance for Reducing Zika Transmission

- All other US states and territories
 - Includes the states represented at this meeting
 - As soon as feasible, but no later than 12 weeks after the guidance issue date

The Zika Funding Crisis

- President Obama asked Congress to allot \$1.9 billion in emergency funds to fight Zika in February 2016
- Congress can't get it together
 - Both parties making it about tangential political issues
- At the end of August, the CDC announced it was nearly out of money for Zika

Zika Today in the US (9/14/16)

United States

- 3,133 travel associated cases
- 1 laboratory acquired case (?!?!?)
- 43 locally acquired cases

Territories

- 65 travel associated cases
- 17, 629 locally acquired cases
 - 17, 315 in Puerto Rico

Take Home Points

- Zika infection has serious complications, including birth defects and Guillan -Barre Syndrome
- Most Zika infections are asymptomatic
- Zika infection can most likely be transmitted by blood transfusion
- The blood banking community has successfully faced numerous emerging pathogens and we are ready to handle Zika virus

**MONEY ISN'T
EVERYTHING.**

Save up to three lives without spending a cent.
Call 13 14 95 or visit donateblood.com.au



Australian Red Cross

BLOOD SERVICE

It takes someone special to give blood.



Questions?