



Advancing Transfusion and  
Cellular Therapies Worldwide

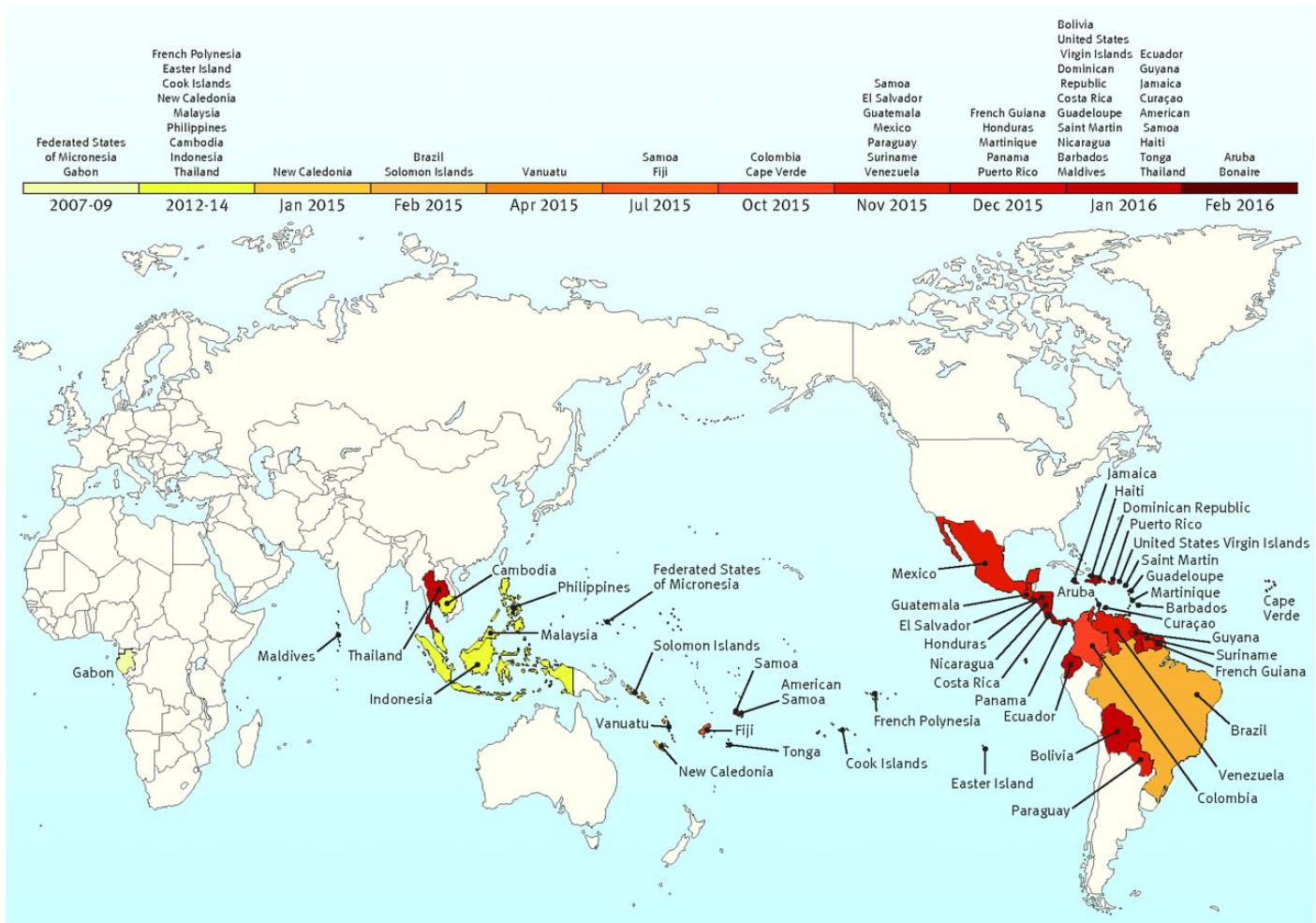
# Challenges Resulting from Implementing Donor Screening Recommendations to Reduce Risk of Zika Transmission: Background

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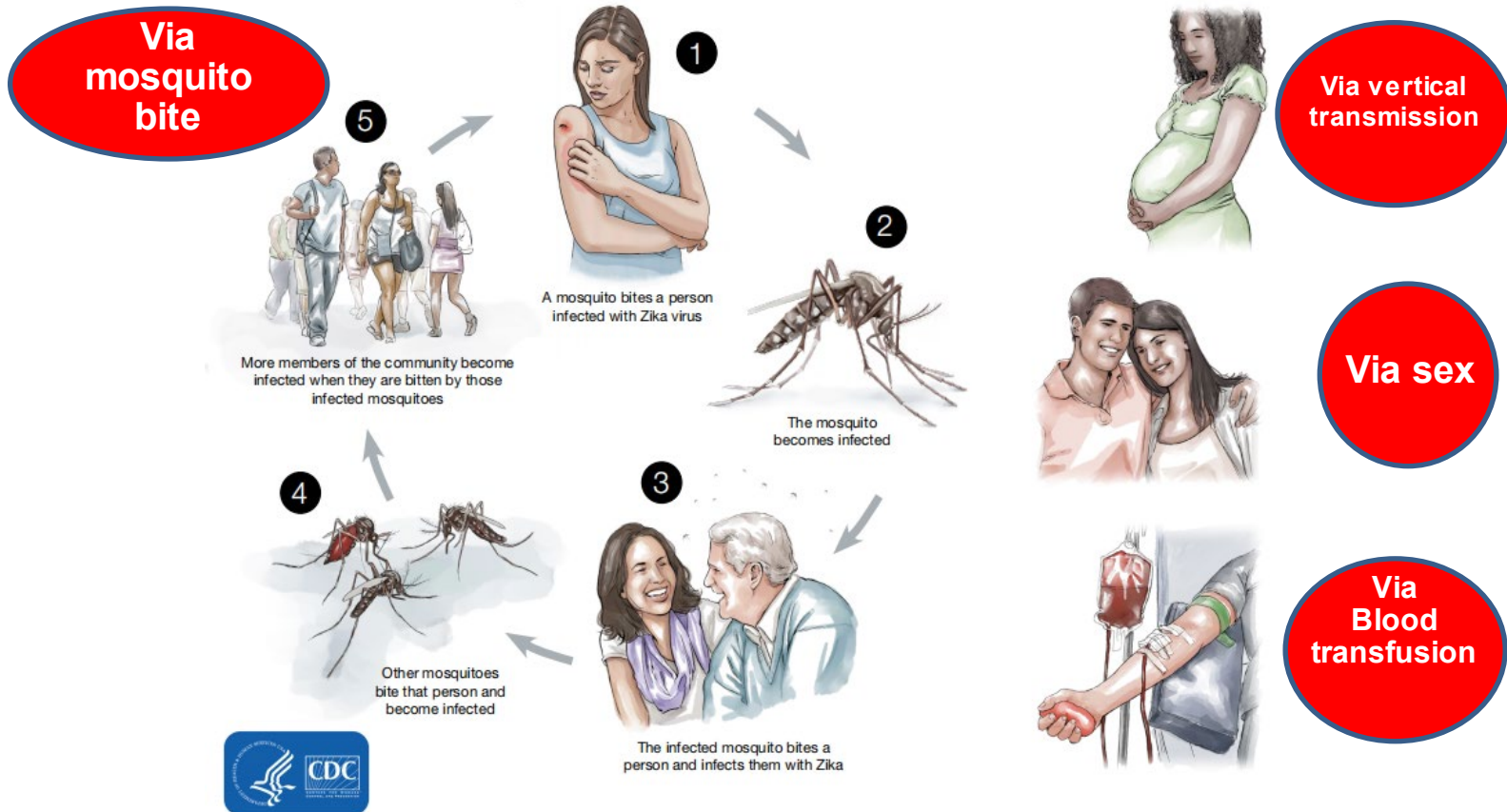
# Zika Virus- Background

- Flavivirus from non-human primates reported in Uganda, 1947 in monkeys and 1952 in human (Zika Forest). Related to dengue, yellow fever, and West Nile Virus
- Transmitted by *Aedes aegypti*
- Human illness Africa, 1960s, trivial, dengue-like
- Yap Island 2007
  - ≈75% attack rate
  - 80% of infections without symptoms
- Guillain-Barre in French Polynesia 2013-14
- Microcephaly *et al* association, Americas 2015
- 4 likely transfusion transmissions in Brazil
- Virus found in Semen, urine, breast milk, saliva... Kidney, liver, brain, lung, and other organs

# Zika spread: 2007-16



# Zika virus (ZIKV) transmission

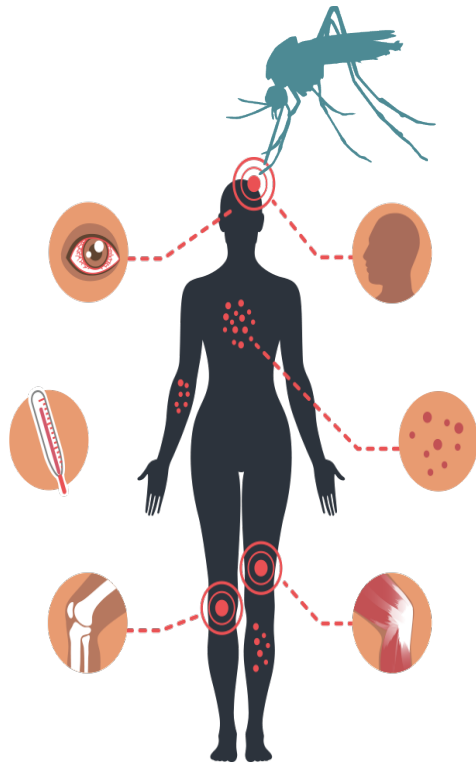


<https://www.cdc.gov/zika/prevention/transmission-methods.html>

# Zika infection: Symptoms and outcomes

## Mild symptoms

- Fever
- Rash
- Headache
- Joint pain
- Red eyes
- Muscle pain



- ZIKV infection during pregnancy (particularly first trimester) may cause severe brain defects & microcephaly



80-90% of infected individuals are asymptomatic

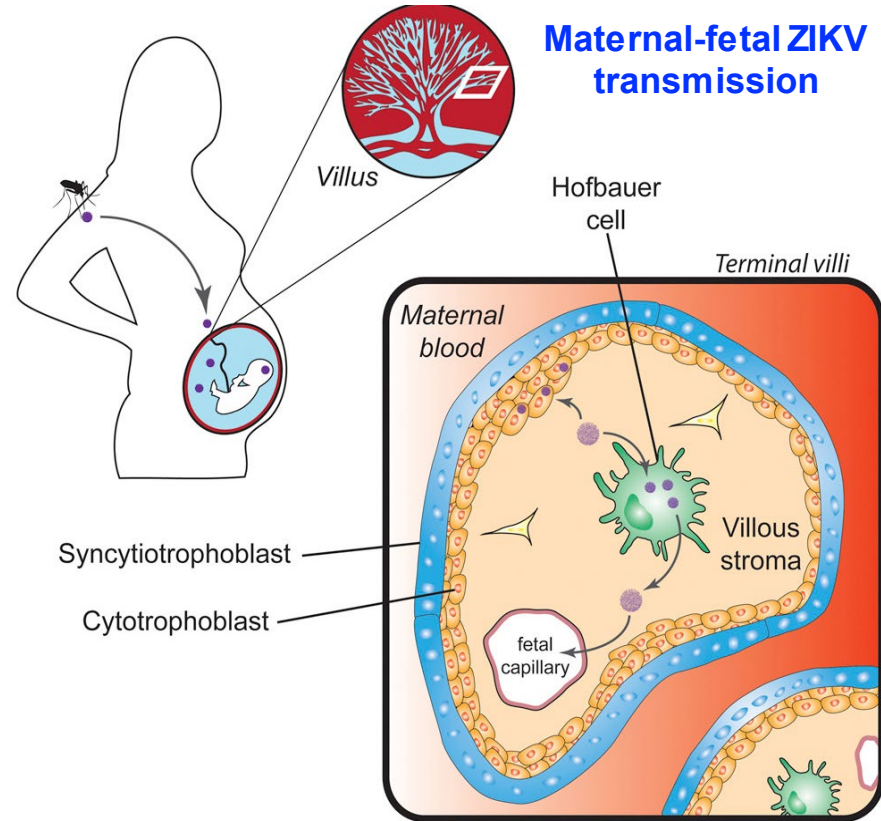
# Outcomes and potential mechanisms of vertical ZIKV transmission

Fetal abnormalities detected by ultrasonography are presented in **29%** of women with ZIKV infection during pregnancy.

**Microcephaly**



**Normal head size**



# Risk of cord blood units being infected and risk of Zika transmission

- Zika infects placental macrophages, cytotrophoblasts, umbilical cord mesenchymal stromal cells
- Detected even if maternal infection occurred in first trimester

# Congenital Zika Syndrome

Severe neurodevelopmental delay, epilepsy, blindness, hearing loss, and hypotonia.

Five features of congenital Zika syndrome

1. Severe microcephaly in which the skull has partially collapsed
2. Decreased brain tissue with a specific pattern of brain damage, including subcortical calcifications
3. Damage to the back of the eye, including macular scarring and focal pigmentary retinal mottling
4. Congenital contractures, such as clubfoot or arthrogyposis
5. Hypertonia restricting body movement soon after birth

Other abnormalities associated:

- Brain atrophy and asymmetry
- Abnormally formed or absent brain structures
- Hydrocephalus
- Neuronal migration disorders
- Excessive and redundant scalp skin
- Reported neurologic findings
- Hyperreflexia
- Irritability
- Tremors
- Seizures
- Brainstem dysfunction
- Dysphagia
- Reported eye abnormalities:
- Focal pigmentary mottling and chorioretinal atrophy in the macula
- Optic nerve hypoplasia
- Cupping
- Atrophy
- Other retinal lesions
- Iris colobomas
- Congenital glaucoma
- Microphthalmia
- Lens subluxation
- Cataracts
- Intraocular calcifications





# Neurologic complications

- Guillain-Barre syndrome (60% ICU, 30% mechanical ventilation, and 5% death)
- Myelitis
- Encephalitis
- Meningoencephalitis
- Acute disseminated encephalomyelitis
- Sensory polyneuropathy
- Optic neuropathy

# Zika: Implications for Blood safety

There is a possibility that ZIKV can be spread through blood transfusions.

- ~ 80% of infections are asymptomatic, viremic donors may feel well enough to donate
- Evidence ZIKV is prevalent in the blood donor population during active outbreaks.
  - During French Polynesian Zika virus outbreak, 2.8% (42/1505) of blood donors tested positive for Zika
  - In Puerto Rico (April 3 to June 11, 2016) 0.5-1% of donors tested positive by PCR
- Infection may lead to severe clinical outcome (severe neurological sequela /microcephaly)
- To date, there have been NO confirmed blood transfusion-transmitted Zika (TTZ) cases in the United States.
  - There have been Four reported cases of TTZ in Brazil
    - Additional cases have been reported are being investigated.
      - There is still uncertainty surrounding Transfusion-transmissibility and Clinical penetrance

# FDA Recommendations for Blood and Blood Components

- February 2016
  - Areas without active transmission: Donor history deferral- infection, travel, or sexual history
  - Areas without active transmission: Pathogen reduction or testing
- August 2016
  - NAT or pathogen reduction on all blood components (implementation roll-out based on state risk). Donor questions removed.
- July 2018
  - MP-NAT allowed (ID-NAT in active areas)



# Investigational Testing for Zika Virus Among U.S. Blood Donors

**Table 1.** Performance Characteristics of the Procleix Zika Virus (ZIKV) Assay Based on the Number of Reactive Donations, June 20, 2016, to September 9, 2017.\*

Test	Tested	TMA Reactive	Confirmed Positive	False Positive	Specificity	Positive Predictive Value
		<i>number of donations</i>			<i>percent</i>	
TMA						
Minipool	393,713	0	0	0	100.000	—
Individual donation	3,932,176	160	9	151	99.996	5.63
All	4,325,889	160	9	151	99.997	5.63
Repeat reactive	4,325,889	6	6	0	100.000	100.00

N Engl J Med 2018;378:1778-88.



**Table 2. Confirmed ZIKV-Positive Donor Demographic Characteristics and Risk Factors.\***

Donor	State	Collection Date	Sex	Age in Yr	Travel†	Days from Return to Donation	Symptoms‡	Sexual Contact§
1	Texas	Nov. 2, 2016	Male	62	Yes	8	No	No
2	California	Nov. 18, 2016	Male	61	Yes	14	No	No
3	Florida¶	Dec. 5, 2016	Male	68	No	—	No	Yes
4	Massachusetts	Dec. 27, 2016	Female	58	Yes	73	Yes	No
5	Florida	Jan. 10, 2017	Female	20	Yes	2	No	No
6	Florida¶	Jan. 12, 2017	Male	22	No	—	No	No
7	New York	Jan. 31, 2017	Female	26	Yes	59	Yes	Yes
8	West Virginia	Mar. 13, 2017	Male	67	Yes	31	No	No
9	Massachusetts**	May 16, 2017	Female	19	No	—	No	No

# Zika Virus Biovigilance Network

Start Date

12/1/2015



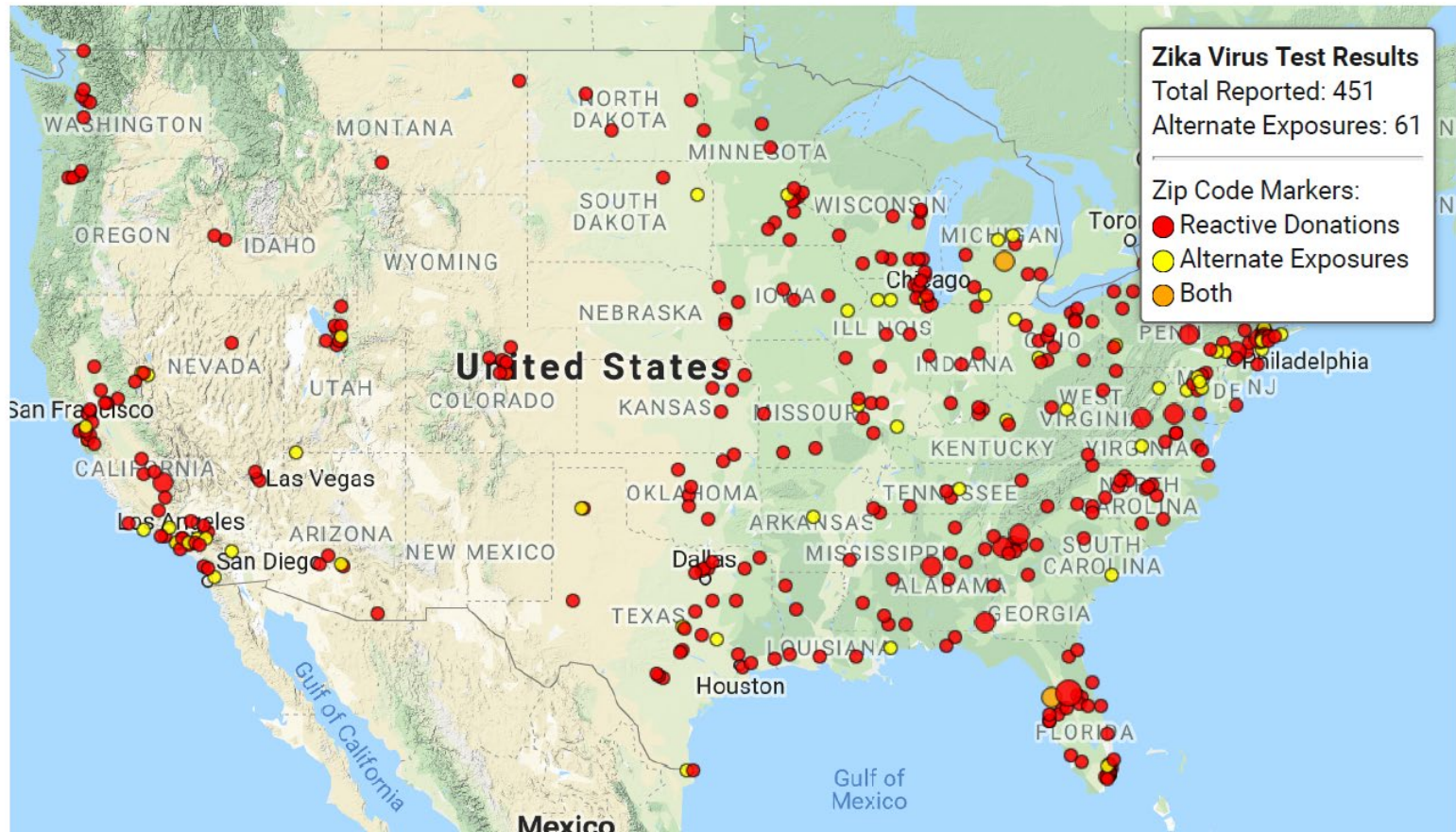
End Date

12/1/2017



LAST 30 DAYS

LAST 90 DAYS



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<http://www.aabb.org/research/hemovigilance/Pages/zika.aspx>

Start Date

7/28/2019



End Date

8/27/2019



LAST 30 DAYS

LAST 90 DAYS



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# Zika Virus

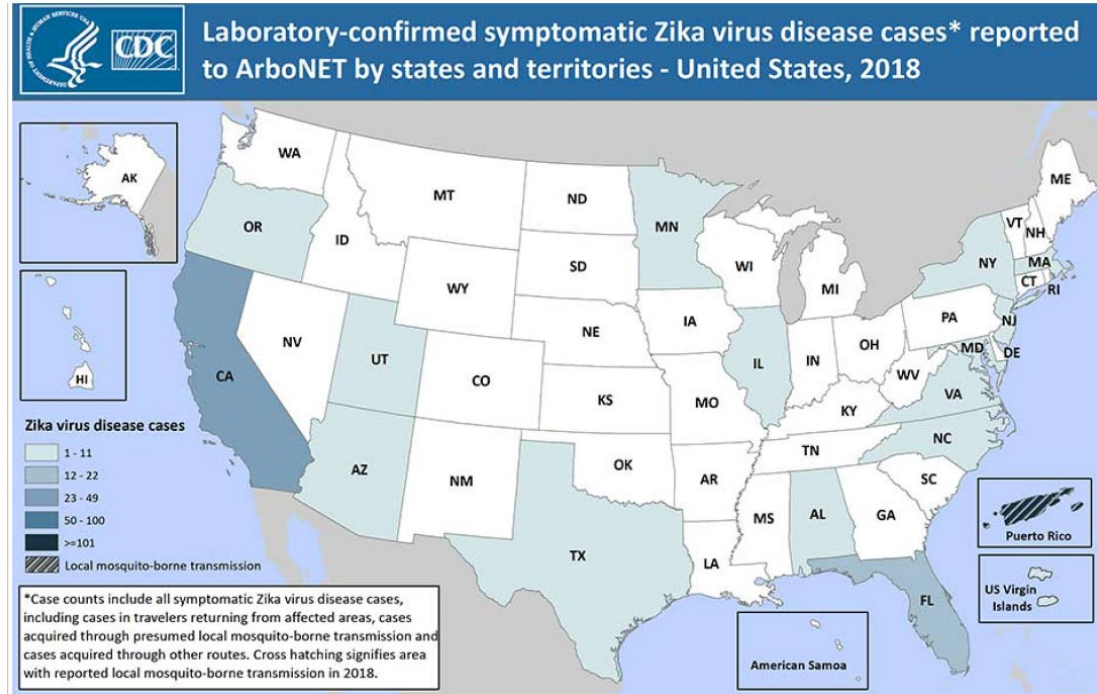
## Final data reported to ArboNET

### US States

- 74 Zika virus disease cases reported<sup>†</sup>
  - 73 cases in travelers returning from affected areas
  - 0 cases acquired through presumed local mosquito-borne transmission
  - 1 case acquired through laboratory exposure; 0 cases acquired through sexual transmission

### US Territories

- 148 Zika virus disease cases reported<sup>†</sup>
  - 1 cases in travelers returning from an affected area
  - 147 cases acquired through presumed local mosquito-borne transmission
  - 0 cases acquired through other routes<sup>†</sup>





**Donor Screening Recommendations to  
Reduce the Risk of Transmission of  
Zika Virus by Human Cells, Tissues,  
and Cellular and Tissue-Based  
Products**

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**Guidance for Industry**

**March 2016**

**A. Recommendations for Living Donors of HCT/Ps<sup>1</sup>**

Living donors of HCT/Ps should be considered ineligible if they have any of the following risk factors:

1. Medical diagnosis of ZIKV infection in the past 6 months.
2. Residence in, or travel to, an area with active ZIKV transmission within the past 6 months.
3. Sex within the past 6 months with a male who is known to have either of the risk factors listed in items 1 or 2, above.

Additionally, donors of umbilical cord blood, placenta, or other gestational tissues should be considered ineligible if the birth mother who seeks to donate gestational tissues has any of the following risk factors:

4. Medical diagnosis of ZIKV infection at any point during that pregnancy.
5. Residence in, or travel to, an area with active ZIKV transmission at any point during that pregnancy.
6. Sex at any point during that pregnancy with a male who is known to have either of the risk factors listed in items 1 or 2, above.



**A. Recommendations for Living Donors of HCT/Ps<sup>1</sup>**

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5. Residence in, or travel to, an area with an increased risk for ZIKV transmission at any point during that pregnancy.
6. Sex at any point during that pregnancy with a person who has either of the risk factors listed in items 1 or 2, above.

Note: Limited instances for which use of HCT/Ps recovered from an ineligible donor is not prohibited, or in which a DE determination is not required, are described in 21 CFR 1271.65(b) and 21 CFR 1271.90, respectively.

# Important Information for Human Cell, Tissue, and Cellular and Tissue-Based Product (HCT/P) Establishments Regarding Zika Virus Transmission Risk in the World

Regarding references to use when screening living donors of HCT/Ps:

First access the CDC webpage for Blood and Tissue Safety.

(<https://www.cdc.gov/zika/areasatrisk.html>)

*To evaluate domestic travel*, the “Areas at increased risk for Zika virus transmission through blood or tissue donation in U.S. states” is listed first and continues to be defined at the county level within a state. For the purpose of screening HCT/P donors, do not use other CDC webpages or maps for evaluating travel within the United States.



# Important Information for Human Cell, Tissue, and Cellular and Tissue-Based Product (HCT/P) Establishments Regarding Zika Virus Transmission Risk in the World

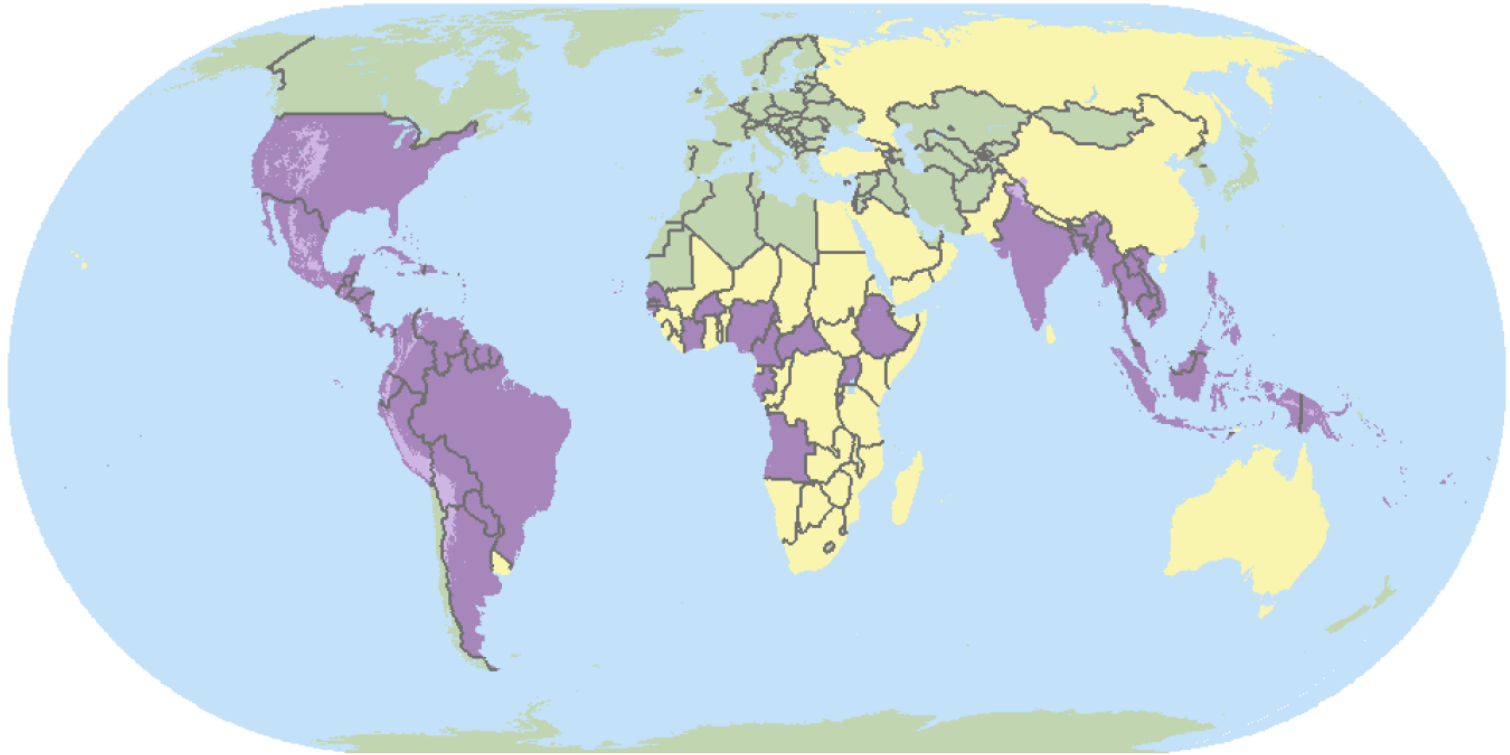
*For evaluating travel to areas outside of the U.S. states, use the link to the world map and consider countries and territories categorized as “Red” or “Purple” as areas with increased risk of ZIKV transmission.*

When an area outside the U.S. states becomes shaded as Red or Purple for the first time on the world map, that area and the date of the change will be posted on the Blood and Tissue Safety (<https://www.cdc.gov/zika/areasatrisk.html>) webpage.






The CDC webpage for Blood and Tissue Safety (<https://www.cdc.gov/zika/areasatrisk.html>) should be monitored frequently for any updates.



## World Map of Areas with Risk of Zika



### Map Legend

-  Country or territory with current Zika outbreak<sup>1</sup>
-  Country or territory that has ever reported Zika cases<sup>2</sup> (past or current)
-  Areas with low likelihood of Zika infection because of high elevation (above 6,500 feet/2,000 meters)
-  Country or territory with mosquito<sup>3</sup> but no reported Zika cases<sup>2</sup>
-  Country or territory with no mosquitoes that spread Zika

<sup>1</sup> No areas are currently reporting Zika outbreaks

<sup>2</sup> Locally acquired, mosquito-borne Zika cases

<sup>3</sup> *Aedes aegypti*

What are the process and challenges/limitations for updating the map?

What is the data on travel risk or area of reported infections with transmission?



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Current as of: March 27, 2019

# Donor ineligibility

- Although donor ineligibility due to Zika risk makes the unit ineligible for licensure unit is still able to be stored and used with documented urgent medical need
- Approximately 10% of cord blood inventory through NMDP/BTM has a yes answer to any Zika question
- Cord blood banks are:
  - Tracking donations that are ineligible for licensure
  - Some are testing mothers using the blood donor screening licensed NAT assay
  - Some are following up with mother regarding infant's health one year post donation

## Re: Comments to the Advisory Council on Blood Stem Cell Transplantation (ACBSCT) on Operational Challenges Resulting from Implementing FDA's Zika Screening Guidance

We respectfully request that the ACBSCT work with the Food and Drug Administration, the Centers for Disease Control and Prevention, the Health Resources & Services Administration, our organizations and infectious disease experts to get a more accurate estimate of the risk of ZIKV transmission in the various countries, identify research or data needed to support policy changes, and identify potential ways to test HCT/P donors (in blood or tissue), or possibly, clear donors retrospectively by following up on their health status, and therefore continue to ensure the safety and availability of cord blood units.

- AABB
- America's Blood Centers
- American Society for Transplantation and Cellular Therapy
- Bloodworks Cord Blood Program
- Carolinas Cord Blood Bank at Duke
- Cleveland Cord Blood Center
- Cord Blood Association
- Cryo-Cell International
- Foundation for the Accreditation of Cellular Therapy
- GenCure
- ISCT International Society for Cell & Gene Therapy
- National Cord Blood Program of the New York Blood Center
- NMDP/Be the Match
- StemCyte, A Global Regenerative Therapeutics Company
- University of Colorado and St. Louis Cord Blood Banks



# Potential paths forward

- Validation of current assays for cord blood, birthing tissues, and other stem cell products
- Understanding the process and challenges/limitations for updating the CDC risk map
- Understanding the risk of Zika infection for the increased travel risk areas
- Determining the cord blood or other stem cell sources ability to transmit the Zika virus
- Determining the length of time infective virus is in these cells