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

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President-Elect
AABB
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

Basarab et al. BMJ. 2016
Zika virus (ZIKV) transmission

1. Via mosquito bite
   - More members of the community become infected when they are bitten by those infected mosquitoes.
2. Via vertical transmission
   - The mosquito becomes infected.
3. Via sex
   - The infected mosquito bites a person and infects them with Zika.
4. Via Blood transfusion
   - Other mosquitoes bite that person and become infected.
5. Via mosquito bite

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.
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 arthrogryposis
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 encephalomyelities
- 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.*

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

<table>
<thead>
<tr>
<th>Donor</th>
<th>State</th>
<th>Collection Date</th>
<th>Sex</th>
<th>Age in Yr</th>
<th>Travel</th>
<th>Days from Return to Donation</th>
<th>Symptoms</th>
<th>Sexual Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Texas</td>
<td>Nov. 2, 2016</td>
<td>Male</td>
<td>62</td>
<td>Yes</td>
<td>8</td>
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<tr>
<td>2</td>
<td>California</td>
<td>Nov. 18, 2016</td>
<td>Male</td>
<td>61</td>
<td>Yes</td>
<td>14</td>
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<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Florida</td>
<td>Dec. 5, 2016</td>
<td>Male</td>
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<td>---</td>
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<tr>
<td>4</td>
<td>Massachusetts</td>
<td>Dec. 27, 2016</td>
<td>Female</td>
<td>58</td>
<td>Yes</td>
<td>73</td>
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<tr>
<td>5</td>
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<td>Jan. 10, 2017</td>
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<td>2</td>
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<tr>
<td>6</td>
<td>Florida</td>
<td>Jan. 12, 2017</td>
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<td>---</td>
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<tr>
<td>7</td>
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<td>Jan. 31, 2017</td>
<td>Female</td>
<td>26</td>
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<td>59</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>West Virginia</td>
<td>Mar. 13, 2017</td>
<td>Male</td>
<td>67</td>
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<td>31</td>
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<td>No</td>
</tr>
<tr>
<td>9</td>
<td>Massachusetts</td>
<td>May 16, 2017</td>
<td>Female</td>
<td>19</td>
<td>No</td>
<td>---</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Zika Virus Biovigilance Network

http://www.aabb.org/research/hemovigilance/Pages/zika.aspx
Final data reported to ArboNET

US States
- 74 Zika virus disease cases reported
  - 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
  - 1 case in travelers returning from an affected area
  - 147 cases acquired through presumed local mosquito-borne transmission
  - 0 cases acquired through other routes

*Case counts include all symptomatic Zika virus disease cases, including cases in travelers returning from affected areas, cases acquired through presumed local mosquito-borne transmission and cases acquired through other routes. Cross hatching signifies area with reported local mosquito-borne transmission in 2018.
A. Recommendations for Living Donors of HCT/Ps

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.
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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.

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.

February 28, 2019
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 webpage (https://www.cdc.gov/zika/areasatrisk.html).


February 28, 2019
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?
Donor ineligibility

• Although donor ineligibility due to Zika risk makes the unit ineligible for licensure, the 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 mothers regarding infant’s health one year post donation.
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