ZIKA Virus (ZIKV)

Joan Dunn Williams
Director of Operations, Phoenix

Larry Morgan,
Director of Client Services
Regional Testing Laboratories

Phoenix

Charlotte

St. Louis

Portland

Tampa
Creative Testing Solutions

- = Healthcare Partners
- = Labs
Presentation Overview

- Background information
- Zika test results (CDC, AABB)
- ZIKA Guidance (FDA)
- Zika donor testing strategy
- Frequently Asked Questions
What is Zika Virus?

• Classified as an arbovirus (ARthropod-BOrne)
• Carried by *Aedes aegypti* and *Aedes albopictus* mosquitoes
• Same mosquitoes that spread dengue and chikungunya
• ZIKV is seasonal (peak during warm months)

Other arboviruses:

• Yellow fever virus
• Rift Valley fever
• Chikungunya
• Dengue fever
• St. Louis encephalitis
What is the Risk?

Infection risk for the general population

• 2.2 billion people live in areas defined as being "at risk"
• Zika infections usually result in mild fever with rash and red eyes, but can be more severe
• Link between Zika and Guillain-Barré syndrome
• Most serious risk is to developing fetus
• Babies exposed in first or second trimesters of pregnancy -- brain still forming -- at greatest risk for microcephaly
  • Virus infects NPCs → cell death

What is the Risk to the U.S. Blood Supply?

- ~80% of infections asymptomatic → donors well enough to donate while still viremic
- pre-symptomatic period varies from 3 to 12 days
- Serum transmission may be up to 6-9 months
- viremia is reported to range from $10^3$-$10^7$ copies/ml
- No confirmed blood transfusion transmission cases in the United States
- Multiple reports of blood transfusion transmission cases in Brazil (currently under investigation)
- During the French Polynesian outbreak, 2.8% of blood donors tested positive for Zika

Source: [http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm486359.htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm486359.htm)
Transmission Routes

3 patterns of spread

1. Direct bite by infected mosquito
   • Active transmission
   • Sporadic transmission

2. Trans-placental

3. Sexual
   • Contained in semen

History and Epidemiology of ZIKV

- 1947: First isolated from rhesus monkey - Zika Forest, Uganda
- 1968: First isolated from human - Nigeria
- 2007: First recognized outside Africa and Asia - Micronesia
- 2013: French Polynesia Outbreak – 11% population infected
- 2014: ZIKV reached Americas - Brazil
- 2015: 30 countries with active local transmission
- 2016: CDC reports Zika causes Microcephaly
- Apr: 

![Zika virus](image1)

![Female and Male symbols](image2)

![Micronesia flag](image3)

![World Cup 2014](image4)

![World Map](image5)

![CDC logo](image6)
ZIKA Results

Center for Disease Control and the AABB biovigilance web site
ZIKV Epidemiology: disease cases decreased

- **2016**
  - U.S. territories: ~36,500 cases
  - US states: ~5,000 cases in ZIKV cases

- **2017**
  - U.S. territories: 665 local cases; 1-travel
  - US States: 451 symptomatic (436 travelers; 7-local transmission; 7-sexual transmissions; 1-lab
  - New York, Florida, Texas, California
Cumulative Zika Virus Disease Case Counts in the United States, 2015-2018

US States

- 5,716 symptomatic Zika virus disease cases reported.
  - 5,430 cases in travelers returning from affected areas
  - 231 cases acquired through presumed local mosquito-borne transmission
  - 55 cases acquired through other routes, including sexual transmission (N=52) laboratory transmission (N=2), and person-to-person through an unknown route (N=1)

US Territories

- 37,262 symptomatic Zika virus disease cases reported.
  - 147 cases in travelers returning from affected areas
  - 37,115 cases acquired through presumed local mosquito-borne transmission
  - 0 cases acquired through other routes

Provisional Data, as of August 1, 2018

Zika virus disease became a nationally notifiable condition in 2016. Cases are reported to CDC by state, territorial, and local health departments using standard case definitions. This is cumulative provisional data reported to ArboNET for January 1, 2015 – August 1, 2018.
Figure 1: Laboratory-confirmed symptomatic Zika virus disease cases with illness onset in 2016–2018, reported to ArboNET by states – United States (provisional data as of August 1, 2018)

Figure 1 shows provisional data for laboratory-confirmed symptomatic Zika virus disease cases with illness onset in 2016-2018, reported to ArboNET by US states (excluding territories).
Figure 2: Laboratory-confirmed symptomatic Zika virus disease cases* with illness onset in 2016–2018, reported to ArboNET by territories – United States (provisional data as of August 1, 2018)

Figure 2 shows provisional data for laboratory-confirmed symptomatic Zika virus disease cases with illness onset in 2016–2018, reported to ArboNET by territories (excluding US states).
AABB Map: ZIKV Reactive Blood Donors

January, 2017– December, 2017
N= 18 confirmed; 67 unconfirmed; 322 false positives

January, 2018 – August, 2018
N= 3 confirmed; 90 unconfirmed; 130 false positives
Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components

Guidance for Industry

This guidance is for immediate implementation.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
July 2018
Blood Supply Safety: FDA Recommendations Testing or Pathogen Reduction

Blood establishments implement nucleic acid testing of all donations or pathogen reduction technology to reduce the risk of ZIKV transmission.

Key provisions of the final guidance are:

• Test all donations (collected in US and territories) with a licensed NAT for ZIKV
• Using Individual donation (ID-NAT) or Minipool NAT
• ID NAT when ZIKV threshold conditions are present
  – ZIKV reactive donation in defined geographic collection area
  – Notification by CDC or public health authority
• Alternatively, implement pathogen reduction for platelets and plasma
• Whole blood or red blood cells may be pathogen reduced when technologies become available.
• FDA recommendations do not apply to the collection of Source Plasma
Blood Products Advisory Committee

• Universal ID NAT intercepted potentially infectious units from asymptomatic blood donors
• Incidence and prevalence of ZIKV
  – did not support continued universal ID NAT
• Recommended that blood establishments should not stop testing for ZIKV
• Supported the use of MP NAT year-round with defined criteria to switch to ID NAT
• Other donor screening options were not feasible or acceptable:
  – IDNAT to test prescreen donors exposed to ZIKV
  – Providing ID NAT-negative blood components to selective patients
Risk Assessment: Minipool NAT Strategy for ZIKV

• Universal minipool NAT screening as an alternative
• Minipool strategy identifies “trigger conditions” to ID NAT
• Detect early infections, while reducing burden of ID NAT
• Minipool NAT would detect the first ID NAT reactive unit in an outbreak is about 90% (92% MP6; 87% MP16).
• FDA recommends switching from MP NAT to ID NAT:
  – even in the absence of ZIKV- reactive donations,
  – when CDC or state or local health departments identify an area at increased risk for ZIKV transmission
  – affects a defined geographic collection area.
Public Health ZIKV Surveillance

- CDC, state or local health departments
  - identify the first case of Zika infection before MP NAT screening
- Switch from MP NAT to ID NAT, even in the absence of ZIKV-reactive donations
- Previously identified risk areas:
  - Cameron County, Texas, Dec 9, 2016 – Aug 29, 2017.
FDA: Other Considerations

- **Recommended**: Pathogen Reduction: (i.e. platelets and plasma)
- **Not Recommended**: Predonation assessment for ZIKV risk factors (i.e. travel or sexual contact)
- **Testing** allows blood centers to collect products without first “assessing donors” for risk factors (travel or residence)
FDA Recommendations: Testing or Pathogen Reductions

• Whole blood collections and blood components
• In compliance with 21 CFR 610.40(a)(3)
  – Test all donations licensed NAT for ZIKV, using either MP NAT or ID NAT
• Use ID NAT when certain threshold conditions are present:
  – detection or notification of a ZIKV- reactive donation in a defined geographic collection area or,
  – notification of areas at increased risk for ZIKV transmission in the absence of ZIKV-reactive donations
• Prepare blood components using pathogen reduction technology
FDA Recommendations, continued

- Do not need to provide donor educational material
- Do not need to screen donors for ZIKV risk factors, such as travel history,
- However, donor volunteers a recent history of ZIKV infection, blood centers **must not** collect blood or blood components from that individual – defer donor for 120 days
FDA Blood Supply Safety: Minipool NAT vs ID NAT

- Convert from MP NAT to ID NAT when certain threshold conditions present in a defined geographic collection area
  - zip code, county or county equivalent
- Blood donor screening/detection or notification of a ZIKV-reactive donation
- CDC or other public health authority notification in the absence of ZIKV-reactive donations
- Threshold conditions one ZIKV-reactive donation and local mosquito-borne transmission
- ZIKV-reactive minipool with resolution by ID NAT testing, or donation that is reactive by ID NAT
- Communicate (24-hrs) ZIKV-reactive results with other blood establishments
ZIKV Reactive Donation
Switch between Minipool and ID NAT

• County *previously* listed by CDC at risk (e.g., Miami-Dade County, Florida; Hidalgo County, Texas)
  – Local mosquito-borne transmission is presumed and screening result alone triggers to ID NAT

• If collected in geographic area not at risk, further assess the donor within 24-hrs
  – If donor exposure was NOT through local mosquito-borne ZIKV transmission, trigger to ID NAT is not required.
  – Risk factors supporting an alternative ZIKV exposure (30 days prior donation) include: travel to an area at risk; sexual contact
FDA Blood Supply Safety: Minipool NAT vs ID NAT

• Convert from MP NAT to ID NAT screening:
  – Within 24 hours of detection or notification of a ZIKV-reactive donation, or a public health notification

• Unless donor’s infection from identified travel to areas at risk of ZIKV transmission or through sexual contact with an individual with ZIKV or at risk for ZIKV infection and

• Collection area is not at increased risk
“Detrigger”: ID NAT to Minipool

• Resume minipool NAT:
  – Donor investigation shows ZIKV reactive donation is not from local mosquito-borne transmission
  – After 14-days, no additional ZIKV-reactive donations and collection area not at increased risk for ZIKV transmission (CDC or state health department)

• Otherwise must stay on ID NAT until collection area is not longer at risk.
Donor and Product Management

- NAT-reactive minipool using ID NAT manage the donor and the individual donation based on the ID NAT results.
- MP NAT, blood centers may release all units whose test samples comprise a non-reactive minipool.
- Individual donation tests ID NAT reactive for ZIKV, blood centers must not distribute or use the donation unless an exception exists.
- CTS testing laboratory responsibility:
  - Frequency of unresolved minipools exceeds the threshold defined.
  - Determine the cause of the initial reactivity of the unresolved minipool.
Donor Management

• Defer a donor who tests ID NAT reactive for ZIKV and notify the donor of the deferral
• 120 days from the date of the reactive test or from the date of resolution of ZIKV symptoms, whichever timeframe is longer
• Deferred donors must be counseled about the possible medical significance of the results
  – Additional testing on the index donation using the same or different FDA-licensed ZIKV NAT screening assay, an investigational ZIKV NAT test, or serological tests for ZIKV antibodies may be of value in donor counseling.
Product Management

Quarantine and retrieve in-date blood and blood components collected from a donor in the 120 days prior to the donation that is ID NAT reactive

- if such blood components were transfused consignees to have a discussion with the recipient’s physician of record about possible transfusion-transmitted ZIKV.

- At Blood Centers discretion: disposition of blood components that were tested by MP NAT and were collected in a geographic area that is later identified with increased risk for ZIKV transmission
Labeling of Whole Blood and Blood Components

- Circular of Information must include the names and results of all tests performed.
- Update your circular of information to include the non-reactive test result using a FDA-licensed test for ZIKV (21 CFR 606.122(h)).
- Refer to the Circular of Information webpage for more information on the required language.
- The following language, developed by AABB’s Circular of Information Task Force and accepted by FDA, must be added to the Circular until it can be incorporated in a future version:
  - “A licensed nucleic acid test (NAT) for Zika Virus RNA has been performed and found to be nonreactive.”
    - This is not a new requirement.
AABB Supplemental Information

• AABB flowcharts: assist in reviewing the FDA guidance
• Use to update Blood Center policies and procedures
• Flowchart 1 - Conversion to ZIKV ID NAT
• Flowchart 2 - Return to ZIKV MP NAT
• Flowchart 3 - Product Management

Page 12: footnote⁵, “…must not distribute a pathogen-reduced platelet or plasma product collected from an individual who tests ID NAT reactive for ZIKV, unless an exception exists (21 CFR 610.40(h))”.
Implementation

• Implementation of the FDA recommendations is a minor change.
• Blood centers must report this change to FDA in their annual report.
ZIKV Donor Testing
Blood Center Requirements
What has changed/What remains the same

ZIKV licensed assay

• Update your circular of information to include the non-reactive test result using a FDA-licensed test for ZIKV
• No longer need to provide donor education material
• No longer screen donors for ZIKV risk factors, i.e. travel history
  – Alternative procedure under 21 CFR 640.120(b) to the provisions in 21 CFR 630.10
  – If a donor volunteers a recent history of ZIKV infection, do not collect blood or blood components
  – Defer such donor for 120 days after a positive viral test or resolution of symptoms (whichever is longer).
Blood Center Priority Tasks: IDS Implementation of Licensed ZIKV

- If continuing on IDS ZIKV no change to electronic ordering.
- Trigger strategy for minipool testing is not required.
Blood Center Priority Tasks: Implementation of Minipool Testing

• Must be on licensed ZIKV testing
• Must have a “trigger strategy”
  – Based on a local or neighbor reactive donation or
  – Based on CDC or State Department of Health reported geographic Zika in your collection area
• Must create a “test order process”
Blood Center Priority Tasks: ITS

When you chose to implement ZIKV minipool testing

• How to order ID ZIKA:
  – Website cannot be used
  – Electronic order to FTP (“selective ADTEST”-process)
  – Instructions are available
  – For those that cannot order by FTP
    • Order via email – address, “CTS ZIKAIDS@mycts.org”
      – CSV file same file type as FTP ADTEST process
    – Instruction using notepad to create CSV file are available

• Blood Center can “trigger on” by LTL contract: “universal IDS ZIKA”.
  – To Trigger on send email notification to “Results Release Dept.”
  – ZIKA trigger will occur with 24-hours

NOTE: due to the complexity of the FDA guidance document, CTS is unable to trigger clients based on a reactive donation.
CTS ITS: Result Release

• Option 1: Receive current process, single test result
  – Nonreactive, Reactive, Not Tested
  – Blood Centers don’t know if donations were tested by IDS or minipool
• Option 2: Receive test results
  – IDS Nonreactive; Nonreactive (MP); Reactive (IDS); Not Tested
  – For option 2: the individual results codes can be mapped to meet the blood center system requirements.
Blood Center requirements

• Sample ordering validation required when:
  – Blood center method will need to send order file to CTS-ITS
  – FTP
  – Email (all blood centers, backup)

• Mapping/Result validation required for option 2
  – Worksheet will be sent to your IT department
  – Result received validation required (5 units)
  – If not electronic: an example RSM will be sent.
Supplemental Testing for Positive Donations

Options for supplemental testing are currently being verified.
“Frequently Asked Questions”

- Clinical Trial vs. Licensed testing
- IDS testing
- Minipool Testing/Trigger Algorithm
- Questions Pending Answers
<table>
<thead>
<tr>
<th>Clinical Trial vs Licensed Testing</th>
<th>The pricing structure(ratio) for MP vs. IDS is anticipated to be similar or comparable to MP WNV vs. IDS WNV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the price for license ZIKA? Will there be a different price for pool versus IDS NAT ZIKA?</td>
<td>Unknown, but probably not before November 5, 2018</td>
</tr>
<tr>
<td>When will CTS implement license IDS ZIKA testing?</td>
<td>We will no longer be on the IND algorithm. The guidance does not stipulate or mention confirmatory testing.</td>
</tr>
<tr>
<td>Will there be any changes to the testing algorithm?</td>
<td>No.</td>
</tr>
<tr>
<td>Can we drop the clinical trial consent form before implementing the license ZIKA reagent?</td>
<td>No, it requires FDA approval. Grifols has decided not to ask for this exception.</td>
</tr>
<tr>
<td>Can Grifols deem the IND reagent as license ZIKA reagent?</td>
<td>Yes, when you convert to IVD.</td>
</tr>
<tr>
<td>When can we discontinue labeling units with IND notation for ZIKA?</td>
<td>Same as any other licensed test.</td>
</tr>
<tr>
<td>What are the labeling requirements once CTS implements license ZIKA?</td>
<td>Yes. Information can be found within the slide presentations and we recommend that you consult your regulatory group.</td>
</tr>
<tr>
<td>Do we need to update the Circular of information? If so, what is the recommended documentation?</td>
<td>Not initially, but in time if Clients want to know if the donation was tested by minipool or IDS, you will need an ID and MP bucket in your LIS system.</td>
</tr>
<tr>
<td>Will the result file change once we implement license ZIKA?</td>
<td></td>
</tr>
<tr>
<td>IDS Testing</td>
<td></td>
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<tr>
<td>----------------------------------------------------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Our center has decided not to implement the triggering strategy; can we implement 100% IDS NAT ZIKA?</td>
<td>Yes.</td>
</tr>
<tr>
<td>Will CTS enter positive ZIKA data into the AABB Biovigilance?</td>
<td>CTS is currently providing this service; we will evaluate the cost and determine if this is feasible.</td>
</tr>
<tr>
<td>Will we be able to test our HCTP products? If so, can it be tested in MP or only by IDS?</td>
<td>Grifols has a claim that was approved for HCTP, although the HCTP FDA guidance (May 2018) was not changed. …”NAT are not considered appropriate for preventing transmission of ZIKV through HCT/Ps”…</td>
</tr>
</tbody>
</table>
# Minipool Testing/Trigger Algorithm

<table>
<thead>
<tr>
<th>Minipool Testing/Triggering Algorithm</th>
<th></th>
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</thead>
</table>
| When will CTS implement pooling ZIKA testing?                                                         | • After conversion to the “licensed assay”.  
• Clients can choose when they want to implement pooled testing.  
• Client must have a trigger/detrigger process in place and be able to order IDS ZIKA testing electronically or by email. |
| Can CTS provide us a recommendation on the triggering strategy for IDS NAT ZIKA testing?             | No. CTS recommendations Clients follow the FDA guidance.                                           |
| Explain how the trigger will work. Will CTS automatically trigger and de-trigger like WNV or is that up to facility? | Clients will need to develop and implement their own trigger strategy based on geographic reactive donors, CDC/Public Health data. |
| Where can the triggering strategy recommendation be found?                                           | Within the slide presentation and FDA guidance.                                                     |
| Is IDS ZIKA triggering strategy necessary seasonal or year around?                                   | It Is not a defined period like WNV. The guidance implies year round.                              |
### Minipool Testing/Triggering Algorithm

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are we required to notify our neighboring centers when we begin IDS NAT ZIKA?</td>
<td>Yes, per the FDA guidance.</td>
</tr>
<tr>
<td>When CTS implements license ZIKA, will it be MP or IDS NAT ZIKA?</td>
<td>We will be able to do both, but the IUO to IVD conversion does not mean conversion to MP, only to licensed reagent. MP will depend on when the client has a ‘trigger strategy” and is ready to send the order file to CTS.</td>
</tr>
</tbody>
</table>
| How will we order IDS ZIKA testing when we implement the trigger strategy? | • Electronically by FTP or  
  • Email using Notepad (CSV file)  
  • The CTS website is not an option.  
  • Email Record Review                                                                                                           |
<p>| In our area, any positive ZIKA is likely to be from a traveler, not autochthonous. How could we trigger on for IND when the mosquito doesn’t live in our area and no autochthonous cases have ever been identified anywhere in our region? | That will be the case from almost all the US. The guidance indicates that if within 24 hours from the time of the blood center receiving the positive result, they can establish a travel or sexual history of the donor indicating travel exposure risk, and then they do not have to trigger. Alternately, they must trigger within 24 hours and if that information can be established later, then they can trigger back off once established. |</p>
<table>
<thead>
<tr>
<th>Questions Pending Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>If we have a positive, we are interested in further testing for ZIKV antibodies and possibly testing on the alternate FDA licensed ZIKV NAT screening test. Would you be offering these services?</td>
</tr>
<tr>
<td>What window of time do we have for implementation once converted from the Grifols clinical trial to the licensed Zika test?</td>
</tr>
<tr>
<td>Once CTS moves to licensed Zika testing, what supplemental testing can we expect if a sample tests positive for Zika?</td>
</tr>
<tr>
<td>Will customers be assigned new Contract IDs as part of this project? If so, how soon will we know the new numbers? Will there be a hard cut-off to differentiate IND Zika from Licensed Zika? Will it be based on sample collection date or sample receipt date or other criteria?</td>
</tr>
<tr>
<td>If a sample is positive with unlicensed reagents; will the donor continue with the follow up protocol on the license reagents? Or the follow up protocol complete when license reagent is implemented?</td>
</tr>
<tr>
<td>Will CTS assist in publishing positive Zika results in a way similar to notification of WVN positives?</td>
</tr>
<tr>
<td>What are the number of potentially false negative results for pooled testing?</td>
</tr>
</tbody>
</table>
Questions?

For additional information on ZIKA use the CDC website at

Contact your Customer Service Managers:
• O’Dina Hurlburt: ohurlburt@mycts.org
• Lindsey Houghton: lhoughton@mycts.org