CHIKV Crash Lands in the Americas in 2014  
*Blood Safety Implications and Actions* 

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Senior Vice President for Research, BSI  
Professor of Laboratory Medicine, UCSF
Chikungunya Virus

*Makonde language: “to dry up or become contorted”*

- Alphavirus
- 3 genotypes
  - West African
  - East/Central/Southern/East African (ESCA)
  - Asian
- Like dengue
  - Man-mosquito-man transmission cycle
  - *Aedes aegypti* is the traditional urban vector
  - Also spread by *Aedes albopictus*
Chikungunya Virus Disease

- Acute onset of fever and severe pain in multiple joints
- Mortality low but extremely debilitating; symptoms often last months to years
- Most infected persons become symptomatic
- No antiviral therapy; treatment is symptomatic
- Lifelong immunity following infection
- No licensed vaccines; prevention relies on avoidance of mosquito bites and mosquito control (difficult)
Chikungunya Virus Outbreaks in Americas

- Since 2005, major outbreaks in tropical areas of Africa, Asia, Western Pacific
- In 2013, first locally-acquired cases in the Americas reported on islands in the Caribbean
- Large, explosive outbreaks will continue in tropical regions until enough of the population has been infected and community transmission can no longer be sustained
- In continental U.S. expect increase in travel imported cases
- Small, focal autochthonous outbreaks also expected
  — Wide use of AC, window and door screens reduce spread
Reported Chikungunya cases and Number of Countries/Territories With Local Transmission in the Americas, Dec 2013–Mar 2015

>1.3 million suspected or confirmed cases
44 countries/territories
Chikungunya in the Western Hemisphere

Status as of March 2015:

- 44 countries or territories in the Caribbean, Central America, South America, and North America.
- 1,310,925 suspected/confirmed cases
  - 35,000 in Puerto Rico
- Notable local transmissions in North America
  - South Florida
  - Sonora State, Mexico
Approximate Geographic Distribution of *Aedes aegypti* and *Aedes albopictus* Mosquitoes in the United States
Chikungunya in the United States*

Historically, from 2006–2013:
- An average 28 people/year with positive tests for recent chikungunya infection
- (Range 5–65 per year)

Current Outbreak, Continental U.S.
- 47 states reporting cases, and the District of Columbia
- 2,549 travel-associated cases
  - 18% from FL
  - 30% from NY
- 12 locally-acquired cases (FL)

* As of March 24, 2015
Considerations on Impact of CHIKV on Blood Safety

- No case of TT-CHIKV reported to date
- Prevalence of viremia among blood donors?
- Proportion of components derived from viremic donations that transmit infection to recipients?
- Clinical impact on infected transfusion recipients?
- Availability/efficacy of measures to reduce transfusion transmission when required?
- Cost and disruption incurred by those measures
Chikungunya Viremia and Immune Response Model
BSRI/CTS/CDC Study of CHIKV in PR Donors

- Pre/Post-Epidemic CHIKV Serosurvey
  - Anonymized plasma samples from 1000 PR donations from June 2014 and 1000 demographically linked PR donations from March 2015 frozen at CTS Tampa lab
  - Tested for CHIKV IgG Abs at BSRI using Euroimmun assay
    - IgM and PRNT performed on IgG-reactive samples
    - Seasonal incidence and demographic correlates of infection

- CHIKV RNA Testing
  - Anonymized frozen aliquots of ~1700 MPs from PR donations from June-Dec 2014
  - Anonymized frozen aliquots from ~3,000 individual donations from peak epidemic
    - ID-NAT+ samples diluted 1:16 to assess yield of ID vs MP-NAT
    - IgG/IgM/PRNT testing to stake infections
  - Real-time TC-TMA CHIKV/DENV testing of MP and ID samples performed at Hologic
  - Real-time PCR CHIKV/DENV testing of MPs to be performed at Roche

- Analyses in progress to:
  - Correlate seasonal incidence with rates of viremic donations and clinical case reports
  - Estimate lengths of MP-NAT and ID-NAT detection periods
  - Determine infectivity of representative viremic donations in immunosuppressed mice
BSRI/CTS/CDC Study of CHIKV in PR Donors

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  - Correlate seasonal incidence from serosurvey with rates of viremic donations and clinical case reports.
  - Estimate lengths of MP-NAT and ID-NAT detection periods.
  - Determine infectivity of representative viremic donations in immunosuppressed and immuno-competent murine models.
Puerto Rico 2014 CHIKV Serology

Pre-epidemic
June-July '14
(n=115)

Post-epidemic
March '15
(n=1031)

Absorbance

Mean+3SD
Mean+5SD

241/1031
(23.4%)
Puerto Rico 2014 CHIKV Serology

Pre-epidemic
June-July '14
(n=115)

Post-epidemic
March '15
(n=1031)

0.0
0.5
1.0
1.5
2.0
2.5
Absorbance

Mean+3SD
Mean+5SD

241/1031
(23.4%)

3.6 M residents of PR x 23.4% infection rate => 842 K infections in 2014
35 K suspected/confirmed cases reported in PR => 4.2% infections reported
# CHIKV/DENV duplex real-time assay on Panther

**Mini-Pool Testing Results**

<table>
<thead>
<tr>
<th>Panels</th>
<th>N</th>
<th>#R</th>
<th>%R</th>
<th>95% LL</th>
<th>95% UL</th>
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<tbody>
<tr>
<td>SeroNAT study MP</td>
<td>1668</td>
<td>161</td>
<td>9.7</td>
<td>8.3</td>
<td>11.2</td>
</tr>
<tr>
<td>June</td>
<td>106</td>
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<tr>
<td>July</td>
<td>193</td>
<td>8</td>
<td>4.1</td>
<td>2.1</td>
<td>8.0</td>
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<tr>
<td>August</td>
<td>293</td>
<td>26</td>
<td>8.9</td>
<td>6.1</td>
<td>12.7</td>
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<tr>
<td>September</td>
<td>262</td>
<td>51</td>
<td>19.5</td>
<td>15.1</td>
<td>24.7</td>
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<tr>
<td>October</td>
<td>299</td>
<td>57</td>
<td>19.1</td>
<td>15.0</td>
<td>23.9</td>
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<tr>
<td>November</td>
<td>243</td>
<td>12</td>
<td>4.9</td>
<td>2.8</td>
<td>8.4</td>
</tr>
<tr>
<td>December</td>
<td>272</td>
<td>7</td>
<td>2.6</td>
<td>1.3</td>
<td>5.2</td>
</tr>
</tbody>
</table>

1 MP tested DENV reactive sample that was also CHIKV reactive
CHIKV/DENV duplex real-time assay on Panther
Mini-Pool Testing Results

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Viral Load Distributions of MP+ samples

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<tr>
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<tbody>
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<td>7</td>
<td>11</td>
<td>11</td>
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<td>36</td>
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<td>0.5 - 1.9</td>
<td>1</td>
<td>4</td>
<td>10</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>28</td>
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<tr>
<td>2.0 - 2.9</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>0</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>3.0 - 3.9</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>22</td>
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<tr>
<td>4.0 - 4.9</td>
<td>1</td>
<td>4</td>
<td>7</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>21</td>
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<tr>
<td>≥ 5.0</td>
<td>2</td>
<td>6</td>
<td>14</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>35</td>
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<tr>
<td>Total</td>
<td>8</td>
<td>26</td>
<td>51</td>
<td>57</td>
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<td>161</td>
</tr>
</tbody>
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1 MP tested DENV reactive sample that was also CHIKV reactive
Rates of RNA+ MPs during 2014 CHIKV epidemic in PR relative to seasonal incidence

- MP NAT
- IgG*

* IgG performed June and March only
Imputed rates of RNA+ IDs using assay with sensitivity of MP NAT

% NAT reactive

% Seroreactive
CHIKV/DENV duplex real-time assay on Panther

**Individual Donor Testing Results**

<table>
<thead>
<tr>
<th>Panels</th>
<th>N*</th>
<th>#R</th>
<th>%R</th>
<th>95% LL</th>
<th>95% UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>SeroNAT study IDT</td>
<td>3007</td>
<td>56</td>
<td>1.9</td>
<td>1.4</td>
<td>2.4</td>
</tr>
<tr>
<td>September</td>
<td>987</td>
<td>18</td>
<td>1.8</td>
<td>1.2</td>
<td>2.9</td>
</tr>
<tr>
<td>October</td>
<td>1010</td>
<td>21</td>
<td>2.1</td>
<td>1.4</td>
<td>3.2</td>
</tr>
<tr>
<td>November</td>
<td>1010</td>
<td>17</td>
<td>1.7</td>
<td>1.1</td>
<td>2.7</td>
</tr>
</tbody>
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*No DENV reactive sample detected*
### CHIKV/DENV duplex real-time assay on Panther

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<td>2.1</td>
<td>1.4</td>
<td>3.2</td>
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<td>November</td>
<td>1010</td>
<td>17</td>
<td>1.7</td>
<td>1.1</td>
<td>2.7</td>
</tr>
</tbody>
</table>

#### Viral Load Distributions of ID+ samples

<table>
<thead>
<tr>
<th>Estimated Log c/mL</th>
<th>September</th>
<th>October</th>
<th>November</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Unquantifiable</td>
<td>7</td>
<td>10</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>0.5 - 1.9</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>2.0 - 2.9</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>3.0 - 3.9</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>4.0 - 4.9</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>≥ 5.0</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>6</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>18</strong></td>
<td><strong>21</strong></td>
<td><strong>17</strong></td>
<td><strong>56</strong></td>
</tr>
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*No DENV reactive sample detected*
Individual donation CHIKV+ samples diluted to 1:16 to mimic MP NAT

<table>
<thead>
<tr>
<th></th>
<th>Tested Neat</th>
<th>Tested 1:16 (duplicate)</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td># R</td>
<td>%R CHIKV</td>
<td># R</td>
<td>%R CHIKV</td>
<td># R</td>
<td>%R CHIKV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>At least 1 replicate is Reactive</td>
<td>Both replicates are Reactive</td>
<td>Only the first replicate is Reactive</td>
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<tr>
<td>September</td>
<td>987</td>
<td>18</td>
<td>1.82%</td>
<td>9</td>
<td>0.91%</td>
<td>50%</td>
<td>0.81%</td>
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<tr>
<td>October</td>
<td>1010</td>
<td>21</td>
<td>2.08%</td>
<td>10</td>
<td>0.99%</td>
<td>48%</td>
<td>0.59%</td>
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<tr>
<td>November</td>
<td>1010</td>
<td>17</td>
<td>1.68%</td>
<td>5</td>
<td>0.50%</td>
<td>29%</td>
<td>0.30%</td>
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<tr>
<td>Total IDT</td>
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<td>1.86%</td>
<td>24</td>
<td>0.80%</td>
<td>43%</td>
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Detection of CHIKV+ donations by ID vs MP-NAT

<table>
<thead>
<tr>
<th>NAT</th>
<th>Serology</th>
<th>#</th>
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<tbody>
<tr>
<td>ID-NAT+ only</td>
<td>no antibody</td>
<td>2</td>
</tr>
<tr>
<td>1/16 diln (1/2 tests positive)</td>
<td>no antibody</td>
<td>1</td>
</tr>
<tr>
<td>1/16 diln (2/2 tests positive)</td>
<td>no antibody</td>
<td>10</td>
</tr>
<tr>
<td>1/16 diln (2/2 tests positive)</td>
<td>IgM</td>
<td>5</td>
</tr>
<tr>
<td>1/16 diln (2/2 tests positive)</td>
<td>IgG</td>
<td>8</td>
</tr>
<tr>
<td>ID-NAT+ only</td>
<td>IgG</td>
<td>30</td>
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</tbody>
</table>

% NAT reactive

ID NAT only

MP detectable
CHIKV viral loads based on real-time TMA of 56 RNA+ ID-NAT reactive PR donations, by stage of infection
CHIKV infectivity in immunocompromised mice lacking the type I IFN receptor (Ifnar−/−)

Other murine models

- Wild-type neonate mice
  - Day 8-9 C57BL/6 mice, high titer virus (10⁵ pfu) intradermally. Lethal infection 4-6 p.i. Infection inhibited by mAbs.
- Acute arthritic model
  - 6 week old wild-type C57BL/6 mice, 10⁴ pfu subcutaneously in footpad. Develop foot swelling 6-8 days p.i. Symptoms inhibited by mAbs.
Mitigation Strategies for TT-CHIKV

- NAT screening
- Photochemical inactivation of platelets/plasma
- Curtail donations in outbreak areas
- Defer donors from areas experiencing outbreaks
- Enhanced donor deferral
- Enhanced post-donation notification
- Temporary quarantine of donations with proactive post-donation call back
Conclusions Regarding Impact of CHIKV on Blood Safety

- Prevalence of viremia among blood donors
  -- Can be very high for short periods of time during large epidemics

- Proportion of components from viremic donations that transmit infection to recipients
  -- Unknown, but likely high at least until IgG antibody develops
  -- NAT positivity ≠ Infectivity; need for animal and human TT studies

- Clinical impact on infected transfusion recipients
  -- Unknown, but likely some morbidity and low mortality

- Availability of measures to reduce TT when required
  -- Sourcing blood from low risk regions and enhanced deferral or post-donations call-back challenging
  -- NAT screening and PR feasible, but concern over affordability

- Cost and disruption incurred by these measures
  -- Can be high and may not be feasible in high epidemic regions
Acknowledgements

Creative Testing Solutions
Phillip Williamson
PR blood banks
CTS Tampa lab staff

BSRI
Graham Simmons
Kai Lu
Nathan Liss
Marcus Muench
Michelle Quintos

Hologic/Grifols
Jeff Linnen
Vanessa Bres
Maesa Hanhan
Derrek Ocampo

Roche
Tony Hardiman
Subita Sudershana

CDC
Lyle Petersen
Reappearance of Chikungunya, Formerly Called Dengue, in the Americas

Scott B. Halstead

After an absence of ≈200 years, chikungunya returned to the American tropics in 2013. The virus is maintained in a complex African zoonotic cycle but escapes into an urban cycle at 40- to 50-year intervals, causing global pandemics. In 1823, classical chikungunya, a viral exanthem in humans, occurred on Zanzibar, and in 1827, it arrived in the Caribbean and spread to North and South America. In Zanzibar, the disease was known as kidenga pepo, Swahili for a sudden cramp-like seizure caused by an evil spirit; in Cuba, it was known as dengue, a Spanish homonym of denga. During the eighteenth century, dengue (present-day chikungunya) was distinguished from breakbone fever (present-day dengue), another febrile exanthem. In the twentieth century, experiments resulted in the recovery and naming of present-day dengue viruses. In 1952, chikungunya virus was recovered during an outbreak in Tanzania, but by then, the virus had lost its original name to present-day dengue viruses.
Cases reported to PAHO to April 24 (week 16 2015)
50 countries/territories in the Americas

<table>
<thead>
<tr>
<th></th>
<th>Susp’d</th>
<th>Lab conf’d</th>
<th>Imprt’d</th>
<th>Deaths</th>
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<td>US</td>
<td>0</td>
<td>11</td>
<td>2574</td>
<td>0</td>
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<tr>
<td>PR*</td>
<td>31,433</td>
<td>4349</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>All</td>
<td>1,367,343</td>
<td>30,580</td>
<td>3637</td>
<td>191</td>
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