The Potential Introduction of Zika virus into the US – Implications for Public Health and Blood Safety – Lessons Learned from Other Arboviruses

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VP, Scientific Affairs

Thrombosis and Hemostasis Societies of North America 2016 Summit, April 15
Nothing to Disclose
Current Arboviral Threats to the Continental US

• **Dengue:** 1/3 of world population at risk, 30-fold increase in 50 yrs

• **Chikungunya:** Re-emerged in the Americas late 2013; ≈1.7M cases

• **Zika:** evidence of past or current transmission across Africa, Asia, W. Pacific; confirmed in Brazil May 2015; now ass’d with microcephaly and Guillain-Barré syndrome; 62 countries total since 2007; 33 countries in the Americas to 2016
Dengue Incidence is Rapidly Increasing in the Americas

Source: Pan American Health Organization (PAHO)
<table>
<thead>
<tr>
<th>Americas Sub-region</th>
<th>Dengue*</th>
<th>Incidence rate / 100,000 in habitants</th>
<th>Severe Dengue**</th>
<th>Deaths</th>
<th>Case Fatality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America, Central America &amp; Mexico</td>
<td>181,860</td>
<td>108.4</td>
<td>2,747</td>
<td>18</td>
<td>0.01</td>
</tr>
<tr>
<td>Andean</td>
<td>151,459</td>
<td>110.0</td>
<td>1,049</td>
<td>94</td>
<td>0.06</td>
</tr>
<tr>
<td>Southern Cone</td>
<td>1,390,241</td>
<td>539.5</td>
<td>1,149</td>
<td>616</td>
<td>0.04</td>
</tr>
<tr>
<td>Hispanic Caribbean</td>
<td>5,207</td>
<td>20.4</td>
<td>47</td>
<td>47</td>
<td>0.90</td>
</tr>
<tr>
<td>Caribbean</td>
<td>2,108</td>
<td>11.1</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>1,730,875</strong></td>
<td><strong>284.9</strong></td>
<td><strong>4,992</strong></td>
<td><strong>775</strong></td>
<td><strong>0.04</strong></td>
</tr>
</tbody>
</table>

*Sum of Dengue + Severe Dengue

**Includes all forms of Severe Dengue including Dengue Shock Syndrome and Dengue Haemorrhagic Fever
Potential Areas of Infection by Mosquito for Confirmed Dengue Fever Cases

As of December 9, 2015
(HDOH preliminary data - subject to change pending new information)

Total number of confirmed cases 145

Risk level for potential dengue infection*:  🟢 High Risk  🟡 Moderate Risk  🟠 Some Risk

*Risk levels of areas where confirmed cases may have contracted dengue fever are determined by factors including the number of confirmed cases who reported visiting those areas, as well as observed mosquito activity. Individuals should always protect themselves against mosquitoes and mosquito bites island-wide; extra precaution should be taken in areas of risk. For more information on dengue fever and ways to protect yourself from mosquitoes, visit: http://health.hawaii.gov/docd/dengue-outbreak-2015/
DENGLUE FEVER
HAWAII ISLAND OUTBREAK
136 Confirmed Cases
Data provided by the State Department of Health.
Locations may represent multiple cases
Map Updated: 12/4/2015 at 1:00 pm
Chikungunya Virus and the Global Spread of a Mosquito-Borne Disease

Scott C. Weaver, Ph.D., and Marc Lecuit, M.D., Ph.D.

Figure 2. Origin, Spread, and Distribution of Chikungunya Virus and Its Vectors.

The map shows the African origins of enzootic chikungunya virus strains and the patterns of emergence and spread of the Asian lineage and Indian Ocean lineage (IOL) of the virus during epidemics since the 1950s, based on phylogenetic studies. The distributions of the peridomestic vectors, Aedes aegypti and A. albopictus, are also shown. ECSA denotes eastern, central, and southern African.
Puerto Rico: 31,433 cases

French West Indies
1 Dec 2013 – 24 Apr 2015

Guadeloupe: 81,350 cases

Martinique: 72,520 cases
Spread of ZIKA Virus (ZIKV)
Spread of the ZIKV

- **1947**: first detected in Uganda, Africa
- **1947 to 2007**: 14 human infections were reported (Africa and Asia)
- **2007**: First outbreak in Yap, Federated States of Micronesia, Pacific
- **2007 to 2013**: 1 infection in Philippines from retrospective study
- **2013 to 2014**: A large outbreak occurred in French Polynesia with ~32,000 symptomatic cases, 11% of the population 2.8% rate of RNA in blood donors, 11/42 (26%) reported PDI, viral loads 10^3-10^7 copies/mL
- **2014**: Spread throughout the South Pacific
- **2015**: Spread to South America (Brazil and Columbia)

*Jones KE, Patel NG, Levy MA. et al. Nature 2008*
ZIKV publications:
1952-2009 (first description to first outbreak in Yap) = 25
2010-2015 63
2016 225
Figure 1. Areas in Which Zika Virus Infections in Humans Have Been Noted in the Past Decade (as of March 2016).
Only sporadic infections have occurred in Southeast Asia, the Philippines, and Indonesia.
ZIKV Vectors: 
*Aedes* Mosquitoes

- *Aedes (stegomyia)* species mosquitoes
  - *Ae. aegypti* most efficient vector for humans
  - *Ae. albopictus* spread in more temperate zones
- Also transmit **dengue and chikungunya viruses**
- Lay eggs in domestic water-holding containers; tolerate drying
- Live in and around households
- Aggressive daytime biters; can also bite at night
- Multiple humans bitten for a single blood meal
## Arbovirus Comparison

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dengue</th>
<th>Chikungunya</th>
<th>Zika</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus family</td>
<td>Flaviviridae</td>
<td>Togaviridae</td>
<td>Flaviviridae</td>
</tr>
<tr>
<td>Virus genus</td>
<td>Flavivirus</td>
<td>Alphavirus</td>
<td>Flavivirus</td>
</tr>
<tr>
<td>Serotypes</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Genotypes</td>
<td>Multiple per serotype</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Vectors</td>
<td><em>Aedes aegypti</em></td>
<td><em>Aedes aegypti</em></td>
<td><em>Aedes aegypti</em></td>
</tr>
<tr>
<td></td>
<td><em>Aedes albopictus</em></td>
<td><em>Aedes albopictus</em></td>
<td><em>Aedes albopictus</em></td>
</tr>
<tr>
<td>Symptoms / illness</td>
<td>Acute febrile illness</td>
<td>Acute febrile illness</td>
<td>Acute febrile illness</td>
</tr>
<tr>
<td>Symptomatic: Asymptomatic</td>
<td>25:75</td>
<td>75:25</td>
<td>25:75</td>
</tr>
<tr>
<td>Illness outcome</td>
<td>Severe dengue – plasma leakage</td>
<td>Rarely severe, Arthralgias</td>
<td>Rarely severe, Microcephaly, Guillian-Barré</td>
</tr>
</tbody>
</table>
ZIKV
(for AABB Fact Sheet Prior to 2013)

• Mosquito-borne viral disease
• Zika recognized in 1947 in the Zika forest in Uganda in the rhesus macaques; African lineage and Asian lineage
• Usually mild, lasting for 2-7 days
• Main symptoms include:
  – Low-grade fever (<38.5°C)
  – Transient arthritis/arthralgia with possible joint swelling mainly in the smaller joints of the hands and feet
• Maculopapular rash often spreading from the face to the body
• Conjunctival hyperemia or bilateral non-purulent conjunctivitis
• General non-specific symptoms such as myalgia, asthenia and headaches
• Incubation period 3-12 days
• Infection may go unrecognized or be misdiagnosed as dengue, chikungunya or other viral infections giving fever and rash. Asymptomatic infections are the rule, ≈75%
• Disease is usually mild
Clinical Features: 
ZIKV Compared to Dengue (DENV) and Chikungunya (CHIKV)

<table>
<thead>
<tr>
<th>Features</th>
<th>ZIKV</th>
<th>DENV</th>
<th>CHIKV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Rash</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Myalgia</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Headache</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Shock</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
ZIKV and Guillain-Barré Syndrome, 2013-2014

- ZIKV infection historically was thought to produce a mild disease
- With the large outbreak in French Polynesia (~32,000 cases), a rise in cases of Guillain-Barré Syndrome was observed
  - Past incidence was about 5 cases per year
  - During the ZIKV outbreak, 42 cases in 6 months (20X increase)
    - All had ZIKV neutralizing antibody
  - 15 admitted to intensive care units
  - French Polynesia only has 270,000 inhabitants!

![Graph showing ZIKV and GBS cases over weeks]

Courtesy of D. Musso
Zika and Guillain-Barré Syndrome

Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study


OR >34 between GBS and prior ZIKV infection

Now 13 countries/territories report an increase in GBS
ZIKV Genome from the Americas

Asian genotype most closely related to the French Polynesian 2013 strain

Patient with Exanthema and conjunctivitis

Enfissi et al. Jan 6 2016 The Lancet
ZIKV-Associated Microcephaly to Dec 2015

• An etiologic role for ZIKV has not been proven, but .....  
• ZIKV RNA has been isolated from at least 3 cases in Brazil, 2 from amniotic fluid of fetuses with microcephaly on ultrasound and one from blood and tissue of a baby that died at birth  
• 4 mothers of malformed babies in French Polynesia have been found to have IgG anti-ZIKV, but have no history of compatible illness  
• Estimated risk 1:100 in first trimester  
• Diagnostic testing required to differentiate DENV, CHIKV and ZIKV  
  – Note: other causes include infections (toxo, rubella, herpes, syphilis, CMV, HIV), toxins, alcohol, genetic abnormalities and severe malnutrition during pregnancy
ZIKA Disease in Brazil (Dec 8 2015)
1,761 reported in 422 municipalities in 14 Brazilian states with 19 fatalities

Protocol from the Secretary of Health Surveillance re monitoring for ZIKV-associated microcephaly and fetal malformations:

1. Possible ZIKV infection during pregnancy.
2. Fetal CNS changes with possibly related ZIKV infection during pregnancy.
3. Miscarriage due to possible association with ZIKV infection during pregnancy.
4. Stillborn due to possible infection during pregnancy ZIKV.
5. Newborn live with microcephaly possibly associated with infection ZIKV during pregnancy.
Rates of Microcephaly Over Time: the Americas and the Caribbean

20-fold increase in rates of microcephaly in the Americas and Caribbean from 2010-2014 and 2015

Updated as of Epidemiological Week 52 (December 27, 2015 – January 2, 2016)

Microcephaly rates by state in Brazil (cases per 1,000 live births)

- 0.1-1.0
- 1.1-15.0
- 15.1-30.0
- 30.1-45.0
- 45.1-88.6
- Countries

Countries with Zika confirmed cases

- Epi Week 52 2015
- Country limits
- Brazil State Boundaries

Data Source:
Reported from the IHR National Focal Points and through the Ministry of Health websites.

Map Production:
PAHO-WHO AD CHA IR ARO

ZIKV in Brazil

- Estimated number of infections
  - 498,000 to 1,482,000
- 27/27 states have reported cases of microcephaly
- 2982 reported cases in 2015
- 2908 reported cases in 2016 (thru March 27)
  - Previously 147-175 (2010-2014)
- 907 confirmed plus 4293 under investigation
- 46 confirmed deaths
  - 130 under investigation
Pregnant female returns from Rio Grande do Norte state; weeks 20-28 normal pregnancy
During 13\textsuperscript{th} week, she had high fever, musculoskeletal and retroorbital pain, itching and rash
Abnormalities at week 32 => pregnancy terminated
\begin{itemize}
  \item intrauterine growth retardation, microcephaly, brain structures blurred,
  \item extremely calcified (including the placenta), severe brain disease
  \item no other causes of microcephaly (family)
\end{itemize}
ZIKV RNA by RT-PCR $6.5 \times 10^7$ copies/mg brain tissue; all other flaviviruses and other viruses neg
Full genome sequenced from the fetal brain; dense particles resembling virus and
enveloped structures resembling replicative complexes also observed
99.7% genetic relatedness to French Polynesia 2013 strain and Sao Paulo 2015 strain
No presence of ZIKV and no pathological findings detected in any other fetal organs =>
\textbf{Strong neurotropism of the virus}
Figure 4. Phylogenetic Analysis of the Complete Genome of Zika Virus.
Zika virus in the Americas: Early epidemiological and genetic findings – Cases appeared 2 years after its introduction into Brazil

Fig. 1 Time series and cartography of reported ZIKV and microcephaly cases in Brazil

Nuno Rodrigues Faria et al. Science 2016;science.aaf5036
Fig. 2 Maximum likelihood phylogeny of ZIKV complete coding region sequences
Fig. 3 Timescale of the introduction of ZIKV to the Americas

A

B

C

Nuno Rodrigues Faria et al. Science 2016;science.aaf5036
Other modes of ZIKV transmission (other than mosquito, intrauterine)

- Sexual

  2 health care workers returned from Senegal in 2008 (Foy et al. EID 2011 from CDC)
  - Sexual tx from case 1 to his wife (case 3) upon return to CO
  - Sexual intercourse 1 day after his return; 3 days later, case 1 developed prostatitis, hematospermia and his wife developed flu-like illness; she had no travel history or known mosquito exposure; semen was not investigated for RNA but both tested ZIKV seropositive
  - ZIKV RNA isolated from semen and urine published in EID, Feb 2015 by group in Tahiti (Musso et al.)
    - Fever, weakness days 1-3; arthralgia days 5-7
    - Hematospermia 2 weeks later; ZIKA RNA pos from semen; repeated 3 days later and confirmed in semen (10^7 copies/mL) and urine (10^3 copies/mL); blood negative; virus also culture pos from semen
  - ZIKV RNA recovered from semen of a patient returning from the Cook Islands on days 27 and 62 after symptom onset (Atkinson et al., EID 2016)
  - Cases investigated in the US (6 countries now reporting)
We describe the kinetics of Zika virus (ZIKV) detection in serum and urine samples of 6 patients. Urine samples were positive for ZIKV >10 days after onset of disease, which was a notably longer period than for serum samples.

Triangles=urine; squares=serum
Dashed line indicates >2 day interval between sampling
Viral Ramp-up Study in 3 Macaques infected with ZIKV

Viral loads: plasma

10^6 copies/mL

10^4 copies/mL

Viral loads: oral swab

Viral loads: pan_uree

10^4 copies/mL

Days since Zika virus infection

https://zika.labkey.com/project/OConner/begin.view
Mice lacking IFN receptor support disease and mortality when ZIKV challenged. Age dependent response (3wo => death vs 11 week => disease but recovered). Growth in the brain by day 3 with neurologic disease by day 6. Robust replication in the testes.
Other modes of ZIKV transmission

• Transfusion - high viral titers up to 14 days
  – 2 cases from Brazil (both Campinas, Sao Paulo State)
  – First March 2015 reported to HV
    • 3 days post-donation, report DENV-like symptoms from donor, later diagnosed as ZIKV => ZIKV RNA pos (neg DENV/CHIKV)
    • Platelets => liver recipient, remained asymptomatic for ZIKV, but RNA pos (and culture pos; pre-tx sample neg)
    • Sequence identity between donor/recipient
  – 2nd case April 2015
    • Gunshot victim rec’d 18 components => died
    • Recipient unexplained thrombocytopenia prior to death; ZIKV culture pos (neg DENV/CHIKV)
    • Retention samples from 18 components were part of a repository study => identified one ZIKV RNA pos component received by recipient
    • 3 days post-donation, donor reported symptoms: rash, conjunctivitis, severe itching, generalized pain, hypotension
Updated ZIKV Info (4/10/16)

• CDC Public Health alerts – 41 areas including 33 in the Americas, 7 islands in the S. Pacific, and 1 Africa (Cape Verde)
  – Usual mosquito avoidance measures, DEET, long sleeves, pants, sleep under a bed net, remove standing water
  – Pregnant women avoid travel; condoms, avoid contact with semen

• Feb 1 WHO declares public health emergency of international concern to trigger a coordinated global effort for education, surveillance, diagnostics, treatment, prevention (mosquito control and vaccine development), research into congenital malformations and neurological complications
  – Only 4th in recent years: EBOV, Polio, H1N1 flu
  – Est’d 3-4 million cases in the Americas in the next 12 months modeled after DENV in the Americas in 2015 with ~ 2 million cases (A. aegypti in the “dengue-belt”)


All Countries and Territories with Active Zika Virus Transmission (4/10/16)
Considerations for Blood Safety

• Surveillance
• Stop collections and rely on imports
• Enhanced donor symptom screening
• Enhanced call back (PDI) => Quarantine
• 14- or 28-day travel deferrals used in nonendemic areas
• Routine blood donation testing (NAT)
• Pathogen inactivation
Detecting ZIKV RNA and antibodies

- Zika Virus RNA
- Anti-Zika IgM Antibodies

Symptom Onset

TIME
## Inactivation of Emerging Pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Inactivation In PC (Log(_{10}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>West Nile virus</td>
<td>&gt; 6.0</td>
</tr>
<tr>
<td>Chikungunya virus</td>
<td>&gt; 6.4</td>
</tr>
<tr>
<td>H1N1 virus</td>
<td>&gt; 4.1</td>
</tr>
<tr>
<td>H5N1 virus</td>
<td>&gt; 5.9</td>
</tr>
<tr>
<td>Dengue viruses</td>
<td>&gt; 5.0</td>
</tr>
<tr>
<td>SARS-HCoV</td>
<td>&gt;6.3</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>4=&gt;5.5</td>
</tr>
<tr>
<td>Orientia tsutsugamushi</td>
<td>&gt; 5.5</td>
</tr>
<tr>
<td>Trypanosoma cruzi</td>
<td>&gt; 5.3</td>
</tr>
<tr>
<td>Babesia microti</td>
<td>&gt; 5.3</td>
</tr>
<tr>
<td>Leishmania mexicana</td>
<td>&gt; 5.0</td>
</tr>
</tbody>
</table>
Validation of Intercept inactivation for ZIKV in plasma units

<table>
<thead>
<tr>
<th>Plasma samples</th>
<th>Mean viral titers (log₁₀ TCID₅₀/mL)</th>
<th>Mean RNA loads (log₁₀ copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-inactivated</td>
<td>6.57</td>
<td>10.25</td>
</tr>
<tr>
<td>Post-inactivated</td>
<td>N</td>
<td>9.51</td>
</tr>
<tr>
<td>Post-inactivated after 1ˢᵗ passage</td>
<td>N</td>
<td>3.86</td>
</tr>
<tr>
<td>Post-inactivated after 2ⁿᵈ passage</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Post-inactivated after 3ʳᵈ passage</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Post-inactivated after 4ᵗʰ passage</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Post-inactivated after 5ᵗʰ passage</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

N: no virus detected by IF or no RNA detected by PCR

Aubry et al. Transfusion 2016
FDA Guidance 2/16/16

• Areas with active ZIKV transmission; 2-week implementation (March 1) or immediate for pregnant women, intrauterine transfusion or other risk groups as defined by the physician; exceptions require physician approval if deemed urgent
  – Obtain whole blood and components for tx from areas of the US where no active tx is occurring
  – Can prepare platelets and plasma using an FDA-approved PI method (or method approved under IDE)
  – Can test using a licensed NAT (or method approved under IND)
  – DHQ modified to ask about a dx or s/s (cdc.gov) of ZIKV infection in the past 4 weeks; history of sexual contact in the past 4 weeks with a man who has been dx with or had s/s suggestive of ZIKV in the 3 months prior to the last sexual contact
FDA Guidance 2/16/16

• Areas **without active** ZIKA transmission; 4-week implementation (March 15)
  – Donor educational materials allowing donors to self defer for 4 weeks
    • Risk factors and s/s of ZIKV infection within the last 2 weeks of leaving an active ZIKV area ([cdc.gov](http://cdc.gov))
    • History of ZIKV infection until 4 weeks after resolution of symptoms
    • Sex with a man who has been dx with ZIKV or who traveled to or resided in an active ZIKV area in the 3 months prior to the last sexual contact
    • Travel not specifically mentioned, but should be included (risk factors)
  – DHQ modified to ask about residence or travel w/in last 4 weeks ([cdc.gov](http://cdc.gov))
  – PDI as above with donor deferral for 4 weeks
  – Product quarantine/retrieval of indate components for those collected from a donor at risk or dx during the 4-week deferral period or reported as PDI within subsequent 2 weeks of collection; consignee notification from a donor with a ZIKV dx within the prior 4 weeks of donation or 2 weeks following donation
ZIKV Signs/Symptoms (2 or more) from cdc.gov

• Fever
• Rash
• Joint pain
• Muscle pain
• Conjunctivitis (red eyes)
• Headache
### Estimated donor deferral rate (%) in the US from a 14- or 28-day deferral by geographic region comparing 2 surveys

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fixed sites only; paper survey; Americas only primarily N=33,408</td>
<td>All sites; electronic survey; Worldwide N=19,879</td>
</tr>
<tr>
<td>14-day %</td>
<td>28-day %</td>
<td>14-day %</td>
</tr>
<tr>
<td>Mexico</td>
<td>0.19</td>
<td>0.52</td>
</tr>
<tr>
<td>Caribbean</td>
<td>0.16</td>
<td>0.48</td>
</tr>
<tr>
<td>Central and South America</td>
<td>0.05</td>
<td>0.13</td>
</tr>
<tr>
<td>All above*</td>
<td>0.39</td>
<td>1.17</td>
</tr>
<tr>
<td>All travel (global)*</td>
<td>N/A</td>
<td>2.64</td>
</tr>
</tbody>
</table>

*Individual areas and sums are not the same due to incomplete reporting of travel destination and travel to multiple places.

Spencer et al., AABB 2015; Plenary
ZIKV disease cases reported to CDC by US state or territory — 2015–2016 (4/10/16)

<table>
<thead>
<tr>
<th>Local</th>
<th>Travel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cont US</td>
<td>0</td>
</tr>
<tr>
<td>Territories</td>
<td>351</td>
</tr>
</tbody>
</table>
Emergency Use Authorization: Trioplex Real-time RT-PCR for DENV, CHIKV and ZIKV multiplex rRT-PCR and ZIKV MAC-ELISA (both CDC assays)
ESTIMATED range of *Aedes aegypti* and *Aedes albopictus* in the US, 2016 Maps

*Maps updated from a variety of sources; they represent CDC's best estimate of the potential range of *Aedes aegypti* and *Aedes albopictus* in the US. Maps are not meant to represent risk for spread of disease.*
This map estimates which US cities face the highest risk from ZIKV

Factors favoring transmission/spread of ZIKV: *Aedes aegypti*, overcrowding, extreme poverty.

“In crowded places, mosquitoes have lots of access to lots of people. Poor people often live in proximity to garbage, including old tires, plastic containers and drainage ditches filled with stagnant water, where this species of mosquito lives and breeds. And they often have homes with torn screens on their windows.”
Potential for local transmission is likely low (as taken from CDPH)

A viremic person would need to return to a region where there are *Aedes* mosquitoes and be bitten by an *Aedes mosquito* that lives long enough to become infectious and bite another person.

*Aedes* takes 10-11 days to become infectious after becoming infected and that the average life span is only 14 days. Thus, many infected mosquitoes will die before being able to transmit.

Mitigating factors: Patchy *Aedes aegypti* and *albopictus* distribution.
Use of air conditioners, window and door screens.
Better water management than in other countries.
Good mosquito control!

If an outbreak were to occur, it would likely be limited in scope and duration.
The few local outbreaks of DENV and CHIKV in the US have been contained.
Therefore, the US will probably not experience the same extensive outbreaks currently being experienced in Latin America.
Comparison of US-reported cases of DENV and CHIKV to the CDC, 2014-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>DENV</th>
<th>CHIKV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Local</td>
<td>Imported</td>
</tr>
<tr>
<td>2014</td>
<td>7 (FL)</td>
<td>654</td>
</tr>
<tr>
<td>2015</td>
<td>1 (FL)</td>
<td>540</td>
</tr>
</tbody>
</table>
ZIKV cases due to blood transfusion have been reported – none in US yet! *(as taken from CDPH)*

Upon detection of local ZIKV transmission in any state local public health agencies would investigate and enhance surveillance and mosquito control in the area

Blood banks would be informed of local transmission so that donors from the area (to be defined) would be deferred from donating blood until blood screening is in place
Key Messages
(as taken from CDPH)

Risk of local transmission of chikungunya, dengue, and Zika viruses in the US is likely low

However, transmission is possible and we must be prepared to aggressively respond once a case without travel history has been reported

Ongoing surveillance and control of Aedes are critical

Individuals with Zika, dengue, or chikungunya should be informed to take precautions to avoid mosquito bites during illness to avoid initiating local transmission

Should there be local transmission, the area of exposure risk would be determined based on human and mosquito surveillance data and geographic boundaries, such as zip code, city, or county would be defined and reported
• Provide state and local senior officials with information and tools needed to improve Zika preparedness and response within their states and jurisdictions.
• Increase knowledge on the latest Zika science, including implications for pregnant women.
• Increase knowledge of best communications practices, including crisis and risk communication principles.
• Accelerate readiness for local Zika transmission through training and technical assistance to states to help establish and support surveillance and share best practices for vector control.
• Identify possible gaps in preparedness and response at the federal, state, and local levels; begin to address possible gaps.
Definition of areas of active vector-borne transmission that would activate blood safety intervention (including FDA guidance) – DRAFT CONCEPT

Two or more laboratory-confirmed infections due to local vector-borne transmission (e.g., no travel history, no common sexual exposure), and epidemiologically unrelated to each other (e.g., not same household) occurring within two weeks in an affected area.

The affected jurisdiction will determine, on the basis of surveillance, population density and vector ecology, an area of likely local transmission and define such area on the basis of a cluster of ZIP codes. This cluster of ZIP codes will be defined as the area of intervention.

The cluster of ZIP codes will be reported by the State to the CDC.
Issues

• Blood safety
  – Screening should be in place prior to appearance of virus => outbreaks – not the current model

• Mosquito control
  – Traditional methods ineffective against *Aedes*
  – Biologic/genetic vector control
    • Infected or engineered mosquitoes to yield sterile offspring

• Vaccine
  – Time for development
  – Antibody-dependent enhancement (ADE); would prior flavivirus vaccination (YFV) or prior primary infection, or ZIKV vaccine exacerbate disease in a secondary infection?
    • Vaccine-induced Guillain-Barré syndrome
ZIKV control requires an urgent and coordinated response