Blood Supply Monitoring

Zika Virus in the Americas: An HHS Expert Consultation to Accelerate the Development of Countermeasures
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North Bethesda, MD

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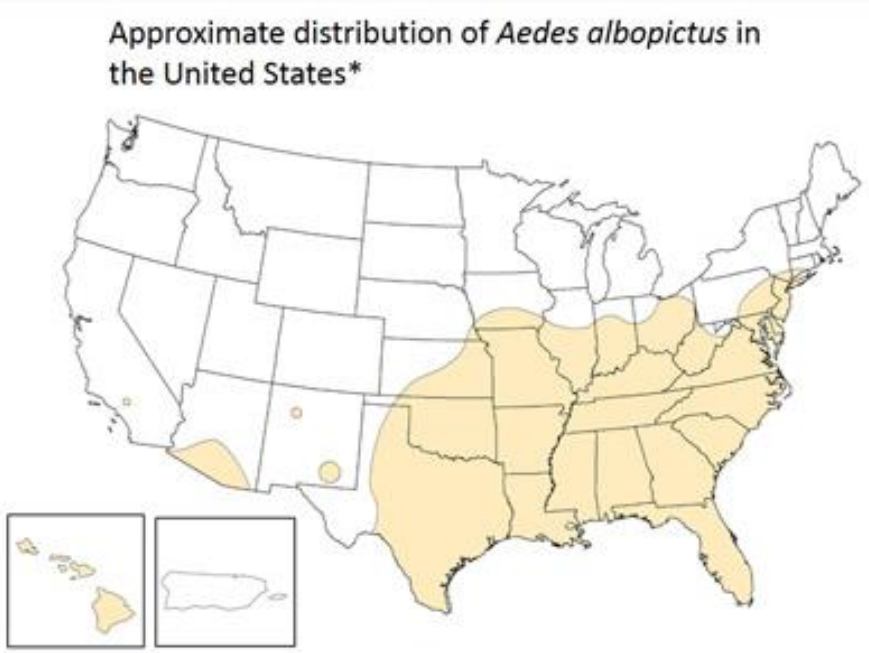
Basis for Blood Safety Concerns

- rapidly expanding Zika virus (ZIKV) epidemic in the Americas
- past experience with arboviruses, particularly West Nile virus
- outbreak on Yap Island (2007)
- outbreak in French Polynesia (2013-2014)
- current outbreak in Brazil
  - evidence for transfusion-transmitted ZIKV in Brazil
- current outbreak in Puerto Rico
- risk of spread to US States

Distribution of *Aedes aegypti* and *Aedes albopictus* in the U.S.



http://www.cdc.gov/chikungunya/resources/vector-control.html

Past Experience with Arboviruses

- transfusion-transmission documented for other flaviviruses (i.e., WNV, DENV and YFV vaccine strain)
  - all produce detectable viremia during asymptomatic and symptomatic infections
- West Nile virus experience
  - epidemic rapidly spread across U.S.
  - caused asymptomatic infections in about 80% cases
  - viremic period can precede symptoms by up to 2 weeks and may last for more than 1 month
  - virus titer in blood lower than other TT viruses
  - **tipping point**: 23 cases of transfusion-transmitted WNV described during 2002 outbreak
    - Pealer et al., N Engl J Med 2003;349:1236-45.
  - 2002 U.S. outbreak identified other modes of transmission
    - transplantation, breast-feeding, transplacental and occupational by percutaneous injury

Zika Outbreak on Yap Island

- 2007 outbreak characterized by rash, conjunctivitis and arthralgia in patients
  - testing by RT-PCR identified ZIKV RNA
- study initiated to define epidemiologic features and clinical manifestations
  - subjects tested by ELISA for IgM Ab, neutralizing Ab by PRNT and RT-PCR for RNA
  - patients in acute phase tested by RT-PCT for ZIKV
  - 185 cases of suspected Zika infection identified
    - 49 cases confirmed and 59 cases considered probable
    - ZIKV RNA detected in 15 (33%) of 45 confirmed patients
  - attack rate of 14.6 per 1000 confirmed/probable patients
- 73% of Yap residents $\geq$ 3 y.o. had been infected with ZIKV

Duffy et al., N Engl J Med 2009;360:2536-43.

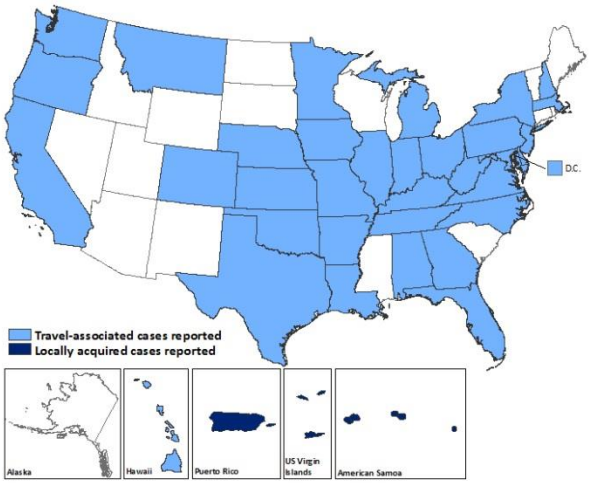
Zika Outbreak in French Polynesia

- outbreak involving ~28,000 cases in 2013-2014
- to prevent transmission of ZIKV by blood transfusion, specific NAT implemented
  - donor samples tested retrospectively and prospectively over 3 mo.
  - tested in minipools ($\leq$ 3) using in-house RT-PCR
    - sensitivity of 25-100 copies/assay (based on RNA extracted from 200 µL of serum)
  - 42 (2.8%) of 1,505 donors tested positive by RT-PCR
  - 11 (26%) of 42 positive donors reported post donation symptoms
  - viral load ranged from 3.40 to 6.91 $\log_{10}$ copies/mL
    - mean of 4.85 $\log_{10}$ copies/mL
  - *demonstration of viral RNA in asymptomatic blood donors suggested substantial transmission risk*

Musso et al., Euro Surveill 2014;19(14):pii=20761.

Current Outbreak in the Americas

- May 2015, first locally-acquired cases of ZIKV in the Americas reported in Brazil
- rapid spread to other countries (n≥33) in the Americas including the Commonwealth of Puerto Rico and the U.S. Virgin Islands
  - 259 locally acquired cases in Puerto Rico; 10 in U.S. Virgin Islands
- U.S. implications to date (March 16, 2016):
  - 258 travel-associated cases in U.S. states
  - 0 locally acquired vector-borne cases in U.S. states



http://www.cdc.gov/zika/index.html

Sexual Transmission of Zika Virus

- to date, all reported cases of sexual transmission have been from symptomatic male partners
- first case involved infection acquired in Senegal (2008)
  - Foy et al., Emerg Inf Dis 2011;17:880-2.
- increasing number of U.S. cases reported to the CDC
  - 14 suspected cases: 6 confirmed/probable, 2 excluded and 6 under investigation
  - Hills et al., MMWR Morb 2016;65:215-6.
- length of viral persistence unknown, but viral RNA has been demonstrated in semen by RT-PCR for up to 62 days after illness onset
  - RNA loads of 1.1×10^7 to 2.0×10^7 copies/mL reported
    - Musso et al., Emerg Inf Dis 2015:359-61.
  - testes represent an “immunologically privileged” site
- *current recommendations: abstain from sex or use condoms to prevent transmission*

Transfusion-Transmitted Zika Virus

- two probable cases of transfusion transmission reported from Campinas, Brazil
  - to date, only in media reports (i.e., no peer reviewed publications)
- donations occurred in March and April 2015
  - donors asymptomatic at the time of donation
  - donors developed symptoms 1 and 3 days post donation
  - one archived donor sample tested; positive for ZIKV RNA
- both recipients were positive for ZIKV RNA

Risk of ZIKV Transmission by Blood Transfusion

- an estimated 80% of ZIKV infections are asymptomatic
- infection may lead to severe clinical outcomes (i.e., microcephaly, GBS)
- pre-symptomatic period varies from 3 to 12 days
- viremia is reported to range from 10^3-10^7 copies/ml
- 2.8% of samples from asymptomatic blood donors in French Polynesia were ZIKV RNA positive
- two possible cases of transfusion-transmission in Brazil
- intrauterine and prenatal transmission have been reported
- sexual transmission has been reported
- an FDA-licensed blood donor screening test does not exist

Potential Interventions

- blood importation from non-endemic areas
  - expensive and logistically difficult to maintain
- donor deferral
  - 28 day deferral currently implemented
- pathogen reduction
  - feasibility demonstrated experimentally
  - to date, only licensed for plasma and apheresis platelets
  - requires treatment of red cell products
- blood screening
  - will require NAT when/if it becomes available
- quarantine/retest (i.e., hold RBCs, test and release)

Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus

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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
February 2016

http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM486360.pdf

- recommendations apply to collection of whole blood and blood components for transfusion, not source plasma
- provides recommendations for both areas *with* and *without* active transmission of ZIKV
- for the purpose of the guidance, an area with "*active transmission of ZIKV*" is an area included on the CDC website listing of countries and U.S. states and territories with local vector-borne transmission of ZIKV: http://www.cdc.gov/zika/geo/index.html
- this is a final guidance for immediate implementation posted on 2/16/16
- follow-up Q/A regarding guidance available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM490435.pdf

Recommendations for Areas *With* and *Without* ZIKV Active Transmission Include

- donor educational materials
- donor history questionnaire
- donor deferral
- blood collection
- post-donation information and product management
- product disposition and labeling
- implementation

Specific Strategies Recommended for Areas with *Active* Transmission of ZIKV

- obtain whole blood and blood components from areas of the U.S. without active transmission of ZIKV to fulfill orders, except that you may,
  - collect and prepare platelets and plasma locally if pathogen reduction technology using an FDA-approved device is implemented, or
  - collect blood components locally and blood donations tested with an FDA-licensed blood donor screening test for ZIKV, when such a test becomes available.
  - collect and prepare RBCs locally with an FDA-approved pathogen reduction device, when such a test becomes available
- *use of an investigational donor screening test under IND or investigational pathogen reduction under IDE may be permitted in situations where approved technologies are unavailable*

Development of ZIKV RNA Reference Reagent for NAT

- two human ZIKV isolates were used to produce viral stocks by infecting susceptible cell cultures and harvesting the supernatant
  - PRVABC59: Puerto Rico, 2015 provided by CDC. GenBank #KU501215
  - FSS13025: Cambodia, 2010 provided by UTMB. GenBank #JN860885
- viral stocks were heat inactivated (HI) and inactivation efficiency demonstrated by lack of growth on cell culture
- RNA concentrations of HI-ZIKV stocks were determined by NAT performed on serial dilutions of the HI-ZIKV stocks in human plasma
- prototype reference reagent was produced by diluting HI-ZIKV in human plasma to simulate clinical samples at a concentration of 10^7 RNA copies/mL.
- in addition to the reference reagent, a prototype panel has been formulated and sent to independent laboratories and test kit manufacturers for further characterization

Actions Taken to Assure Blood Safety in Puerto Rico

Since March 7, 2016 the federal government has provided blood components from unaffected US States to meet all transfusion needs in Puerto Rico, pending local implementation of blood safety measures:

- An expanded indication for use of an approved pathogen reduction technology for platelets was granted by FDA on March 15, 2016
- Efforts are ongoing to expedite the availability of investigational donor screening tests for Zika virus RNA
- Efforts are ongoing to expedite the availability of investigational pathogen reduction technologies for whole blood and/or red blood cells

BARDA and CDC are providing financial and logistical support for rapid development and implementation of these safety measures.

Open Scientific Questions

- ZIKV dynamics not fully understood
- viral ramp-up studied in rhesus macaques (n=3) infected with different doses of ZIKV
  - concentration of ZIKV RNA measured in plasma, urine, CSF, saliva and feces
  - viremia peaked in plasma at $\geq 1 \times 10^6$ copies/mL in 2/3 animals
  - plasma viremia resolved by ~ 10 day post-infection
    - blip in one animal at 16 days
  - viral RNA detected in urine from 2 of 3 animals for slightly longer than blood
  - viral RNA detected in saliva of all animals
- implications for MP vs IDNAT
- minimum infectious dose?

O'Conner and Osorio:
https://zika.labkey.com/project/OConnor/ZIKV-001/begin.view.

Thank You!