How much safety is enough? (and who decides?)

“Arboviruses ‘R’ US”

Louis M. Katz MD
Chief Medical Officer, America’s Blood Centers, Washington DC
Adj. Clinical Professor, Infectious Diseases, Carver College of Medicine, UIHC, Iowa City
How we got where we are:

AIDS from blood by quarter of case report

CDC: AIDS public use data file
“You wonder where the yellow went”

Post-transfusion hepatitis risk: 1969-2005
NIH Clinical Center

Volunteer (unpaid) donors
HBsAg (CIE and RIA)

ALT
Anti-core
HCV EIA 1.0
HCV EIA 3.0
HCV RNA
HBV DNA

% With post-transfusion hepatitis

Year of Introduction of Test


Courtesy Harvey Alter. DTM. NIH.
6 layers of transfusion safety

• Donor education for self-exclusion
• The donor interrogation
• Post-donation information, quarantine, consignee notification & product retrieval processes
• Pharmaceutical cGMPs with cleared Blood Establishment Computer Systems
• In vitro donor testing
• Restrictive transfusion practices

Largely invisible to hospitals
Relative risks in life:

Probability of event/unit transfused

HIV
HCV
HBV

Death: general anesthesia
Death: medical error
Death: hospital infection
Bacteria in platelets

Fever
Fever

TRALI
DTR

TACO (CHF)

Yay us! TT-WNV in US

- Imported 1999 into “virgin” populations
- TTI suspected and recognized in US 2002
- Sx deferral then MP-NAT in <12 mo. (≈June 03)
- 23 transmissions 2002
- 2003 ff. evolution of MP $$\rightarrow$$ ID NAT conversion
- 2004-2014, 13 subsequent transmissions

Lessons learned

- Acute infections, including arboviruses, can be TTIs
- Importation unpredictable and can be overwhelming
- NAT is way faster than serology to implement
- Pooled NAT testing can be “insensitive” (duh!)
Geographic extent of autochthonous ChikV: 10 March 2015: WHO
ChikV in the United States

2006-13
- 28 positive tests/yr
- All travelers

2014
- 2799 total cases
- 46 states
- ~1/2 in NY/NJ & FL
- **11 autochthonous in FL**

2015 (to Jan 12, 2016)
- 679 total cases
- 39 states
- **No local cases**

http://www.cdc.gov/chikungunya/geo/united-states.html
ChikV and the prerequisites* for TTI

• Presence of agent in blood of well, susceptible donors
  o ~20% of infections asymptomatic, and \( \sim 2d. \) \textit{viremia before symptoms}

• Agent infectious by parenteral inoculation
  o Lab accidents & macaque model (Labadie et al. JCI. 2010)

• Survives modern blood processing and storage
  o Limited understanding

• Clinically recognizable morbidity by this route
  o Limited understanding

# ChikV by transfusion model results from 3 studies

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Duration viremia (days)</th>
<th>Before symptoms</th>
<th>After symptoms</th>
<th>Percent without symptoms</th>
<th>Est. viremia prevalence/100,000 donations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Thailand(^1)</td>
<td>5.3%</td>
<td>1.5</td>
<td>8.0</td>
<td>10%</td>
<td>38</td>
</tr>
<tr>
<td>Reunion(^2)</td>
<td>35%</td>
<td>1.5</td>
<td>6.0</td>
<td>15%</td>
<td>132</td>
</tr>
<tr>
<td>No. Italy(^3)</td>
<td>.03%</td>
<td>2.0</td>
<td>6.0</td>
<td>15%</td>
<td>NA</td>
</tr>
</tbody>
</table>

\(^1\)Appassakij, *Transfusion*. 2014.
Est. weekly ChikV transfusion risk

Assumptions: viremia 2d before symptoms, 15% of infections are asymptomatic and 100% transmission from viremic donor

<table>
<thead>
<tr>
<th></th>
<th>Peak population incidence/wk</th>
<th>Peak risk/10^5 donations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palm Beach 1 case</td>
<td>0.0000007</td>
<td>0.03</td>
</tr>
<tr>
<td>Palm Beach 2 cases</td>
<td>0.0000015</td>
<td>0.06</td>
</tr>
<tr>
<td>Palm Beach 5 cases</td>
<td>0.0000037</td>
<td>0.16</td>
</tr>
<tr>
<td>Palm Beach 10 cases</td>
<td>0.0000074</td>
<td>0.32</td>
</tr>
<tr>
<td>Palm Beach 100 cases</td>
<td>0.0000737</td>
<td>3.21</td>
</tr>
</tbody>
</table>

Lyle Petersen, CDC/DVBD, for TTD 09-15-14
So, why don’t we see ChikV TTIs?

- The “needle in the haystack” amid explosive epidemics
- We haven’t really looked
- How do you exclude vector-borne infection?
- “Asymptomatic” donors may not feel well and stay away
- **Something different about mosquito-borne vs. parenteral infection (mosquito “spit”)?**
Dengue (re)emergence

- *Flavivirus* transmitted from *Aedes* mosquitos to humans
- 4 serotypes: DENV-1, 2, 3, 4 (DHF/DSS = severe dengue)
- >2.5 billion at risk: most important human arbovirus
  - 50-100,000,000 symptomatic infections annually
  - 500,000 severe dengue (i.e. DSS and DHF)
- Asymptomatic viremia and TTI well documented

**Countries with autochthonous dengue**

- 1955-59: 2
- 60-69: 8
- 70-79: 13
- 80-89: 37
- 90-99: 52
- 00-07: 65
- 08-15: 128
Dengue in Houston


**Month of Symptom Onset**

- **X** = fatal case;  **+** = positive by PCR;  **#** = history of travel to Mexico

![Dengue vector Distribution in US](image-url)
TT-dengue: seven cases/clusters by yr.

- Hong Kong, 2002: 1 case with PCR and serologic, no sequence confirmation
- Singapore, 2007: 3 cases in cluster of from single donation, confirmed by envelope sequencing
- Puerto Rico, 2007: 1 case confirmed by envelope sequencing
- Puerto Rico, 2011-12: 2 cases from Ag negative, RNA positive donors
- Brazil, 2012: 6 cases from “viremic” donors transmit with minimal disease
- Brazil, 2014: 1 case from regular platelet donor without sequence comparison
- Singapore, 2014: 1 case with sequence identity with donor
Dengue-4 in Brazilian donors: a “sheep in wolf’s clothing”??

0.51% confirmed RNA positive in Rio

39,134 donors consented

42 DENV RNA + units into 35 recipients

16 to 16 susceptible recipients

37.5% (6/16) infected vs. 0.93% of control recipients

0.80% confirmed RNA positive in Recife

Record review finds no significant differences between cases and controls re: morbidity or mortality

Sabino EC et al. JID. 2015. (early online)
Zika: what it is

- Flavivirus closely related to dengue isolated from non-human primates in Uganda, 1949.
- Human illness in Africa, Asia, 1950s-60s, trivial, dengue-like
- Yap Island 2007 and rest is “history on the fly”
- ≈75% attack rate over 4 months, 80% asymptomatic
- French Polynesia 2013-14
- 2.8% of donors with +PCR
- Retrospective spike in Guillain-Barre Syndrome
- Brazil and Americas 2015
- Microcephaly et al association
- Virus in semen, urine, breast milk, saliva,
- 0.47% +PCR donors in Puerto Rico in 2016 (MMWR)
Zika spread: 2007-16

Transfusion-transmitted Zika: Brazil

1. March 2015, the Brazilian Hemovigilance System notified that donor from Sao Paulo was retrospectively ZIKV positive, after reporting symptoms 1 day after donation. Platelets transfused to a liver transplant recipient who remained “well”, but was retrospectively positive for Zika virus RNA.

2. April 2015, transfusion recipient, (died from gunshot wounds after 3 mos. in ICU), lab abnormalities suggesting infection led to trace-back revealing he had received blood from a donor with retention sample positive for ZIKV. Donor reported illness c/w Zika 3 days after donating.
These maps show where the mosquitoes are or have previously been found.

Mapping global environmental suitability for Zika virus.


**Environmental** suitability for Zika virus
Zika and GBS: French Polynesia

- 42 cases
- 0.24/1000 Zika infections
- ≈2X more likely to have Zika IgM than controls

Zika in pregnancy: prelim. report

- 88 pregnant Brazilian women with acute rash, followed through pregnancy (09-2015 to 02-2016) (so far)
- 72 had Zika in blood or urine, 16 without
- Fetal ultrasound in 42 infected moms
  - 12 fetal abnormalities vs. none in 16 uninfected women
    - 2 fetal deaths
    - 5 with growth retardation
    - 7 other CNS lesions
    - 7 with abnormal amniotic fluid volumes or cerebral or umbilical artery flow patterns
  - Abnormal findings following infection in all 3 trimesters
  - Sonographic findings confirmed in all 8 births to date

“...findings point to a link between ZIKV and abnormal fetal and placental development or placental insufficiency in a subgroup of ZIKV positive women”.

Shepard’s criteria for “proof” of human teratogenicity:
- 4/7 met, 1 partial, 1 not met (animal model), and 1 NA

Bradford Hill criteria for evidence of causation:
- 7/9 met, 1 not met (animal model), and 1 NA
Areas without local transmission

- Update educational materials to facilitate self-deferral of symptomatic donors for 4 weeks after recovery.

- **28 day deferral for travel/residence to areas with local Zika transmission per CDC website.** 28 day deferral after recovery for dx or symptoms of Zika arising within 2 weeks of departure from Zika area.

- **Self-deferral for 4 weeks after sex with a male with Zika or who traveled or resided in an area with active Zika in 3 months before the sexual contact**

- Instruct donors with recent travel or residence re: PDI for diagnosis or symptoms of Zika for donors within 2 weeks of donation.
What’s the worst that could happen?
AABB TTD Survey: travel in interval before donation

Percent donor “loss” with alternate deferral approaches*

<table>
<thead>
<tr>
<th></th>
<th>Summer-14d</th>
<th>Summer-28d</th>
<th>Winter-14d</th>
<th>Winter-28d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>0.19%</td>
<td>0.52%</td>
<td>0.40%</td>
<td>0.92%</td>
</tr>
<tr>
<td>Caribbean</td>
<td>0.16</td>
<td>0.48</td>
<td>0.48</td>
<td>1.16</td>
</tr>
<tr>
<td>C. America</td>
<td>0.02</td>
<td>0.06</td>
<td>0.13</td>
<td>0.26</td>
</tr>
<tr>
<td>S. America</td>
<td>0.03</td>
<td>0.07</td>
<td>0.07</td>
<td>0.20</td>
</tr>
<tr>
<td>Total “Americas”</td>
<td>0.39</td>
<td>1.17</td>
<td>0.96</td>
<td>2.23</td>
</tr>
<tr>
<td>Total ex-US &amp; Canada</td>
<td>NA</td>
<td>2.64</td>
<td>1.35</td>
<td>4.02</td>
</tr>
</tbody>
</table>

*Rows 1-4 may not sum to row 5 due to incomplete reporting of travel destination and travel to multiple places.

Spencer B et al. P1-030A. Transfusion. 2015
Travel deferrals?

- Simple
- React with moderation to existing threats
- Proactive against new acute infections in the future
- Impact not “great” away from borders, and can be reduced substantially by staging donor education and deferral implementation over a year or so.
- Katz “votes” yes—“now and forever”
Canadian Monte Carlo model
Risk of viremic donation after travel deferral

- 6.35% of donors travel to Zika zone x 8 wk (95% CI 5.9-6.9%)
- Mean travel 10 days (range 7-14 d.)
- Exposure to viremia 5 days (upper 99th percentile 12 d.)
- Zika symptomatic in 20%, presymptomatic viremia 2 d
- Asymptomatic viremia 5 d (upper 99th percentile 18 d.)
- Risk of infection .0005-.001 dependent on travel duration (using resident attack rates from dengue outbreaks)
- Simulation run 20 times with 10,000,000 iterations

\[ P_{\text{viremic donation}} = \begin{cases} 1:312,500 & \text{no deferral} \\ 1:22,000,000 & @ 14d deferral \\ \leq 1:200,000,000 & @ \geq 21 \text{ day deferral} \end{cases} \]

Areas with local transmission *(still undefined for the purposes of blood collection)*

- Get blood from areas without local transmission unless…
  - PRT (licensed or IND—platelets and plasma only?)
  - Tested with licensed donor screening assay (licensed or IDE)

...If still collecting using PRT or testing

- Donor ed. materials to instruct on signs and sx of Zika and self-deferral for 28 days after well
- 28 day deferral for sex with male with dx/sx of Zika in 3 months before sexual contact
- PDI for dx, signs or sx within 2 weeks after donation
**ARCBS sexual contact model**

**How safe is safe enough?**

- Incidence of Zika in areas visited by donors = 1/319
- Incidence of male donor travel to epidemic region = 1.78%
- Assume 100% of female donors have sex with male
- Assume 10% of sexual contacts result in transmission

**Sexual transmission from “travelling” male to a female partner = 1/179,643**

- Assume 50% of 320,000 donors in six month interval are female
- Assume viremia is 7 days
- Assume 0% effectiveness of travel deferrals

**Risk of viremic donation from sexually infected female donor = 1/9.37 million**

- Assume 100% infectivity of viremic donation
- Assume 80% of infected donors asymptomatic
- Assume 1% of transfusion to obstetrics
- Assume bad fetal outcome in 50%

**Risk of stillbirth or severe developmental abnormality = 1/1,874,000,000**

**Risk if 8.9% visit Brazil for Olympics during 6 month interval = 1/375,000,000**

Tony Keller et al. ARCBS
Donor (not diagnostic) testing

- Antibody (IgM and IgG): maybe useful for diagnosis but appear after viremia and generally will not be useful for donor screening. Also substantial cross reactivity for other flaviviruses.

- Plasma/serum RT-PCR under IND: Roche Molecular Systems on Cobas 6800/8800.

- Plasma/serum TMA: Grifols, Hologic on Panther. IND submission pending.

- ID NAT testing until performance characteristics known

- Urine PCR — NOT!!
The INTERCEPT Blood System for Platelets

Step 1: Amotosalen
Step 2: Illumination
Step 3: CAD
Process Complete
Storage

The INTERCEPT Blood System for Plasma
Mirasol Process for Platelets and Plasma

1. Transfer product to Illumination bag
2. Add Riboflavin
3. Illuminate for 6-10 min.
4. Transfer to Pls storage bag

Ready to store or transfuse!
**Bugs making us nervous**

**log\(_{10}\) reductions in titer**

<table>
<thead>
<tr>
<th></th>
<th>Intercept</th>
<th>Mirasol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WNV</strong></td>
<td>≥6.0</td>
<td>≥5.1</td>
</tr>
<tr>
<td><strong>Denguevirus</strong></td>
<td>≥4.3</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Chikungunya</strong></td>
<td>≥5.7</td>
<td>≥3.7</td>
</tr>
<tr>
<td><strong>Zika virus</strong>*</td>
<td>≥6.0</td>
<td>Pending</td>
</tr>
<tr>
<td><strong>Babesia microti</strong></td>
<td>≥4.9</td>
<td>&gt;5.0</td>
</tr>
<tr>
<td><strong>Staph. Epi.</strong></td>
<td>≥6.1</td>
<td>≥4.2</td>
</tr>
<tr>
<td><strong>E. coli</strong></td>
<td>≥6.3</td>
<td>&gt;4.4</td>
</tr>
</tbody>
</table>

*FFP only.

“We now have the means to protect patients from existing & emerging bloodborne threats—all we need is the will.”

The Safety of the Blood Supply — Time to Raise the Bar

Edward L. Snyder, M.D., Susan L. Stramer, Ph.D., and Richard J. Benjamin, M.D., Ph.D.
PR for platelets: health economic summary

• Dependent on
  – How you model the clinical impact of bacteria (i.e. exposure vs. recognized sepsis vs. QALYs)
  – 7-day dating and outdate rates
  – What can you stop doing??

• Maintain cultures, passive hemovigilance for sepsis $\cong$ $750,000-1,000,000$/QALY

• Active surveillance for bacterial contamination and stopping cultures, 7-days $\cong$ $200,000$/QALY
  – Does not consider emerging TTls
  – Does not consider lost revenue from irradiation and CMV screening

Custer, B. AABB PR Symposium. April 2015
Platelet PR Implementation

• Long use in EU, excellent safety in hemovigilance programs
• Effective approach to bacterial contamination
• Proactive for many known & emerging infections
  – Eliminate some current testing requirements?
  – Avoid testing for new agents?
• Eliminate irradiation or shift charge to offset PR?
• Centers bear costs, will hospitals bear price?
• Cost Recovery: none yet under current system
Now what?

- Declining use of RBCs. Rest flat.
- Adequate supply (sorta)
- Safety/quality/regulatory burden ↑↑↑↑
- Increasing price competition for hospital/system business

Commoditization of blood

No Δ fixed costs=declining margins
Margins at ABC centers 2010-14

Source: ABC Financial Ratio Surveys
47th ACTBSA Nov. 2015

• “Whereas…dramatic reductions in blood use…ongoing since 2008 have created a current crisis of economic instability in blood banking…

• Instability…threatens to exacerbate existing spot blood shortages, reduce resilience in the face of public health emergencies through elimination of surge capacity, and reduce ability to provide the most appropriate routine and specialty products and services

These findings indicate a clear and present need to address the immediate crisis and to manage a longer term paradigm shift to stabilize blood centers in the U.S. and ensure it continues to meet public health needs”
How safe is safe enough, who decides and how? From a zero-risk paradigm to risk-based decision making

Jay E. Menitove,¹ Judie Leach Bennett,² Peter Tomasulo,³ and Louis M. Katz⁴

- Explicit policy foundations
- **Systematic** consideration of relevant information *from a societal perspective*
- Decision support tools provided, expected outputs are explicit
- Iterative as new information is developed

https://allianceofbloodoperators.org/abo-resources/risk-based-decision-making.aspx
ALARA: “as low as reasonably achievable”

- Risk is a continuum
- Risk is tolerable in proportion to the benefit realized and “resources” available for mitigation
- Medical, economic, social & ethical concerns contribute to tolerability
- Structures exist for continuous reevaluation & stakeholder engagement
Risks from classic TTDs

Risk/unit transfused

1:100
1:1000
1:10,000
1:100,000
1:1,000,000

HCV
HBV
HIV

Infuse bacterially contaminated platelet
Septic platelet reaction
Septic death from platelet

Adapted from Busch, Transfusion. 2006.
Jacobs et al. Transfusion. 2011
Lafeuillade et al. Transfusion. 2015

HBsAg HIV Ab HCV Ab HIV p24 Ag HC/HIV NAT WNV NAT T cRuzi Ab HBV NAT

NANB hepatitis surrogate testing (ALT and anti-HBcore)
vCJD Deferrals

Revised Donor Deferral Criteria
