Risks of major TTVs linked to interventions, and accelerating rate of EIDs of concern to blood safety

Perkins HA, Busch MP. Transfusion-Associated Infections: 50 Years of Relentless Challenges and Remarkable Progress. Transfusion, 2010; 50(10):2080-99

Fatalities by Product Type

Evaluating an EID threat to blood safety

3 basic questions need to be answered:
Is it in the blood supply?
- Requires the agent have an asymptomatic or ‘silent’ phase
- Requires a way to measure the agent in donors during epidemics
- Estimation of donor risks: prevalence, incidence, duration of detection
- Estimation of risk by blood component type
- Temperature, preparation, storage duration affects on infectivity?
- Is antibody in the infected donor or co-transfused components protective?

Is it transfusion-transmitted and what is the risk?
- Is transmission risk dependent on stage of infection or VL in the donor/component
- Do recipient antibodies from prior infection protect from TT

If transmissible by transfusion, does it have a clinical impact in transfused recipients?
- Is TT disease more or less severe than usual routes of infection

Reducing the Risk of Transfusion-Transmitted Infections

- Donor history
- Donor (mini-medical) examination
- Testing
- Diversion Pouches
- Leukoreduction
- Post donation information
- Donor deferral registries
- Limit exposures to transfusion – appropriate indications
- Pathogen reduction/inactivation

HIV viremia during early infection

Closing the WP through improved screening tests
**What is the infectious window period?**

![Graph showing viral load levels at different days](image)

**HIV and HCV NAT RNA +/-Ab – “Yield” Donors, ARC 1999-2008**

![Graph showing yield donors](image)

**Transfusion-Transmissible Infections Monitoring System (TTIMS)**

- Monitor HBV, HCV and HIV in US blood donors by developing and maintaining a complete database including data from participating blood centers representing nearly 60% of the US blood supply.
- Develop consensus definitions for concordant positives and NAT yields.
- Daily data exports, QC, data sharing, identification of key units for LRCC.

- Perform relevant data analyses; report results.
  - Prevalence by sex, donation status, age, self-reported race/ethnicity, DHHS reporting region.
  - Incidence and Residual Risk.

**Transfusion-Transmissible Infections Monitoring System (TTIMS)**

- Perform recency testing on HIV plasma samples from donors with HIV concordant positive donations.
- Conduct viral genetic sequence analyses on plasma samples for HIV (NAT yield and seropositive), HCV (NAT yield) and HBV (NAT yield) positive blood donors to determine genotypes and drug resistance (where applicable) of donor infections.
- Lead and support collection and analysis of risk factor data in donors with confirmed infections (cases) and donors who test false positive (controls).
  - Risk factors by sex, age groups, self-reported race/ethnicity, donation status, DHHS reporting regions.
  - Compare risk factor data to those obtained in the REDS-II Viral Marker Prevalence and Donor Risk Factor Study.

**TTIMS: 4 Centers of Donations for 24 Months**

<table>
<thead>
<tr>
<th>Year</th>
<th>ARC</th>
<th>BSI</th>
<th>NYBC</th>
<th>OB</th>
<th>All Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total by Center</td>
<td>9,683,685</td>
<td>1,889,756</td>
<td>748,546</td>
<td>1,608,307</td>
<td>13,930,294</td>
</tr>
<tr>
<td>Percent by Center</td>
<td>69.5%</td>
<td>13.6%</td>
<td>5.4%</td>
<td>11.5%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
A Typical Incidence Assay Dynamic

Optimizing the Performance of Recency Assays

- Sedia Limiting Antigen (LAg) Avidity test
  - Mean Duration of Recent Infection (MDRI) for HIV clade B: ~130 Days (95% CI 118 – 142 days)
  - False Recent Rate (FRR): 1.6%
  - Normalized Optical Density (ODn) using internal calibrators for each run

Duong et al. PLoS One. 2015 Feb 24;10(2)e0114647

HIV Recency Testing of US Blood Donors

Objective
- Classify HIV-positive donors as having recently acquired or longstanding infection
- Convenience sample of available plasma specimens from HIV concordant positive donations (confirmed NAT + serology reactive) from all participating organizations
- Pre-TTIMS Period – existing specimens stored under routine procedures by testing labs/blood centers
- TTIMS Period plasma units retrieved from whole blood donations, aliquoted and placed in repository as part of TTIMS

Analyses
- Overall proportion with recently acquired HIV by year and various demographic and donation groups
- Categorical groups compared for differences in proportions using $\chi^2$ statistics
- $p < 0.05$ considered significant

LAg Testing Results by Year

<table>
<thead>
<tr>
<th>Donation Year</th>
<th>Recent n (%)</th>
<th>Total Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>21 (32.3)</td>
<td>65</td>
</tr>
<tr>
<td>2011</td>
<td>48 (28.4)</td>
<td>169</td>
</tr>
<tr>
<td>2012</td>
<td>42 (28.0)</td>
<td>150</td>
</tr>
<tr>
<td>2013</td>
<td>34 (29.3)</td>
<td>116</td>
</tr>
<tr>
<td>2014</td>
<td>33 (34.7)</td>
<td>95</td>
</tr>
<tr>
<td>2015*</td>
<td>21 (24.1)</td>
<td>87</td>
</tr>
<tr>
<td>2016</td>
<td>34 (25.6)</td>
<td>133</td>
</tr>
<tr>
<td>2017 (through Q2)</td>
<td>13 (29.6)</td>
<td>44</td>
</tr>
</tbody>
</table>

* Includes period before and during TTIMS

No evidence of significant differences by year

LAg Testing Results by Demographics

<table>
<thead>
<tr>
<th>Donor Characteristic</th>
<th>Recent n (%)</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donation History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat</td>
<td>137 (36.4)</td>
<td>376</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>First-time</td>
<td>109 (22.9)</td>
<td>483</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>209 (30.4)</td>
<td>687</td>
<td>0.021</td>
</tr>
<tr>
<td>Female</td>
<td>37 (21.5)</td>
<td>172</td>
<td></td>
</tr>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-19</td>
<td>71 (44.9)</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>119 (35.6)</td>
<td>334</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>30-39</td>
<td>23 (14.5)</td>
<td>145</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>19 (15.2)</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>16 (16.5)</td>
<td>97</td>
<td></td>
</tr>
</tbody>
</table>
**TTIMS HIV Molecular Surveillance**

- HIV, HBV, HCV
  1. For HIV, a fragment of 1275 base pairs (bp) of polymerase including the Protease (PR) and Reverse Transcriptase (RT) genes
  2. For HCV, a fragment of 363 bp in the core gene
  3. For HBV, a fragment of 2015 bp, including the envelope and polymerase genes

- Followed by Next Generation Sequencing (NGS) using MiSeq

- Reporting of HIV genotypes and drug resistance

- To be reported: HCV and HBV genotypes (and neutralization/drug resistance)


**HIV Subtypes in Initial TTIMS Period**

**HIV Drug Resistance Mutations**

- K103N is a nonpolymorphic mutation selected for in patients receiving Nevirapine and Efavirenz

**Flight Traffic Patterns**

On an average day over 8,000,000 people travel by airplane

- [https://www.youtube.com/watch?v=G1L4GUA8arY](https://www.youtube.com/watch?v=G1L4GUA8arY)

**World Distribution and Spread of WNV**

**U.S. WNV Blood Donor Screening Timeline**

All transfusion-transmitted infections (TTIs) traced to WNV RNA(+) / Antibody(-) transfusions, except for 2013 case in which donation had very low VL with IgM and IgG

Lignage 1
- Clade 1a
- Clade 1b
- Clade 1c

Lignage 2

1. TTI reported
2. WNV found in Queens, NY
3. MP NAT adopted
4. ID NAT enhanced
5. ID NAT triggered enhanced
6. ID NAT reported

**Zika virus (ZIKV)**

- **Arbovirus surveillance** (Dick et al. 1952):
  - Isolated from the blood of a sentinel rhesus monkey (placed in the forest in 1947)
  - Isolated from a pool of *Aedes africanus* mosquitoes in *Zika forest, Uganda* (1952)

- **Humans:**
  - Serosurveillance: detection of neutralizing antibodies in human sera collected from East Africa (Smithburn et al. 1952)
  - Isolated from a human in Nigeria in 1954
  - First isolation of the virus itself from ZIKV-infected human (Simpson et al. 1964)
ZIKV is a Flavivirus related to DENV

Classification:
- Flaviviridae family
- Flavivirus genus
- West Nile virus
- Dengue
- Japanese encephalitis
- Yellow fever
- Spondweni virus clade

Structure:
- 50 nm in diameter
- Enveloped: cell membrane derived
- Capsid: icosahedral symmetry
- + single stranded RNA ~11kb

Transmission Cycle of ZIKV

Map estimates which US cities face the highest risk from ZIKV

Distribution of suspected and confirmed ZIKV cases by epidemiological week and sub-region Americas, 2016 – 2017

Why ZIKV Transfusion Transmission Concerns?
- Up to 80% of ZIKV infections asymptomatic/illness is generally mild
- Public health surveillance based on clinical case reporting is insensitive
- ZIKV can result in severe congenital syndromes & Guillain-Barré syndrome
- ZIKV RNA detected in asymptomatic blood donors
- ZIKV transfusion transmission reported – 4 cases (Brazil); 3 donors
- ZIKV may persist in whole blood longer than plasma
  - 1-3 months vs weeks (diagnostic assays)
- Unknown impact of travel/sexual contact
- ZIKV interventions are available
  - 2 investigational screening assays on newly available platforms
  - Licensed pathogen inactivation for plasma/platelets; investigational methods in development (red cells/whole blood)
- FDA classification as a Relevant Transfusion-Transmitted Infection
**Weekly Detection Rate of ZIKV RNA in Blood Donated in Puerto Rico**

This project has been funded in whole or in part with Federal funds from the Biomedical Advanced Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response, Office of the Secretary, Department of Health and Human Services, under Contract #HHSO100201600010C.

This is a summary of the weekly detection rate of ZIKV RNA in blood donated in Puerto Rico.

**4 ZIKV TTIs; all reported via PDI (3-5 days) Brazil**

<table>
<thead>
<tr>
<th>Underlying Condition</th>
<th>Symptoms</th>
<th>Sex</th>
<th>Age</th>
<th>Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver transplant</td>
<td>None</td>
<td>M</td>
<td>55</td>
<td>Platelet pool</td>
</tr>
<tr>
<td>Trauma</td>
<td>Thrombo- cytopenia</td>
<td>M</td>
<td>38</td>
<td>RBCs</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>None</td>
<td>F</td>
<td>54</td>
<td>Apheresis platelets*</td>
</tr>
<tr>
<td>AML/bone marrow transplant</td>
<td>None</td>
<td>F</td>
<td>14</td>
<td>Apheresis platelets* same donation</td>
</tr>
</tbody>
</table>

*Barjas-Castro et al, Sept 15 2016, NIGM; neg pre-tx; genetic linkage
*Motta et al, June 21 2016, Transfusion; genetic linkage

**Zika RNA positive donor enrollment and follow-up activities**

Extended Follow-up
- Characterization of humoral and cellular immunity
- Discriminate recent vs remote infections
- Detect ZIKV reinfections

**54 ZIKV Confirmed Positive US Blood Donations**

Data collected under IND

<table>
<thead>
<tr>
<th>To Nov 4, 2017 No. Screened</th>
<th>No. Reactive</th>
<th>No. Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>13,580,225</td>
<td>469</td>
<td>54</td>
</tr>
<tr>
<td>1:30,000</td>
<td>1:251,500</td>
<td></td>
</tr>
<tr>
<td>PPV: 11.5%</td>
<td>Specificity: 99.997%</td>
<td></td>
</tr>
</tbody>
</table>

Alt NAT pos or equiv/IgM neg 10
Alt NAT pos or equiv/IgM pos 7
Alt NAT neg/IgM pos 37

6 symptomatic travelers
Serum + for 3 days; WB + for 2 months

5 Asymptomatic donors
Plasma - 10 days (range 7–37)
WB - 22 days (range 14–100)
VL higher in whole blood
Longer persistence of ZIKV RNA in whole blood and RBC blood compartments than in plasma and body fluids

1. Testing whole blood extends detection period for diagnosis of clinical cases and monitoring pregnant women and travelers.
2. Impact on donation policy: to extend deferral period or consider NAT testing whole blood.
3. Considerations for testing for solid organ, tissue and semen donations.
4. Is RBC-associated virus infectious?

Chikungunya Virus
Makonde language: “to dry up or be 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*

YFV-17D vaccine complications
*CDC, MMWR 2010;59:34-7*

- Viremia detected 3-7 days post-vaccination
- Associated disease incidence 0.4/100,000 vaccine recipients
- Single TT-cluster
  - 89 military trainees rec’d vaccine 4 days prior to donation
  - Retrieval actions occurred; however, 3 platelets, 2 FFP and 1 pRBCs were transfused to 5 recipients
  - 4 surviving recipients – no complications; 3 developed IgM suggesting TT of vaccine virus

- DENV 1990s S America and the Caribbean
- WNV 1999 endemic now in the continental US
- CHIKV in 2013 S America and the Caribbean
- ZIKV emerged in March 2015 Brazil
- YFV outbreak in Dec 2015 in Angola => DRC
  - Vaccination reserve depleted
    - 20% standard vaccine dose used
    - Dec 2016 expanded to rural areas of Brazil; sylvatic cycle mosquitoes and NHPs; human incidental hosts
  - Concern for adjacent large urban centers with unvaccinated populations

Substantial morbidity and mortality.

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**Perspective**

**The NEW ENGLAND JOURNAL OF MEDICINE**

**Yellow Fever — Once Again on the Radar Scenge in the Americas**

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**Fig. 1.** Chikungunya Virus: The Global Spread of a Mosquito-Borne Disease

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**Fig. 2.** The Pathogenesis of Yellow Fever: A Perspective

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**Fig. 3.** The Development of a Vaccine for Yellow Fever: A Perspective

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**Fig. 4.** The Public Health Impact of Yellow Fever: A Perspective

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**Fig. 5.** The Future of Yellow Fever: A Perspective

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**Fig. 6.** The Economic Impact of Yellow Fever: A Perspective

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**Fig. 7.** The Social Impact of Yellow Fever: A Perspective

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**Fig. 8.** The Epidemiological Impact of Yellow Fever: A Perspective

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**Fig. 9.** The Policy Impact of Yellow Fever: A Perspective

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**Fig. 10.** The Treatment Impact of Yellow Fever: A Perspective

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**Fig. 11.** The Prevention Impact of Yellow Fever: A Perspective

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**Fig. 12.** The Control Impact of Yellow Fever: A Perspective

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**Fig. 13.** The Surveillance Impact of Yellow Fever: A Perspective

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**Fig. 14.** The Education Impact of Yellow Fever: A Perspective

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**Fig. 15.** The Research Impact of Yellow Fever: A Perspective

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**Fig. 16.** The Training Impact of Yellow Fever: A Perspective

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**Fig. 100.** The Training Impact of Yellow Fever: A Perspective
Babesiosis

- Malaria-like illness caused by Babesia spp.
  - Asymptomatic and fatal
  - Non-specific symptoms (malaise, fever, etc.)
  - Hemolytic anemia
  - Onset 1-9 weeks after exposure
- General mortality 5-9%
  - 21% immunocompromised
- At risk: infants, elderly, immunocompromised, asplenic, red cell disorders
- But risk groups not limited to above

Fang and McCullough, 2016, Trans Med Reviews
Herwaldt et al., 2011, TTB in the US, Ann Intern Med
Meldrum et al., 1992, Babesiosis in NY, Clin Infect Dis

June 2012-Sept 2014 tested donations from 4 states (CT, MA, MN, WI) by investigational antibody (AFIA) and DNA (PCR)
- Determined parasite loads (qPCR) and infectivity (parasitemia in hamsters)
- Followed donors for Ab/DNA clearance
- Hemovigilance system used compared rates of TTB: screened vs unscreened blood

Possible Mitigation Strategies for TT-EIDs

- 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

- Serological screening
- Nucleic Acid Amplification Technology (NAT) screening
- Photochemical inactivation of platelets/plasma/RBC

Assessing the risk of transfusion-transmission for newly discovered pathogens

- June 2012-Sept 2014 tested donations from 4 states (CT, MA, MN, WI) by investigational antibody (AFIA) and DNA (PCR)
- Determined parasite loads (qPCR) and infectivity (parasitemia in hamsters)
- Followed donors for Ab/DNA clearance
- Hemovigilance system used compared rates of TTB: screened vs unscreened blood

Are There Consistent Patterns to Potential TT-EIDs?

<table>
<thead>
<tr>
<th>Disease Agent Attribute</th>
<th>Traditional TTID Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral agent</td>
<td></td>
</tr>
<tr>
<td>Chronic, persistent infection</td>
<td></td>
</tr>
<tr>
<td>Detectable in plasma</td>
<td></td>
</tr>
<tr>
<td>Transmitted sexually</td>
<td></td>
</tr>
<tr>
<td>High incidence: transmission in MSM</td>
<td></td>
</tr>
<tr>
<td>High incidence: transmission in IDU</td>
<td></td>
</tr>
<tr>
<td>Vector-borne</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Stramer and Dodd, 2013
Summary

- There is a continuing need to manage (prevent) transfusion-transmitted infections
- Testing has reduced residual risks to remarkably low levels
  - Testing approaches are not available for all of the known threats
- Infections continue to emerge at an alarming rate
- Technology can now identify more microbes than diseases
  - There is hope that threats can be anticipated
- Is there a solution?
  - Continued vigilance and potentially pathogen reduction/inactivation

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- Rebecca Townsend

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