Vector-Borne Diseases and Blood Donation Screening

http://www.aabb.org/resources/bct/eid/Pages/eidpostpub.aspx

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Vector-Borne Diseases: Exploring the Environmental, Ecological and Health Connections
Institute of Medicine Forum on Microbial Threats
Sept 16-17 2014
Implementation of Donation Screening Tests in the US

- HBV NAT
- Dengue Ag/NAT
- Babesia Ab/NAT
- Anti-T. cruzi
- WNV Nucleic Acid Testing, NAT
- HIV & HCV NAT
- HIV Ag
- Anti-HCV
- Anti-HTLV
- ALT
- Anti-HBc
- Anti-CMV
- Anti-HIV
- HBsAg
- Syphilis 1938

Timeframe:
- 1970
- 1975
- 1980
- 1985
- 1990
- 1995
- 2000
- 2005
- 2010
Vector-Borne agents that are, or have the potential to be, transfusion transmitted

<table>
<thead>
<tr>
<th>Arboviruses</th>
<th>Rickettsia</th>
<th>Bacteria</th>
<th>Protozoa</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Dengue*</td>
<td>- Anaplasma phagocytophilum*</td>
<td>- Borrelia burgdorferi*</td>
<td>- Babesia spp.*</td>
</tr>
<tr>
<td></td>
<td>- Chikungunya</td>
<td>- Ehrlichia ewingii*</td>
<td>- Leishmania spp.</td>
</tr>
<tr>
<td></td>
<td>- St Louis Encephalitis*</td>
<td>- Ehrlichia chaffeensis*</td>
<td>- Plasmodium spp.*</td>
</tr>
<tr>
<td></td>
<td>- Colorado Tick Fever</td>
<td>- Orientia tsutsugamushi</td>
<td>- Trypanosoma cruzi</td>
</tr>
<tr>
<td></td>
<td>- Crimean Congo HF*</td>
<td>- Rickettsia prowasekii</td>
<td>- Trypanosoma brucei</td>
</tr>
<tr>
<td></td>
<td>- Eastern Equine Encephalitis*</td>
<td>- Rickettsia rickettsii*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- JEV (including West Nile*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- LaCrosse</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Tick-borne Encephalitis Complex (Powassan)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Western Equine Encephalitis*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BOLDED and UNDERLINED agents are transfusion transmissible

* Notifiable diseases in the US

- Severe fever with thrombocytopenia syndrome
Key questions to assess risk of transfusion transmissibility of an infectious agent

Dodd 2012: Practical Transfusion Medicine

**Transfusion-Transmitted Cases?**

- Yes
- No

**Agent**
- Asymptomatic Blood-Borne Phase
- Survive Component Preparation & Storage
- Cause Disease (Blood Recipients)
  - Severity, Mortality, Treatability
  - Immunosuppression favors Severe Clinical Outcome
- Donor Prevalence
- Public Concern

**Effective Interventions for Elimination or Reduction of TT?**

- Present
- Increasing
- Declining
EUFRAT: risk model scheme

(Donor) population infectivity

Population

Donors

Infected

Donations

Whole blood

Plasma pheresis

Platelet pheresis

Released components

RBC

Plasma recovered

Platelets pooled

Plasma-pheresis

Platelet-pheresis

End products

RBC: 1/1

FFP: 1/1

Platelets: 5/1

FFP: 1/2

Platelets: 1/1

Recipients

STEP 1

Prevalence of infection in (donor) population

STEP 2

Number of infected donations

STEP 3

Number of infected released components

STEP 4

Number of infected end products

STEP 5

Risk of infection in recipients

Testing

DHQ

Blood processes and interventions

Recipients
West Nile virus as a Model of Success

- Emerged and is endemic in the US
  - 16,196 WNND cases (2002-2012)

- Transmitted by a large number of mosquitoes
  - 58 different mosquito species, mostly *Culex* spp.

- Amplified by bird hosts
  - 288 avian species

- > 80% asymptomatic

- Transfusion/transplant transmitted
  - 23 transfusion transmissions (2002)

- Intervention US/Canada = 2003 testing by MP/ID-NAT
  - MP-NAT “surveillance”; ID-NAT “seasonal”; 13 transmissions
  - 3725 RNA confirmed-pos donors (2003-2012)

- Outside of the US = 28-day travel deferrals
Incidence of WNV Neuroinvasive Disease
Annual Incidence per 100,000 by county 1999-2011

Unpredictable and Difficult to Control — The Adolescence of West Nile Virus

Lyle R. Petersen, M.D., M.P.H., and Marc Fischer, M.D., M.P.H.
What happened in the US?

• Unexposed population, human and avian
• US strain virulent to corvids
• Mosquito feeding preference shifts to humans in summer due to the dispersal of breeding birds
• Irrigation patterns, standing water (abandoned swimming pools), tires, etc.
• Movement into Caribbean, Central and S Americas
  – Human disease, however, is infrequent
• Why aren’t there overlapping WNV and dengue – chikungunya epidemics?
  – Nov 11, 2013 first conf’d cases of autochthonous CHIKV in the Americas
  – St Martin, coincident with on-going dengue outbreak
Percent WNV confirmed-positive donors requiring ID-NAT for detection, 2002-2012, ARC

ID-NAT only Identifiable

Percent of Confirmed Cases

Percent of Confirmed Cases

13 breakthrough infections from low-level viral loads not detected by MP-NAT
### Start and end dates of identification of WNV confirmed-positive donors requiring ID-NAT for detection

<table>
<thead>
<tr>
<th>Year</th>
<th>Seronegative</th>
<th>Seroreactive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start</td>
<td>End</td>
</tr>
</tbody>
</table>
Viral load distributions at index for 1477 of 1576 confirmed-positive donors with available samples, 2003-2012, ARC

Viral loads (VL) are given in copies/mL (31 samples with viral loads <100 copies/mL were excluded); those listed by each marker category (ID-NAT required for identification or MP-NAT identifiable and antibody [Ab] negative [N] or positive [P]) are the medians, range for median 50% values and maximum values.
WNV: What did we learn?

• Imported infections unpredictable and may be overwhelming
• Acute infections transmissible by transfusion
• NAT offers rapid route to testing
• Pooled testing may have inadequate sensitivity
• Epidemic continues to be unpredictable
Dengue viruses

- Mosquito-borne flavivirus; 4 closely related “types”
- Most important arbovirus
- Rapidly expanding global footprint; >2.5 billion people (~1/3 world’s population) live in areas of risk; endemic in >100 countries
  - Asia/Latin America – leading cause of hospitalization in children
- Humans are the amplifying host
- No vaccine or specific treatment; vector control is the only effective intervention
- Immunity to a given type is lifelong but cross reactivity between types is short lived and increases risk for severe dengue
- **50-80% asymptomatic**
- **3 clusters of transfusion transmission reported**
  - Hong Kong
  - Singapore
  - Puerto Rico
- Kidney, BM transplant, needle-stick and lab infections
- No FDA-licensed test
- Testing under IND in Puerto Rico; yield comparable to WNV
2007 Puerto Rico Donation Retrospective Study
Stramer et al. Transfusion 2012;52:1657

- 29 of 15,325 TMA (+) 1:529; 12 PCR (+) 10^5-10^9 copies/mL, DENV-1, 2, 3
- 12 infected mosquito cultures, 6 IgM (+)
Maximum Likelihood Sequence Analysis of DENV-2 Env
(1482 nucleotides)

DENV-2 best studied
All are highly conserved, but identical sequences (D/R)

Subclades:

Asian American
Transfusion transmission
10^8 copies/mL DENV-2
pRBC recipient developed DHF 3 days post transfusion

SE Asian

Indian Pacific

South American

Sylvatic

Stramer et al. Transfusion 2012;52:1657
Comparison to estimated prevalence of viremic donations - PR, 1995-2010; Petersen et al. Transfusion 2012 (Aug)

Dashed lines are simultaneous 95th percentile-t confidence bands; light lines depict 100-sample realizations of the 500 used to compute the average prevalence of dengue viremia.

boxed% = RNA (TMA) donor prevalence from all years of testing

2005 0.07%
2007 0.19%
2010 0.31%
2011 0.03%
Dengue Blood Donation Screening under IND in Puerto Rico (2010-2013)

<table>
<thead>
<tr>
<th></th>
<th>No. Donations Tested; N=323,498</th>
<th>No. Reactive; N=386</th>
<th>No. (%) Confirmed Positive; N=173</th>
<th>Rate of Confirmed Positives</th>
<th>No. False Positive; N=213</th>
<th>Rate of False Positives</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS1 Ag 2010-2012</td>
<td>181,232</td>
<td>117</td>
<td>10 (9)</td>
<td>1:18,123</td>
<td>107</td>
<td>1:1,693</td>
</tr>
<tr>
<td>Retrospective TMA 2010-2012</td>
<td>53,449</td>
<td>98</td>
<td>8 (8)</td>
<td>1:6,681</td>
<td>90*</td>
<td>1:594</td>
</tr>
<tr>
<td>Prospective TMA 2012-2013</td>
<td>88,817</td>
<td>171</td>
<td>155 (91)</td>
<td>1:573 (0.17%)</td>
<td>16</td>
<td>1:5,551</td>
</tr>
</tbody>
</table>

* NS1 Ag positive control cross contamination
+ 20 (13%) NS1 Ag positive at index
Procleix Dengue Virus Assay
Preliminary Analytical Sensitivity

*Similar Detection of 4 Dengue Virus Types*

- Two panels (for each type) made from in vitro synthesized transcripts
  - One panel made by Gen-Probe manufacturing group and the other made by R&D; combined results are shown
  - Panel members: 100, 30, 10, 3, 1, and 0 copies/mL tested (90 replicates at each level) tested with 1 reagent kit lot
- Probit analysis to determine 50% and 95% detection levels

<table>
<thead>
<tr>
<th>Dengue Type</th>
<th>50% Detection Probability* (95% Fiducial Limits)</th>
<th>95% Detection Probability* (95% Fiducial Limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DENV 1</td>
<td>5.1 (4.1 - 6.0)</td>
<td>20.5 (16.3 - 27.9)</td>
</tr>
<tr>
<td>DENV 2</td>
<td>5.8 (4.7-6.8)</td>
<td>22.5 (18.0 - 29.9)</td>
</tr>
<tr>
<td>DENV 3</td>
<td>4.8 (3.9 - 5.8)</td>
<td>23.9 (18.7 - 32.9)</td>
</tr>
<tr>
<td>DENV 4</td>
<td>6.5 (5.3 - 7.8)</td>
<td>29.4 (23.3 - 39.9)</td>
</tr>
</tbody>
</table>

*Probit analysis was performed with SAS version 9.2; limits of detection determined using combined data from testing 2 RNA transcript lots for each DENV serotype*
NS1 Ag Screening 2010
Dengue Seroconverter (DENV-1)

Duration (+):
- <12 days RNA by PCR
- <19 days NS1 Ag
- ~36 days RNA by TMA (mid-point)
Dengue Donor Follow-up

- Follow donors to development of symptoms, determine viral and immune dynamics
- 13 symptoms occurred at significantly higher rates in RNA-pos donors (cases) vs false pos (controls)
  - Secondary (n=72) >> Primary (n=6); of those at p ≤ 0.01
    - **Fever**, backache, headache, chills, sore throat, body pain, joint pain
    - **Rash**, backache, chills, fever
- Viral median decline from first detection => 7.5 days
- IgM median appearance => 4 days => 21.5 days to maximum => decline by day 50
Comparisons of DENV viral loads

**DENV-1**
- Primary: $7.0 \times 10^8$
- 2nd: $7.1 \times 10^7$
- $p = 0.0382$

**DENV-4**
- Primary: $1.3 \times 10^{10}$
- 2nd: $7.7 \times 10^7$
- $p = 0.0003$

**DENV-1**
- IgM Neg: $5.3 \times 10^8$
- IgM Pos: $4.5 \times 10^7$
- $p = 0.0325$

**IgM Reactivity**
- Symptomatic: $1.0 \times 10^9$
- Asymptomatic: $4.6 \times 10^7$
- $p = 0.2665$
Why are there only 3 clusters of TT dengue despite high levels of viremia in donors?

- Unknown why the number of TT-dengue cases is so low in the face of massive outbreaks
  - Lack of effective hemovigilance
    - Cannot distinguish mosquito from blood-borne transmission
  - Lack of development of symptoms in recipients due to immunosuppression (active or due to underlying disease) or transfusion of Ab-pos units
- Recipients in an endemic area have antibody
  - Heterologous type => severe dengue
- Different outcomes dependent on the route of transmission: mosquito vs transfusion
Chikungunya at the Door — Déjà Vu All Over Again?

David M. Morens, M.D., and Anthony S. Fauci, M.D.

In 2008, we noted that the global reemergence of dengue fever threatened U.S. residents. An outbreak of locally acquired dengue subsequently occurred in Florida, and the risk of U.S. dengue outbreaks will probably continue indefinitely.

We now face a new threat posed by the unrelated chikungunya virus, which causes a disease clinically similar to dengue in a similar epidemiologic pattern, which is transmitted by the same mosquito vectors, and for which there is no effective treatment or vaccine. In 2014, the Pan American Health Organization had reported more than 355,000 suspected and confirmed cases of chikungunya fever from more than 20 countries or jurisdictions in the Americas, with continuing local transmission and epidemic spread.

In 2014 in the continental Unit-
Figure 2. Viremia and immune response following Chikungunya virus infection.

<table>
<thead>
<tr>
<th>NAT</th>
<th>IgM</th>
<th>IgG (PRNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>+</td>
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<tr>
<td>-</td>
<td>-</td>
<td>+</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Days 1-3</th>
<th>Days 4-8</th>
<th>Days &gt;8</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>-</td>
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<td>+</td>
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<tr>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Chikungunya Virus Response

- 2005-2007 Reunion and islands of the Indian Ocean, >300,000 cases; >40% of population infected with 75% symptomatic
  - Mutation viral env protein associated with increased viremia
  - ECSA strain
- 2006 N Italy 337 cases (spread via Ae. albopictus, ECSA strain imported from India); risk of a viremic donation est’d @ 1.05/100,000 donations

- Interventions:
  - Suspend/stop blood collection in areas with “risk” above a certain threshold (e.g., > that of HBV transfusion risk)
  - Implemented platelet pathogen inactivation
  - CHIKV NAT
  - Donor deferral if lives in or traveled to an epidemic area
- Public concern undoubtedly demanded an intervention

Petersen, Stramer, Powers. Transfusion Med Reviews 2010;24
Distribution of CHIKV symptomatic infections per week
Reunion Island

Overall risk = 132 per 100,000 dtns (1:758)
Peak risk = 1500 per 100,000 dtns (1:67)
Transfusion of platelet components prepared with photochemical pathogen inactivation treatment during a Chikungunya virus epidemic in Ile de La Réunion

Volume 49, June 2009  TRANSFUSION  1083

Patrice Rasonglès, Marie France Angelini-Tibert, Philip Simon, Caroline Currie, Herve Isola, Daniel Kientz, Marc Slaedts, Michele Jacquet, David Sundin, Lily Lin, Laurence Corash, and Jean Pierre Cazenave

• EFS implemented universal PI-treated platelets (INTERCEPT)
• Allowed safety to be assessed in routine clinical practice
• Retrospective obs study using medical records/HV to assess safety
  • 1950 patients transfused: 335 adults, 51 peds, 41 infants
  • 10 AEs classified as ATRs: 2 adult, 6 ped hem/onc, 0 infants
  • Mainly Grade 1 s/s: urticaria, itching, chills, fever, anxiety
  • Rate 1.6% vs background 2.2-5.4%

CONCLUSIONS: INTERCEPT-CPAs were well tolerated in a broad range of patients, including infants. ATR incidence was low and when present ATRs were of mild severity.
Prospective detection of CHIKV in blood donors, Caribbean 2014

Martinique Feb 24-Apr 9
4 RNA pos/2149 screened
10^4 - 2x10^8 copies/mL
10 - 2x10^5 pfu/mL
2 symptomatic (61-66 years old)
2 asymptomatic (41-43 years old)

Gallian et al.,
BLOOD, 5 JUNE 2014 • VOLUME 123, NUMBER 23
Chikungunya virus disease cases reported by state – US, 2014 (as of Sept 9, 2014)
Chikungunya virus disease cases reported to CDC in Puerto Rico, August 19 2014
5371 suspected cases, 1631 lab confirmed of which 19 are associated with recent travel

Municipios con casos confirmados en las semanas 30-33
What should we do?

Our options are:

1. Do nothing and watch, as we did before the emergence of WNV in summer 2002, responding if and when transfusion-transmission risk is demonstrated.
2. Enhance our ability to identify the approximately 80 percent of donors who would be expected to have symptoms, by effectively eliciting call-backs by donors who get sick after a donation, so that we can recall their products. This strategy is in progress through the TTD committee.
3. Understand donor travel and temporal donation patterns following travel, allowing us to model the impacts of a short-term deferral for travel to affected areas. While operationally challenging, this may mitigate many acute tropical virus “sins.” Discussions on this option are underway.
4. Engage our test builders to have “on-the-shelf” nucleic acid assays to detect Chikungunya using available test platforms. These conversations are occurring, but testing companies want to know the return on investment – currently hard to know.
5. **Stop collections**

Endemic area

1. No actions relative to higher risk from mosquitoes/resources applied to vector control
2. Enhanced PDI with quarantine of blood products until donor returns
3. Import blood products from non-endemic areas, if feasible
4. Testing
5. Pathogen Inactivation
Association Bulletin #14-03

Date: June 6, 2014
To: AABB Members
From: Graham Sher, MD, PhD – President
       Miriam A. Markowitz – Chief Executive Officer
Re: Chikungunya Virus

Summary
This bulletin was developed by the AABB Transfusion Transmitted Diseases Committee in response to the ongoing outbreak of chikungunya virus, or CHIKV, in the Caribbean islands to provide:

- Information about the potential for transfusion-transmitted CHIKV.
- Educational postdonation information (PDI) materials for use by blood collection organizations (see attachments 1 and 2).
- Considerations for the collecting facility in response to PDI reports.
Pre-donation:
Risk screening questions: Make the following additional questions in the donor questionnaire at the time of donation.
• In the last 7 days, have you had any of the following symptoms: persistent fever > 39 C and/or headache, muscle pain, pain in joints or bones, or rash?
• In the last 7 days, someone who lives in your home, neighborhood or nearby areas has been diagnosed with dengue or CHIKV?
If there is an affirmative answer to any of these questions, the donor is deferred for 28 days.

Post-donation
Post-donation information (PDI): The blood collection centers will carry out a passive surveillance to identify potential cases of CHIKV and DENV. The donor will be informed that he/she should immediately contact the blood bank if the donor develops fever, weakness, pain in joints and muscles, headache, eye pain, rash, bleeding or bruising. This information should be offered at least three times, i.e., at the time of registration of the donor, during the interview and after the collection. The donor should also be informed that in apheresis donations, he/she may be contacted to verify that he/she has not had symptoms for the last 3 days; if unable to contact the donation may be discarded. Also, the donor will receive a handout with the symptoms of interest described above and the blood bank’s phone number, as part of the post-donation educational material.

If the donor reports any symptoms of interest:
• Discard in-dated components beginning 7 days prior to onset of symptoms
And
• Temporarily defer the donor for a total of 28 days.

Quarantine: Except for plasma and apheresis products, a 72 hour quarantine should be held, to give opportunity of receiving PDI calls.

Increase vigilance for CHIKV and DENV in apheresis and plasma units: if the donor had not contacted the blood bank, the bank will contact the donor to validate the NO disease information. If it is not possible to contact the donor within 72 hrs post-donation, then the discard the components.
Pre-donation:

Ask 2 new questions....last 7 days:
Have you had symptoms/diagnosis of CHIKV/DENV?
Has someone in your neighborhood had symptoms/been diagnosed?
YES => Defer donor 28 days

Post-donation:

Post-donation information (PDI): The blood collection centers will carry out a passive surveillance to identify potential cases of CHIKV and DENV. If a donor develops fever, weakness, pain in joints and muscles, headache, eye pain, rash, bleeding or bruising, he/she should immediately contact the blood bank. The donor will be informed that he/she should receive a handout with the symptoms of interest described above and the blood bank's phone number, as part of the post-donation educational material.

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Blood transfusion during arbovirus outbreaks
French Polynesia: global strategy

Blood product quarantine => rash and fever

Pathogen Inactivation (Intercept)

NAT

Blood safety
## Intercept and Arbovirus Inactivation

<table>
<thead>
<tr>
<th></th>
<th>Platelet (log reduction)</th>
<th>Plasma (log reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WNV</td>
<td>&gt; 6</td>
<td>&gt; 6.8</td>
</tr>
<tr>
<td>CHIKV</td>
<td>&gt; 6.4</td>
<td>≥ 7.6</td>
</tr>
<tr>
<td>DENV</td>
<td>&gt; 5</td>
<td>&gt; 5.7*</td>
</tr>
</tbody>
</table>

*Musso et al., *Transfusion* 54; Aug 2014*
Current dengue, chikungunya and Zika virus outbreaks and circulation in the Pacific as at 7 April 2014

Legend:
- Cases reported are increasing or peaking
- Cases reported are decreasing or viral circulation is ongoing
- Awaiting confirmation of aetiology.

DENV: Dengue virus
CHIK: Chikungunya virus
ZIKV: Zika virus
UNKN: Clinical suspicion of cases of DENV, CHIKV or ZIKV, awaiting confirmation.
Considerations for Safety

• Should more be done?
• If so, what?
  – Surveillance
  – Stop collections
  – Enhanced donor call back (PDI) => Quarantine
  – 14 or 28-day travel deferrals => Questionnaire ongoing (ARC + ABC centers; 100,000 surveys)
  – Routine blood donation testing
  – Pathogen inactivation
• Should actions differ between an endemic and non-endemic area?
**T. cruzi** (small parasite): agent of Chagas disease

- 8 million cases in the Americas

**Chagas Disease**

- Transmission:
  - vectorial
  - congenital
  - organ transplantation
  - blood transfusion
  - ingestion
Transfusion transmission is rare in the US/Canada

<table>
<thead>
<tr>
<th>Case Reported</th>
<th># Recipients Infected Component/Medical Condition (*immunosuppressed)</th>
<th>Donor/Birth Country/Yrs US/Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kessler et al. NYC 2010</td>
<td>2 – platelets (US)</td>
<td>Argentina 40 yrs</td>
</tr>
<tr>
<td>Young et al. Rhode Island 2007</td>
<td>1 – platelets (US); irradiated/LR’d; neuroblastoma*</td>
<td>Bolivia 17 yrs</td>
</tr>
<tr>
<td>Lane et al. Manitoba 2000</td>
<td>1 - 299 platelets/8 RBC units (Canada); prolymphocytic leukemia*</td>
<td>Germany (born) Paraguay (child)</td>
</tr>
<tr>
<td>Leiby et al. Miami 1999</td>
<td>1 – platelets (US); multiple myeloma*</td>
<td>Chile 33 yrs</td>
</tr>
<tr>
<td>Cimo et al. Houston 1993</td>
<td>1 - &gt;500 units (US); colon cancer*</td>
<td>No donor identified</td>
</tr>
<tr>
<td>Grant et al. NYC 1989</td>
<td>1 – platelets (US); Hodgkin’s disease*</td>
<td>Bolivia 16 yrs</td>
</tr>
<tr>
<td>Nickerson et al. Manitoba 1989</td>
<td>1 – platelets (Canada); acute lymphocytic leukemia*</td>
<td>Paraguay 20 yrs</td>
</tr>
<tr>
<td>Geiseler et al Southern CA 1987</td>
<td>1 – blood products (US/endemic travel); acute leukemia*</td>
<td>Likely father (Mexico)</td>
</tr>
</tbody>
</table>
# Combined Lookback Experience

<table>
<thead>
<tr>
<th>Component</th>
<th>No. Recipients Tested</th>
<th>No. ELISA/RIPA Pos (minus other risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARC 48 mos</td>
<td>ABC 22 mos</td>
</tr>
<tr>
<td>RBC</td>
<td>71</td>
<td>81</td>
</tr>
<tr>
<td>Platelets</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Plasma+ Cryo</td>
<td>20</td>
<td>42</td>
</tr>
<tr>
<td>Whole Blood</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Total Conf’d</td>
<td>112</td>
<td>147</td>
</tr>
</tbody>
</table>

* 1 El Salvadoran recipient rec’d random donor platelets from a Brazilian donor; both donor/recipient PCR/HC (-); likely preexisting Ab in recipient
** 2 apheresis platelet recipients (no other risk factors) from 2 difft dtns from an Argentine donor; donor PCR/HC (+)

* Benjamin et al. Transfusion 2012;52 ** Kessler et al. Transfusion 2013;53
## Combined Lookback Experience

<table>
<thead>
<tr>
<th>Component</th>
<th>No. Recipients Tested</th>
<th>No. ELISA/RIPA Pos (minus other risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ARC 48 mos</td>
<td>ABC 22 mos</td>
</tr>
<tr>
<td>RBC</td>
<td>71</td>
<td>81</td>
</tr>
<tr>
<td>Platelets</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Total Conf’d</td>
<td>112</td>
<td>147</td>
</tr>
</tbody>
</table>

< 1% of recipients who received blood from an antibody-positive donor developed infection

Only cases were platelet recipients

* 1 El Salvadoran recipient rec’d random donor platelets from a Brazilian donor; both donor/recipient PCR/HC (-); likely preexisting Ab in recipient
** 2 apheresis platelet recipients (no other risk factors) from 2 difft dtns from an Argentine donor; donor PCR/HC (+)

* Benjamin et al. Transfusion 2012;52 ** Kessler et al. Transfusion 2013;53
Selective Testing

• Assumed most infections are remote, infection rate from remotely infected donors was low, therefore developed selective testing option
• Test donors at first presentation
• Test-negative donors need not be retested
  ▪ Selective testing qualification =>
  ▪ No incident case of infection in 4 years of follow-up of over 4 million donors (and over 6 million pys of observation)
  ▪ Upper 95% CI of 0 confirmed seroconverters = 0.61 per million
3 Algorithms: 7 Years of Screening

  - Ortho ELISA (parasite lysate)
  - All RRs => RIPA (Laboratory-Developed Test; Quest)
- Sept 2011 - July 31 2012; *Selective Testing*
  - Abbott PRISM (recombinant antigens)
  - All RRs => 2\textsuperscript{nd} licensed screen (Ortho ELISA)
  - Only concordant RRs (PRISM + ELISA) => RIPA
- Aug 2012 – Jan 2014; *Selective Testing*
  - Abbott PRISM
  - All RRs => Ortho ELISA + licensed supplemental test
    - Abbott enzyme strip assay (ESA)
Abbott *in vitro* Enzyme Strip Assay (ESA)
An additional, more specific test for human serum/plasma samples found to be RR by a licensed screening test

4 hybrid recombinant proteins from 14 distinct antigenic regions (*identical to those in the PRISM screening test*)

- 2 on-board calibrators
- 1 sample addition control (anti-IgG)
7-Year Results ARC: Jan 29 2007 – Jan 31 2014

- 24,142,185 donations screened
- 5447 RRs = 0.023%
- 678 confirmed = 12% (1:36,000)
- Overall specificity = 99.98%
- Positive predictive value (PPV) 6-20% by algorithm
Babesia Background

- **Babesia microti**
  - Intraerythrocytic parasite
  - Babesiosis: asymptomatic \(\rightarrow\) fatal

- Transfusion-transmitted babesiosis (TTB)
  - 159 well documented cases of *B. microti* TTB between 1979 and 2009 in the US (Herwaldt et al., TTB in the US, Ann Intern Med)
    - 87% in 7 endemic US states
    - 77% occurred between 2000-9
  - 3 additional cases of *B. duncani* (US west coast)
  - 4 random donor platelets; others RBCs; 28 (17.6%) fatalities

- There is no FDA-licensed blood donation screening test
Life Cycle:

1. Tick takes a blood meal (sporozoites introduced into host)
2. sporozoites
3. gamete
4. Tick takes a blood meal (ingests gametes)
5. ookinete enters salivary gland
6. Tick takes a blood meal (sporozoites introduced into host)
7. merozoite
8. trophozoite

Transmitted from human-to-human via blood transfusion

= Infective Stage
= Diagnostic Stage

CDC
http://www.dpd.cdc.gov/dpx
Babesiosis

- Malaria-like illness
- General mortality ~ 5%; higher in TTB (~ 20%)
- Recognized risk groups include: infants, elderly, immunocompromised, asplenic, red cell disorders; however, most cases are not in any risk group (Herwaldt et al).
- Symptom onset 1-9 weeks following tick bite; non-specific & hemolytic anemia

“Maltese cross” formation, a hallmark of babesiosis
The 7 *Babesia microti*-endemic states are:
- Connecticut
- Massachusetts
- Minnesota
- New Jersey
- New York
- Rhode Island
- Wisconsin

Babesia US-endemic states
Current & Potential Interventions
AABB Assn Bulletin #14-05, Babesiosis

- Current donor screening: ask about history of babesiosis
  - Unlikely to be accurate due to poor donor recall
  - Most cases of babesiosis are asymptomatic or mild in healthy individuals (e.g., blood donors)

- Potential screening: questions re. tick exposures/bites
  - Up to 9% of donors regionally report tick bites
  - Infected patients often do not recall tick bites
  - Donors reporting tick bite are
    - Less likely to be infected, because they are....
    - More vigilant and remove ticks promptly

- Potential screening: testing
  - Likely for antibody and DNA
<table>
<thead>
<tr>
<th>AFIA Result</th>
<th>PCR Result</th>
<th>Numbers for Prevalence Calculations</th>
<th>Prevalence (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pos</td>
<td>Neg</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>AZ/OK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactive</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>4,019</td>
<td></td>
</tr>
<tr>
<td>MN/WI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactive</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>4,162</td>
<td></td>
</tr>
<tr>
<td>CT/MA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactive</td>
<td>5</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>5,041</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>13,262</td>
<td></td>
</tr>
</tbody>
</table>

Specificity:

At 1:64, 99.95% (99.82-99.99%)

At 1:128, 99.98% (99.86 – 100.00%)
Number of *Babesia* Reactive Samples by Month (Retro and Pro); n= 370

- **AFIA Neg/PCR Pos**: 8 samples
- **AFIA Pos/PCR Pos (Titer range 128 - ≥1024)**: 63 samples
- **AFIA Pos/PCR Neg (Titer range 64 - ≥1024)**: 299 samples

*13 samples screened PCR neg, but ePCR pos (titer 128 to ≥ 1024)*
Antibody Duration – Window Units

Titer by Weeks Post-Index
(N = 8 donors)
Babesia Parasite Load/mL RBCs; n=64
58% infectious in hamsters
TTB during IND testing
AABB Assn Bulletin #14-05, Babesiosis

• Rhode Island (2009-2014)
  – 0:13,405 tested units
  – 11:351,796 = 1:32,000 untested units
  – 3.7% tested of total collections

• ARC CT, MA (2012-2014)
  – 0:59,848 tested units*
  – 10:200,488 = 1:20,000 untested units*
    * OR 6.3 (95% CI: 0.7-107); p=0.07
  – 23% tested of total collections

• Combined
  – 0:73,253 tested units *
  – 21:552,284 = 1:26,300 untested units *
    * OR 8.4 (95% CI: 0.3-205); p=0.26
Recommendations

1. Hospitals and blood centers in Babesia-endemic areas should consider what interventions are available and may be appropriate to reduce the risk of TTB.

2. Hospitals and/or blood centers interested in testing should contact an IND sponsor.

3. Hospitals and blood centers should fully investigate and report all cases of TTB.
Sustained resurgence of EEEV infections in humans are rare, but EEEV is the most deadly mosquito borne pathogen in North America (35-75% case-fatality rate)
EEEV Cases in Humans in Part of the NE US

Annual number of cases in humans, 1965-2012
Red represents cases in humans occurring during the past 10 years
New Threats: tick-borne bacteria
New Threats: tick-borne bacteria

- *Ehrlichia ewingii*; Regan et al., CID 2013
  - First case of transfusion transmission of an *Ehrlichia* spp.
    - Likely linked to transfusion of *platelets, LR’d and irradiated*
  - Asymptomatic => fatal sepsis
    - 8 yo with ALL – no other risk factors; clusters of organisms (morulae) identified in *granulocytes* on day 11 symptoms; *E. ewingii* identified by PCR and sequenced
    - Donor asymptomatic; reported tick bites in wooded area; IFA titer 1:512
      - *E. chaffeensis* (*monocytes; HME*); never shown to be transfusion transmitted
- *Anaplasma phagocytophilum* (*granulocytes; HGA*); 9 published transfusion transmissions in US; 3 non-LR’d and 6 LR’d RBCs, *platelets (including irradiated)*
New Threats: tick-borne bacteria

- *Borrelia miyamotoi*; distantly related to *B. burgdorferi*; relapsing fever spirochete
  - 46 human clinical disease identified in Russia; 10% with relapsing fever (Platonov et al., EID 2011)
  - 18 Ab pos cases, 3 with clinical disease in NE US; most from a population of confirmed or suspected Lyme disease patients (Krause et al., NEJM 2013)
  - Meningoencephalitis in immunocompromised patient in NE US; *B. miyamotoi* detected by microscopy and PCR in CSF (Gugliotta et al., NEJM 2013)
  - Meningoencephalitis in immunocompromised patient in the Netherlands; *B. miyamotoi* detected by microscopy, culture and PCR in CSF; DNA of patient/ticks in area of recreational parks showed 100% identity (Houris et al., Lancet 2013)
  - 2 cases presenting as HGA but negative for other tick-borne agents; *B. miyamotoi* DNA isolated/sequenced from peripheral blood (Chowdri et al., Annals Int Med 2013)
  - 2 cases in Lyme disease patients in Japan; *B. miyamotoi* DNA isolated from serum (Sato et al., EID 2014)
  - 5% seroprevalence New England (Krause et al., EID 2014)
Vector-borne diseases are an increasingly recognized threat from a wide variety of agents (viruses, protozoa and bacteria)
Interventions are not widely available, have long development times and are costly
Processes for determining when decisions to “do more” are needed