Emerging Infections and the Effect on Testing Strategies

Debra Kessler, RN MS
Content of talk
Reduction of Risk of Transfusion Transmitted Infections

After H. Alter
What is an Emerging Infectious Disease?

- Emerging Infectious Diseases (EIDs)\(^1\) are
  - Incidence in humans has increased in the past two decades or which threatens to increase in the near future.
  - Spread of a new agent, to the recognition of an infection that has been present in the population but has gone undetected, or to the realization that an established disease has an infectious origin.
  - May be the result of the reappearance (or re-emergence) of a known infection after a decline in incidence

- Approximately 70% of recognized EIDs are zoonotic (i.e. transmission from animals to humans)\(^2\)
  - Wildlife an increasingly important reservoirs; mosquitoes are important vectors

---


List and prioritize EIDs lacking a current effective intervention & posing a potential threat to transfusion safety

68 agents identified and Fact Sheets developed

Highest Priority Agents:
- Dengue viruses
- Babesia
- vCJD
- Chikungunya

August 2009
EID Agent Priority Matrix

Range reflects subjectivity/uncertainty geographic variability

high

XMRV

moderate

CWD
B. burgdorferi
Chikungunya virus
SLE virus
HIV variants
Influenza virus subtype H5N1

Public Perception

low

Dengue viruses
B19 virus

very low

HHV-8
HAV

absent

SFV

absent

very low

low

moderate

high

Science/Epidemiology

Theoretical

New York Blood Center
Prioritized (Red) Agents

• What do these agents have in common?
  – Known transfusion transmitted
  – Increasing worldwide frequency (perhaps unknown)
  – Clinically apparent/fatal disease in recipients, may not be properly diagnosed, most without specific treatment
  – All without an effective intervention
Requirements to transmit disease via transfusion

- Asymptomatic blood-borne phase
  - Chronic and/or acute

- Survival of agent in donated blood

- Infectious by IV route

- Susceptible population (recipients)

- Recognized disease in recipients

- Level of concern dependent on
  - Severity, incidence and/or prevalence, rate of emergence
Emerging Infectious Diseases Worldwide

Babesia
Babesiosis – a tick borne disease

• Infection with Babesia microti is often subclinical or can cause benign flu like illness

• It can be fatal in:
  – infants
  – elderly
  – immunocompromised
  – asplenic

• Symptomatic infections are characterized by irregular fevers, chills, headaches, general lethargy, pain and malaise

• In severe cases, hemolytic anemia, jaundice, shortness of breath, and hemoglobinuria occur

• In the U.S. there have been ~136 transfusion transmission cases associated with Babesia

• The rate of new reports is increasing
Babesia in the U.S.

7 states in the US carry the greatest risk for TTB (B. microti)
New York State Experience 2004-2009 Babesiosis Cases
Suffolk & Dutchess Counties vs Entire State

(Linden et.al AABB 2010)
Current Mitigation Strategies

- U.S. donor screening questionnaire asks if there is a history of babesiosis

- Geographic exclusion
  - Southern NE, eastern Long Island, and upper Midwest are endemic areas with no definitive boundaries
  - Many of the endemic areas are heavily populated. Visitors have been implicated in published cases.
Other possibilities?

- Ask about tick exposure? – infected patients often do not recall a tick bite

- Pathogen reduction – not licensed in U.S. for red blood cell components

- Serologic or Nucleic Acid Testing (NAT) screening
  - No currently licensed test for donor screening, but testing starting under IND
Zika Virus
Zika: what it is

- Flavivirus Related to dengue, WNV, JEV
- Human illness Africa, 1960s, trivial, dengue-like
- Yap Island 2007 and rest is “history on the fly”
  - \( \approx 75\% \) attack rate
  - 80% of infections without symptoms
- Guillain-Barre in French Polynesia 2013-14
- Microcephaly et al association, Americas 2015
- 2 likely transfusion transmissions in Brazil
- Semen, urine, breast milk, saliva...
Zika spread: 2007-16

Basarab M et al. BMJ. 2016
Zika vector Distribution in the US

Aedes aegypti

Aedes albopictus
For areas without local transmission

- Added donor screening question about travel to areas with Zika transmission per CDC website - 28 day deferral

- Posted self deferral information for donors:
  - 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 diagnosed with 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
FDA Guidance

For areas with local transmission

Get blood from areas without local transmission unless...

- PRT (licensed or IND—platelets and plasma only)
- Tested with licensed donor screening assay (NAT IND)

...If still collecting using PRT or test

- 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 or sx of Zika in 3 months before sexual contact
- PDI for dx, signs or sx within 2 weeks after donation
FDA Guidance

PDI and product management

• Products from donors who should have been deferred or with dx, signs or sx within 2 weeks:
  • Quarantine and destroy undistributed products
  • Notify transfusion service to quarantine and destroy distributed, untransfused products
  • Notify physician for transfused products to monitor patient for Zika infection
Chikungunya Virus

• RNA virus in *Alphavirus* genus
• Three genotypes: Asian, West African, East Central South African (ECSA)
• Transmitted by mosquitoes of *Aedes* genus Primarily *aegypti* (vector of Dengue)
• Reservoirs are infected humans
• Infection causes Chikungunya fever
Chikungunya Fever

- Mosquito-borne viral disease characterized by acute onset of fever and severe polyarthralgia
- Name “chikungunya” means “that which bends” describing the stooped appearance of persons suffering characteristic painful arthralgia
- Historically self limiting illness
- Often occurs in large outbreaks with high attack rates
Chikungunya Facts

• Chikungunya virus is spread by mosquitoes that bite during daytime.
• Symptoms appear, on average, within 3 to 7 days after exposure.
• Acute-onset fever and joint pain are hallmark symptoms of the infection.
• Recovery typically takes 7 to 10 days.
• Joint pain may persist long term for some patients.
• Newborns, older adults, and those with underlying conditions are at risk of more severe symptoms.
• Supportive care and pain control are the usual treatments.

• Kuehn – Chikungunya found in the U.S.  JAMA published online 8/13/14
Chikungunya History

• Virus first isolated from mosquitoes and humans during Tanzania epidemic in 1952
• Outbreaks are unpredictable and the virus seems to “re-emerge” in endemic areas every 7-8 years
• La Réunion Island outbreak (ECSA-East Central South African)
• 2005 – 2006 outbreak centered in the southwest Indian Ocean featured several new factors:
  – Increased mortality
  – Genetic shift of virus
  – Enhanced vector competence of *A. albopictus*
  – Island population 770,000
  – 1 Mar 05 – 30 Apr 06: 255,000 cases reported
  – 85% of infections were symptomatic

Shift to the Caribbean

- In late 2013, the first local transmission of CHIKV in the Americas was reported in St. Martin
- The vector has been identified as *A. aegypti*
- However, CDC indicates a risk for introduction of the disease into the continental EU and the US due to presence of *A. albopictus*
Chikungunya cases = about 400,000
As of late July 2014
Current situation

• The Caribbean strain is related to strains recently identified in Indonesia, China and the Philippines Asian genotype, not the strain from the Reunion Island outbreak (ECSA – East Central South African genotype)

• However, this episode represents the first evidence for the emergence of autochthonous chikungunya cases in the Americas. It is likely that the chikungunya epidemic will extend to other Caribbean islands, and it also has substantial potential for spreading from this region visited yearly by millions of tourists to the American mainland where *A aegypti* is endemic.

US risk?

• Imported (travel-related) cases
  – From 2006-13 on average 28 people per year in the US were reported with positive tests for recent CHIKV infection; most all cases were tracked to Asia.
  – 2014 484 cases reported as of mid July

• Autochthonous cases
  – Much likely lower risk than Caribbean due to far less time spent outdoors, air conditioning and window/door screens
  – 4 in Florida so far
  – 203 cases in Puerto Rico and the US Virgin Islands
Chikungunya vectors

- Humans, birds, chimps, some domestic animals, reptiles infected, but human-mosquito-human infection occurs without intermediate amplifying host.

- *A. aegypti* present in most of tropical world: extremely efficient urban vector: prefers humans, bites several persons during interrupted blood meals.

- *A. albopictus*: alternate vector to *A. aegypti* incl. ≈1/3 of continental US
  - A mutation (“ECSA”, A226V) allows increased viral loads in *A. albopictus*: believed to be responsible for the severity and extent of the 2005-2007 outbreaks in the Indian ocean, W India, SE Asia and N Italy.
Mosquito penetrance in US
There are no alleged transfusion transmissions

- Asymptomatic infection
  - ChikV: ≈20% (3-38%)
  - Dengue: ≈50%
  - WNV: ≈80%

- Parenteral inoculation of macaques transmits

- Vertical transmission in humans

- 19 days “window” risk from last exposure
Is CHIKV a threat to blood safety?

• If answer is “yes” or “likely” should we intervene
  – As donors return from epidemic areas?
    • Enhanced PDI (done)
    • Temporary self-deferral (coming?)
    • Temporary deferral (impact on supply)
  – For autochthonous spread in US?
    • Quarantine collections, re-interview donors
    • Limit collections (ability to support patients)
    • Testing (NAT)
    • Vaccine?
• Travel Survey
Chagas Disease
Chagas Disease

• Both acute and chronic stages exist
  – Acute stage: Immediate reaction to infection
    • Only occurs in about 1% of people infected
    • Swelling of the eye, tiredness, fever, rash, loss of appetite
    • Can be fatal for infants and very young children
    • Severe in immunocompromised recipients (HIV/AIDS, transplants)
  – Chronic: 10 to 20 years after infection
    • 20-30% cardiomyopathy (arrhythmias, congestive heart failure, cardiac arrest)
    • 9-14% megaesophagus, megacolon
    • 40-50% parasitemia with no symptomatic disease
Where is Chagas Disease Found?

- Primarily found in Latin America
  - Increased infections are being detected in the United States
Reported cases of TT *T. cruzi* in the U.S. and Canada

- 1987  California via Mexican donor
- 1989  New York City via Bolivian donor
- 1989  Manitoba via Paraguayan donor
- 1993  Houston via unknown donor
- 1999  Miami via Chilean donor
- 2000  Manitoba via German/Paraguayan donor
- 2002  Rhode Island via Bolivian donor
- 2009  2 in New York via same Argentinian donor
Testing Models

• Test one-time-only per donor where only new donors are tested; repeat donors questioned re risk and only “yes” responses are tested
  – Assumes donor understands the questions, questions may be culturally sensitive, assumes no autochthonous risk
  – Must be validated; each positive requires knowledge of risk and when it occurred
  – Logistically complex relative to sample tracking and component management
  – Financial benefit has not been validated
  – Confusing message to test kit developers
Testing for Chagas

• In 2006 after FDA licensure of a test to screen blood for Chagas, many centers implemented universal testing (cost $6.50 per test)

• Based upon the expectation that the individual come to the U.S. with the infection and would not likely be infected here AND the extremely low rate of transmission, centers proposed and FDA supported a change to one time only testing (cost went up to $12.50 per test)
What Happened with Chagas’ Testing?

• The test manufacturers are not happy with the introduction of selective testing adopted by the community and allowed by FDA; the manufacturer expected universal testing

• The cost of a Chagas Testing went from $6.50 to $12.50 when centers switched from universal to selective testing

• Manufacturers in general are concerned about the “Chagas’ effect”. Will this model be applied to other tests?

• The worrisome question: will the manufacturers avoid developing new tests because of fears about ROI? Is this the new paradigm?

• Is this an opportunity for small companies to develop tests as a niche market?
World Wide Donor Screening Market - 2007

Donor Screening

~ $1.4B or 4%

WW IVD

~ $32B

~ $34B

2007

McDonough, BPAC 2008
World Wide IVD Market Growth

2007

~ $32B

$.700B

$.675B

~ $34B

DS 4%

2013

$42B

$17B

$.850B

$42B

~ $60B

DS 3%

Other DS Sero DS NAT

Other DS Serology DS NAT New
Market Attractiveness of Donor Screening

• Low growth

• Potential future elimination of:
  – HBsAg
  – Anti HBc
  – Syphilis

• Selective screening strategies

• Introduction of pathogen inactivation
Summary

• Blood collection/transfusion is a mature industry
  – 17 million WB collections
  – ~2 million apheresis platelets collected
  – Little if any prospect for further growth
  – Unknown impact of blood management, biovigilance, etc.
    • Utilization and blood management consultants promising reduction in costs
    • Practice Guidelines in US, Canada, UK

• Manufacturers
  – Less than 1% of revenue of test manufacturers comes from blood screening
  – Profit margins for blood screening are way below those of pharmaceuticals
Challenges

• Infectious agents will continue to emerge
• Target: zero risk or evidenced based?
  – Public expectation
• Lack of interest/participation from the manufacturers due to small market margins
• Regulatory demands high/cycle times long
  – Where will funding come from as threats emerge or current technology becomes antiquated?
New pathogens will continue to emerge
Thank You

dkessler@nybloodcenter.org