



**American
Red Cross**

EIDs: Emerging and Submerging Infections

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International Haemovigilance Seminar,
Montreal
April 27th, 2012

Outline

- EIDs and blood safety
- Risk assessment
- Recognition of transmissibility by transfusion
- Examples
- EIDs and hemovigilance
- Summary and conclusions

Emerging Infectious Diseases

“...those whose incidence in humans has increased within the past two decades or threatens to increase in the near future. Emergence may be due to the 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. Emergence may also be used to describe the reappearance (or reemergence) of a known infection after a decline in incidence.”

(IOM)



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Why do infections emerge?

- **New agent**
 - vCJD
- **Species jump, possibly with mutation**
 - HIV, SARS
- **Environmental change (eg global warming)**
 - Dengue, malaria, babesia
- **Failure of control – resistance and mutations**
 - HBV mutants, malaria, drug resistance
- **Population movements – migration, travel**
 - T. cruzi, chikungunya
- **Transport of agents, reservoirs, vectors**
 - WNV, monkeypox
- **Behavioral change among humans, including conflict**
 - HIV, leishmania
- **Agriculture, urbanization**
- **In most cases (including those mentioned) there are multiple factors**

Emerging infections

- Numerous emerging infections
- All classes of agent
- 60-70% are zoonoses
- Most, if not all transmission routes
- Acute and chronic
- Many derive from human activities
- Transportation has a critical role
- Emergence is unpredictable
- Essentially no features are common to all



Requirements for transfusion-transmitted disease

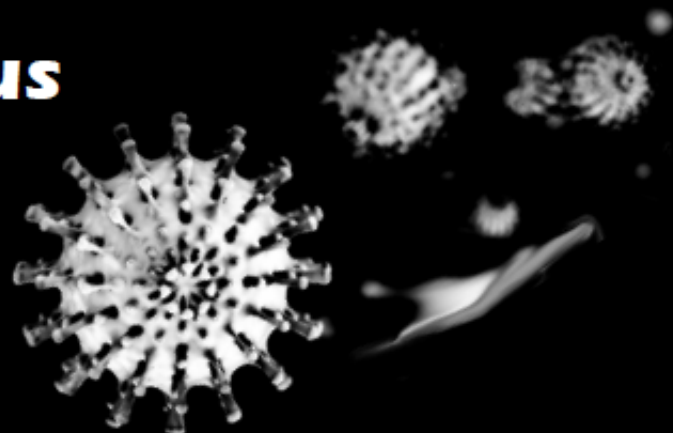
- Asymptomatic blood-borne phase
 - Chronic and/or acute
 - Survival of agent in donated blood
 - Infectious by IV route
 - Susceptibility of recipients
 - Recognized disease in recipients
 - Level of concern dependent on
 - Severity, incidence and/or prevalence, rate of emergence
-

Risk assessment

How NOT to do it:

New HIV-like Virus in the Blood Supply

Up to 20 Million Could Be Infected



FDA and NIH research recently uncovered a new family of retroviruses in 7% of healthy blood donor samples.* This could mean that 20 million Americans are already infected. These viruses were also detected in an astonishing 87% of Chronic Fatigue Syndrome patient samples.

Similar to HIV, this infection is likely to be transmitted through blood.**

Chronic Fatigue Syndrome, also known as Myalgic Encephalomyelitis or ME/CFS, is a serious and sometimes fatal neuroimmune disease that can be as disabling as chemotherapy or late-stage AIDS. ME/CFS afflicts more than 1 million Americans.

Will you or your child be next?

Stop the Suffering
We Need More ME/CFS Research Now

R.E.S.C.I.N.D.



ME/CFS
Worldwide Patient Alliance
mcwpa.org



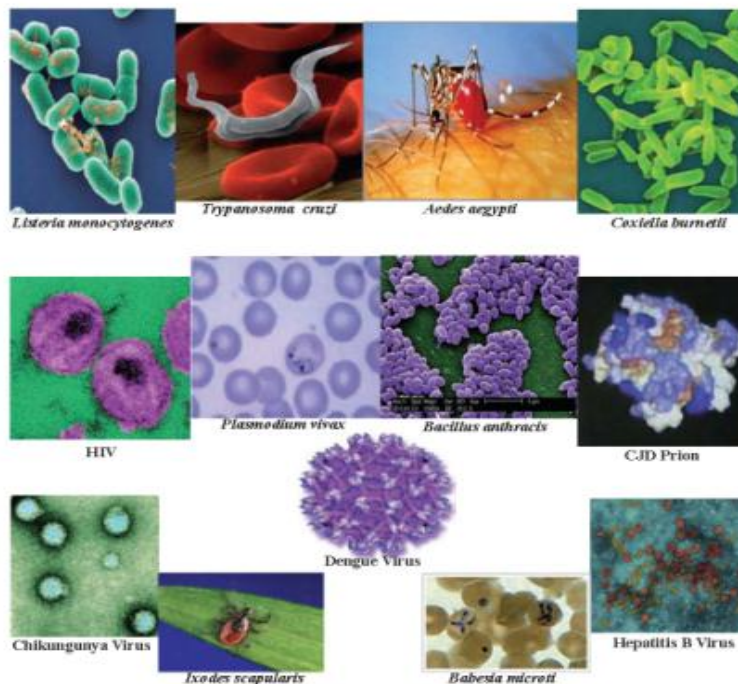
* Detection of MLV-related virus gene sequences in blood of patients with chronic fatigue syndrome and healthy blood donors. Proc. Natl. Acad. Sci., 2010

** "... It would be foolish to think it is not transmitted by blood." Dr. Jerry Holmberg, Department of Health and Human Services, Senior Advisor for Blood Policy, May 2010

Risk Assessment

- Surveillance
 - Horizon scanning
- Evaluate agent properties for TTI potential
- Evaluate epidemiologic characteristics
 - Size, dynamics of threat
- If possible, review incidence, prevalence among donors
 - Does precautionary principle dominate?
- Evaluate interventions
- Implement, review and reevaluate

TRANSFUSION



http://www.aabb.org/Content/About_Blood/Emerging_Infectious_Disease_Agents/appendix2.htm

Emerging Infectious Disease Agents and their Potential Threat to Transfusion Safety



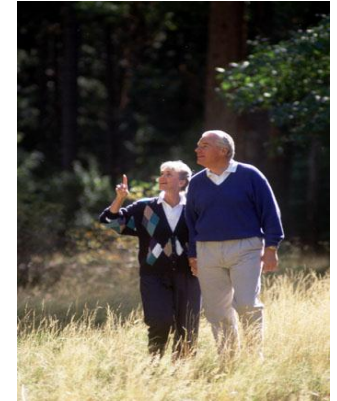
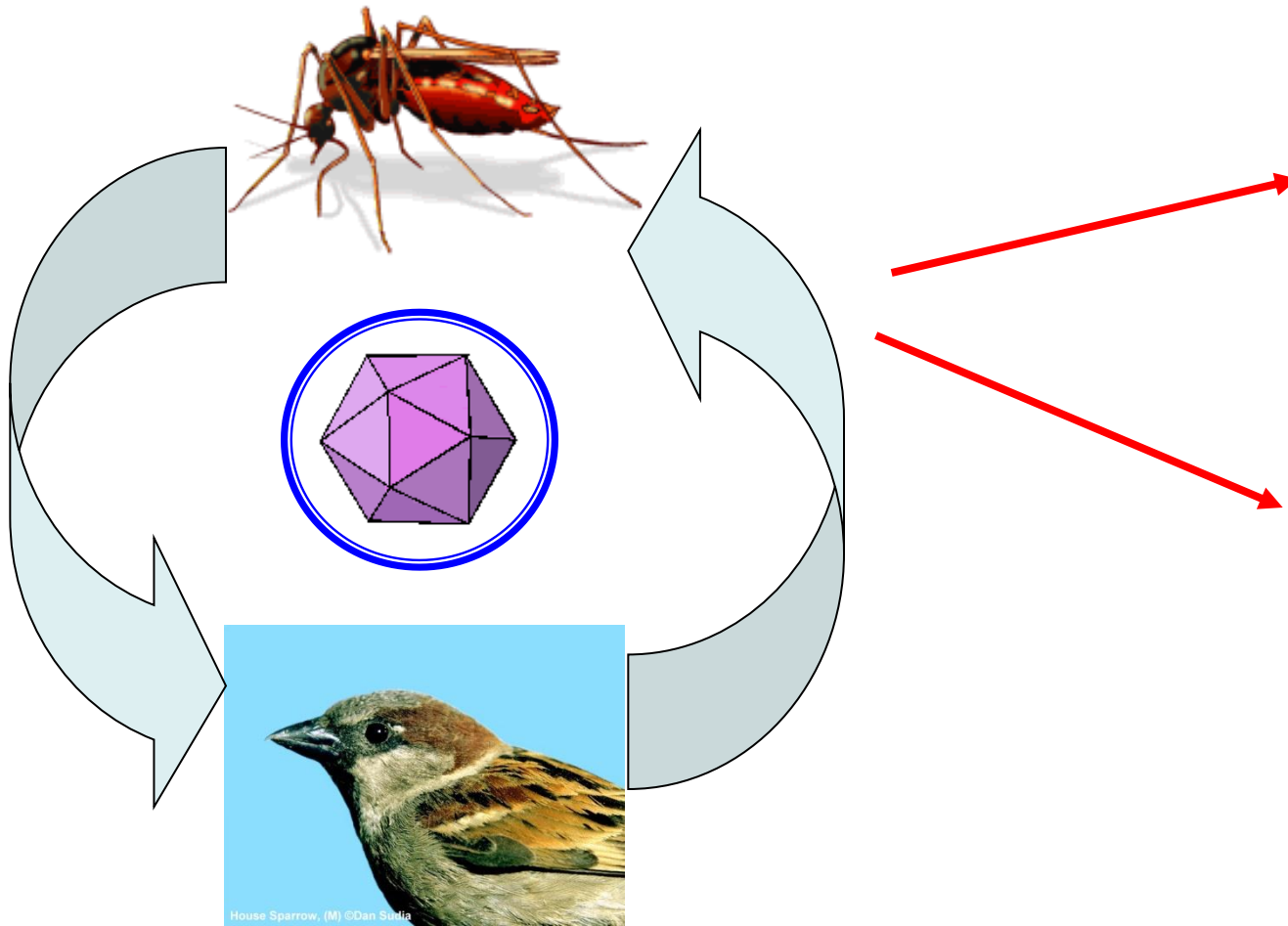
EID Agent Prioritization

- **RED** = low to high scientific/epidemiologic evidence of blood safety risk combined with heightened public or regulatory concern
- **ORANGE** = sufficient scientific/epidemiologic evidence of blood safety risk such that agent may become a future concern
- **YELLOW** = absent to low scientific/epidemiologic evidence of blood safety risk but with public or regulatory concern

EID Agent Prioritization

- **RED** =
 - Dengue virus, *Babesia*, vCJD
- **ORANGE** =
 - *Plasmodium spp.*, *Trypanosoma cruzi*, *Leishmania*, St. Louis encephalitis virus, Chikungunya virus
- **YELLOW** =
 - CWD prion, HHV-8, HIV variants, *Borrelia* (Lyme), Avian influenza virus (H5N1), Simian foamy virus, Parvovirus B19, HAV

West Nile Virus: Basic Transmission Cycle



West Nile fever

- Agent: Flavivirus (RNA), transmitted by culicine mosquitoes
 - S Europe, Africa, Middle East to India, arrived US 1999, endemic in essentially all of the continental US by 2004
 - EID status: Explosive imported outbreak in Americas, but stable elsewhere
 - Up to 400,000 individuals infected in 2002, 2003 in US
 - Species issues: Infects many vertebrates, birds as amplifying hosts, not naturally transmitted between humans
 - Risk status: TTI occurs as a result of high incidence of acute viremia, controlled via NAT in US
-

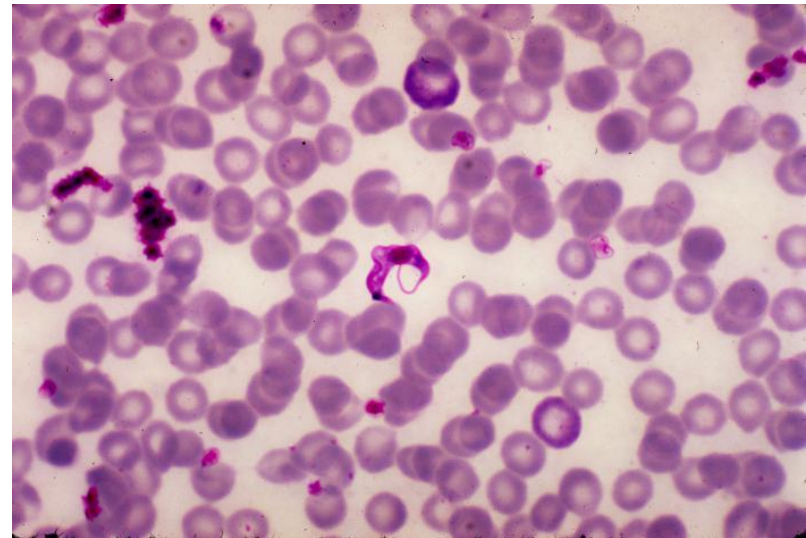
WNV

- 23 cases of TTI reported in 2002
- NAT implemented in 2003
- 11 subsequent cases
 - Donors not detected by pooled NAT
- IDT implemented in areas/times of high incidence

Summary

- WNV first appeared in the US in 1999
 - Spread rapidly across the Americas
 - Major human impact, including transfusion transmission in the US, Canada
 - MP NAT introduced in 2003 (IND mechanism)
 - Universal support for implementation
 - Triggered ID NAT subsequently introduced
 - 99% of results confirmed at index by secondary NAT and/or IgM
 - Test-reactive donors may return after 120 days and a negative NAT
-

Chagas' disease



Chagas Disease

- Agent: Protozoan parasite, *Trypanosoma cruzi*, transmitted by hematophagous insects (reduvid bugs)
- EID status: Substantial vector control in endemic countries, emerging in US, W. Europe through population movement
- Species issues: Widespread among numerous mammalian species; housing location and construction permit interaction of hosts, vectors and humans
- Risk status: TTI, transplant as major risk in non-endemic areas; control by history, testing

Chagas' disease in non-endemic areas

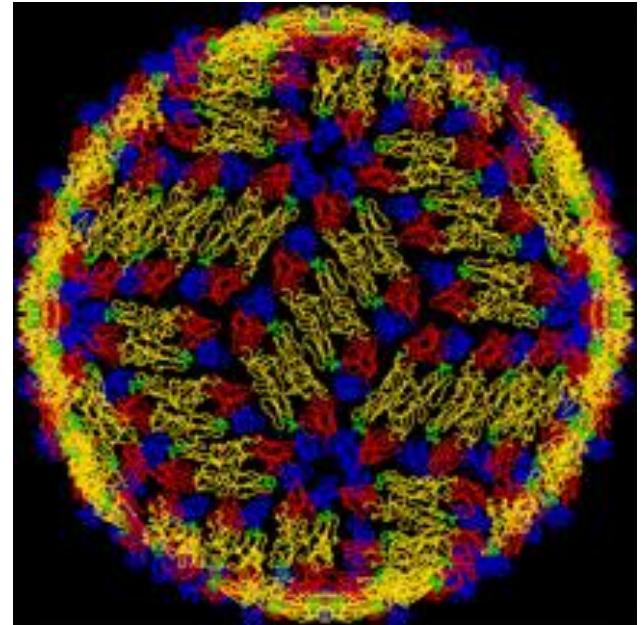
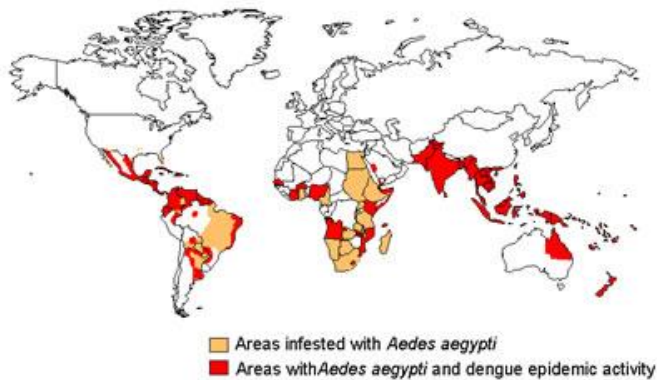
- Imported disease
- Unknown frequency in population
 - 1:30,000 seroprevalence among US donors
- Rare autochthonous cases
- 7 North American transfusion cases (2 in Canada)
- At least 4 transfusion cases in Spain
- 3 transplant clusters in US
- Test licensed in US, December, 2006
- US testing since Jan 29, 2007
- Selective testing in Europe, etc.

Current Situation

- A selective testing strategy based on qualifying a donor by a single negative donation has high sensitivity and has significantly reduced the amount of testing required without compromising recipient safety
- Questions remain re the risk of US-derived cases and alternate strategies based on platelet recipients
- Could pathogen reduction eliminate the need for testing?

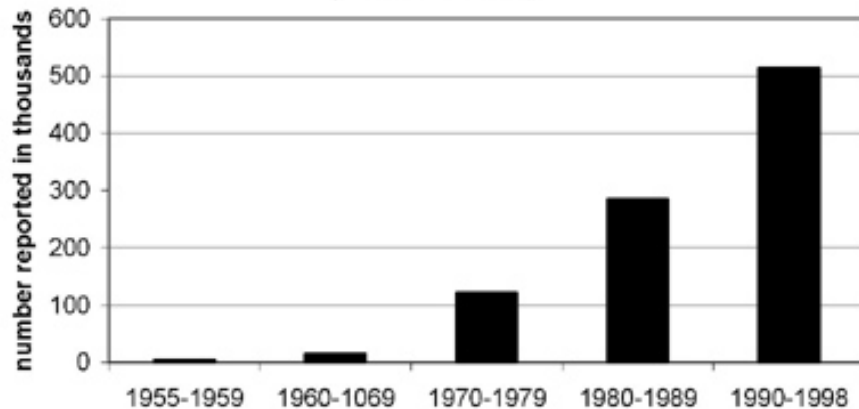
Dengue

World Distribution of Dengue - 2005



REPORTED CASES OF DHF

(global level, 1955–1998)



Source: World Health Organization (WHO)



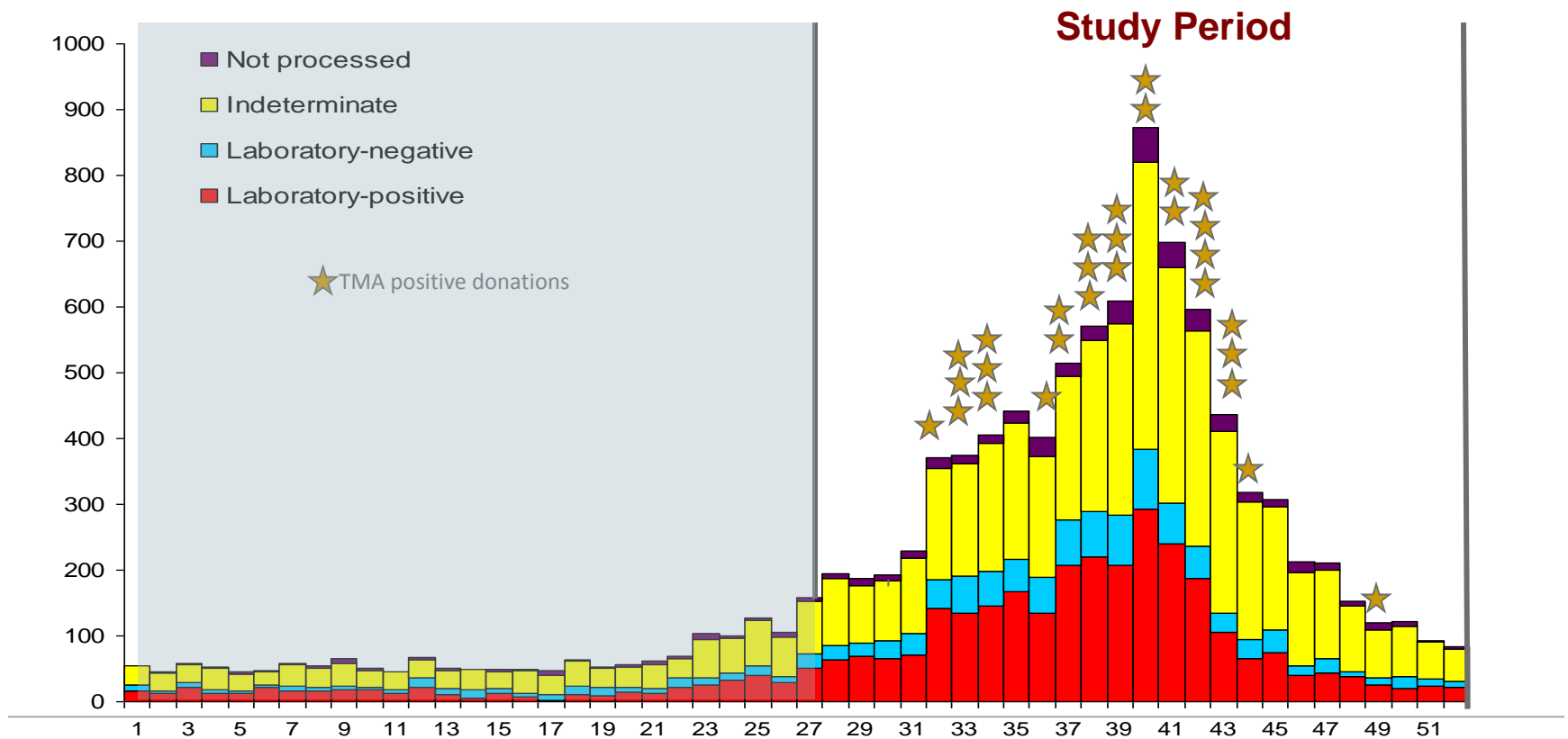
Dengue

- Flavivirus, enveloped
- 4 viruses, limited (short-term) cross-protection
- Dengue fever, dengue hemorrhagic fever
- Transmitted by Aedes mosquitoes
- Known to cause very large epidemics: 50×10^6 cases p.a.
 - (Almost 800,000 cases in Brazil in 2002)
- In many ways, similar to WNV
- Known viremia
- Three documented transfusion transmission clusters (Hong Kong, Singapore, Puerto Rico)
- One possible BMT transmission
- Needlestick transmissions known



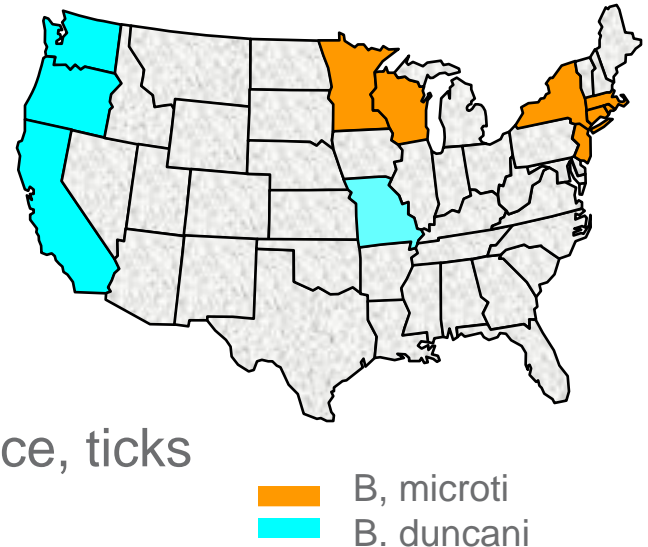
2007 Puerto Rico Donation Repository Testing

- Units distributed in US and PR tested (lookback study)
- 29 of 15,325 TMA (+) **1:529**; 14 (+) @ 1:16, 12 PCR (+) 10^5 - 10^9 c/mL, DENV-1, 2, 3 detected, 12 infected mosquito cultures, 6 IgM (+)

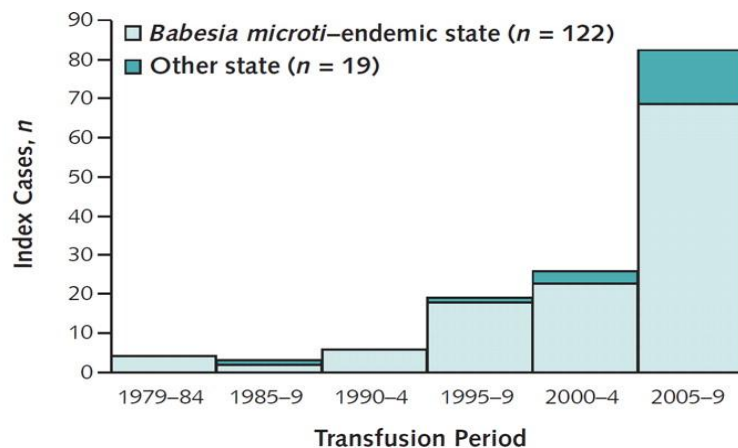


Babesia spp. and Disease

- Agents of human babesiosis
 - *B. microti* – US
 - *B. divergens* – Europe
- Intraerythrocytic parasite
- Transmitted by *Ixodes* ticks (deer tick)
 - Infections in humans, white-footed mice, ticks
 - Deer mechanical vector
- Causes flu/malaria-like illness, but can be fatal in
 - Elderly
 - Immunocompromised
 - Asplenic
- 162 cases investigated/confirmed transfusion transmission in the US; 5 cases in Europe
 - Hildebrandt et al., Eur J Clin Microbiol Infect Dis 2007;26:595-601



Distribution of U.S. transfusion-associated *Babesia microti* index cases, 1979–2009



(n = 141 of 162 cases)

Cases, n

Endemic states*

Massachusetts	2			2	12
New York	2		7	10	26
Connecticut		1	4	7	6
Minnesota		1	1	1	8
Rhode Island			1	8	11
New Jersey			2	1	4
Wisconsin				1	2

Other states†

New Hampshire‡	1				
Maryland§			1		2
Pennsylvania				1	2
Texas				1	1
Washington				1	
Ohio					2
Indiana					1
Delaware					1
North Carolina					1
California					1
Florida					2
Virginia§					1

Total index cases

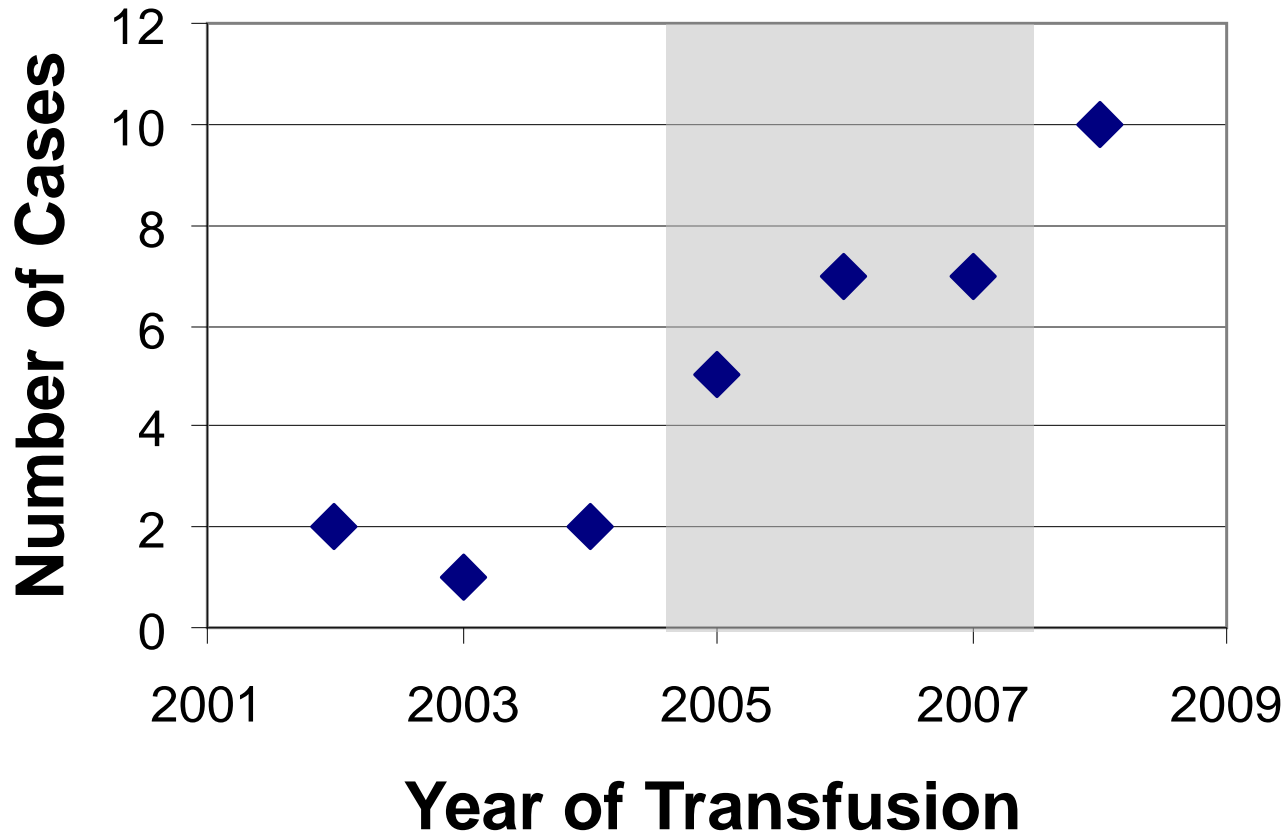
per period	4	3	6	19	26	83
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Herwaldt B L et al. Ann Intern Med doi:10.1059/0003-4819-155-8-201110180-00362

Annals of Internal Medicine

Transfusion-transmitted Babesiosis

ARC Hemovigilance Program, 2002-8



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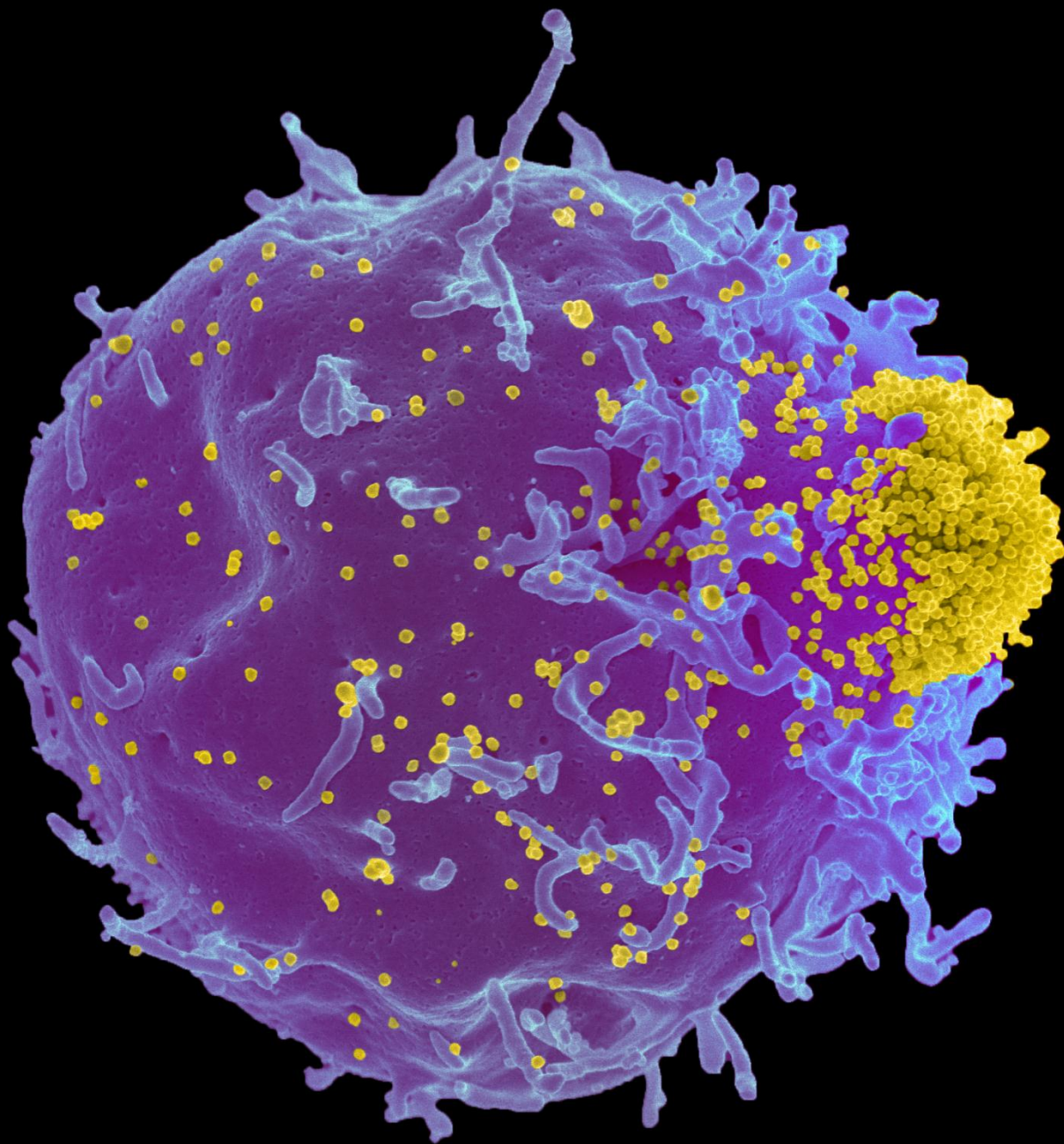
Shaded years described in Tonnetti et al., Transfusion 2009

Interventions

- Question donors about history of Babesiosis
- Question donors about tick-exposure
 - Up to 9% of donors regionally report tick bites
 - Infected patients often do not recall tick bite
 - No significant difference from post-card survey
 - tick-bites (1.3% EIA+ / 0.4% IFA+)
 - controls (1.3% EIA+ / 0.3% IFA+)
- Parasite removal by leukoreduction / inactivation
 - Parasite survives 21-35 days in RBCs including cryo-preserved RBCs
 - LR' d RBCs associated with transmissions
 - Extracellular parasites reported
 - Doesn' t survive freezing
- Antibody donor screening test for Ab (IFA) and/or by PCR “investigationally”

Outline

- What is XMRV?
- What did the early studies suggest?
- Why was it considered a threat to blood safety?
- How was this threat managed?
- What did later studies show?
- What did we learn?



Brief history

- An unusual new virus, XMRV, recognized in cases of prostate cancer in 2006
- The same virus identified in 67% of CFS patients and 3.7% of controls in 2009
- Possibility of transfusion transmission noted
- Controversy, observations not repeated
- FDA/NIH find related virus in 87% of CFS patients and 6.8% of blood donor controls in 2010
- More negative studies
- Increasing evidence suggesting laboratory contamination as explanation of “positive” findings
- NHLBI-funded study shows test data not meaningful
- Red Cross study shows no XMRV in donors or recipients
- “Positive” studies retracted in late 2011

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M. McPHERSON

EIDs and hemovigilance

- None of the EIDs discussed were identified through hemovigilance, but through:
 - Astute clinical observation
 - Observation based upon anticipation
 - Lookback
 - Prospective studies
 - Serendipity
 - This also true of recent transplant-related EID infections

Recipient hemovigilance is poorly suited to new agent discovery

- Designed to identify expected events
 - Many TTIs not apparent until long after hospital release; inapparent infections
 - Investigation of presumed transfusion transmission is lengthy and complex and a presumed association is frequently found to be incorrect
 - Blood recipients are unlikely to be the first group to be recognized as infected
-

NHSN Investigation triggers

- Identification by (recipient testing) of an unexpected organism, virus or parasite
- Same findings in transfused unit
- Unexplained clinical events
- Evidence of infection with a (donation) tested pathogen within 6 months
- Predefined agent list provided
- Imputability evaluation critical

NHSN imputability

Definite:

- Evidence that the recipient was not infected with this organism prior to transfusion

AND

- Laboratory evidence of infection with the same organism in the donor by testing of the donor, the recipient unit (or retained segment), or co-component from the original donation

OR

- Laboratory evidence of infection with the same organism in another recipient that received blood from the same donor.

Donors are an important resource

- It is relatively easy to work with donors
 - Available samples, demographic information
- Perform prevalence studies
- Seek evidence of recipient infection through lookback
- Determine infectivity markers
- Examples:
 - *T. cruzi*, *Babesia*, Dengue, XMRV

Red Cross experience

- Consistent (if not complete) reporting of post-transfusion sepsis through hemovigilance
- Many presumed cases of HIV, HCV reported from hospitals
- Careful investigation failed to confirm any (zero of ~100) HIV cases as transfusion-transmitted (HCV currently under investigation).

Key points

- Infections continue to emerge, but unpredictably
- Resultant disease usually recognized in the community (not through transfusion)
 - TTI a minor percentage of any epidemic
- Specific studies needed to define TTI risk
- Known infections could be tracked by hemovigilance, if acute and immediate, and if recognized criteria are established