America's Blood Centers®
It's About *Life.*

20th Bill T. Teague Lectureship in Transfusion Medicine Houston TX, May 2016

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

"Arboviruses 'R' US"

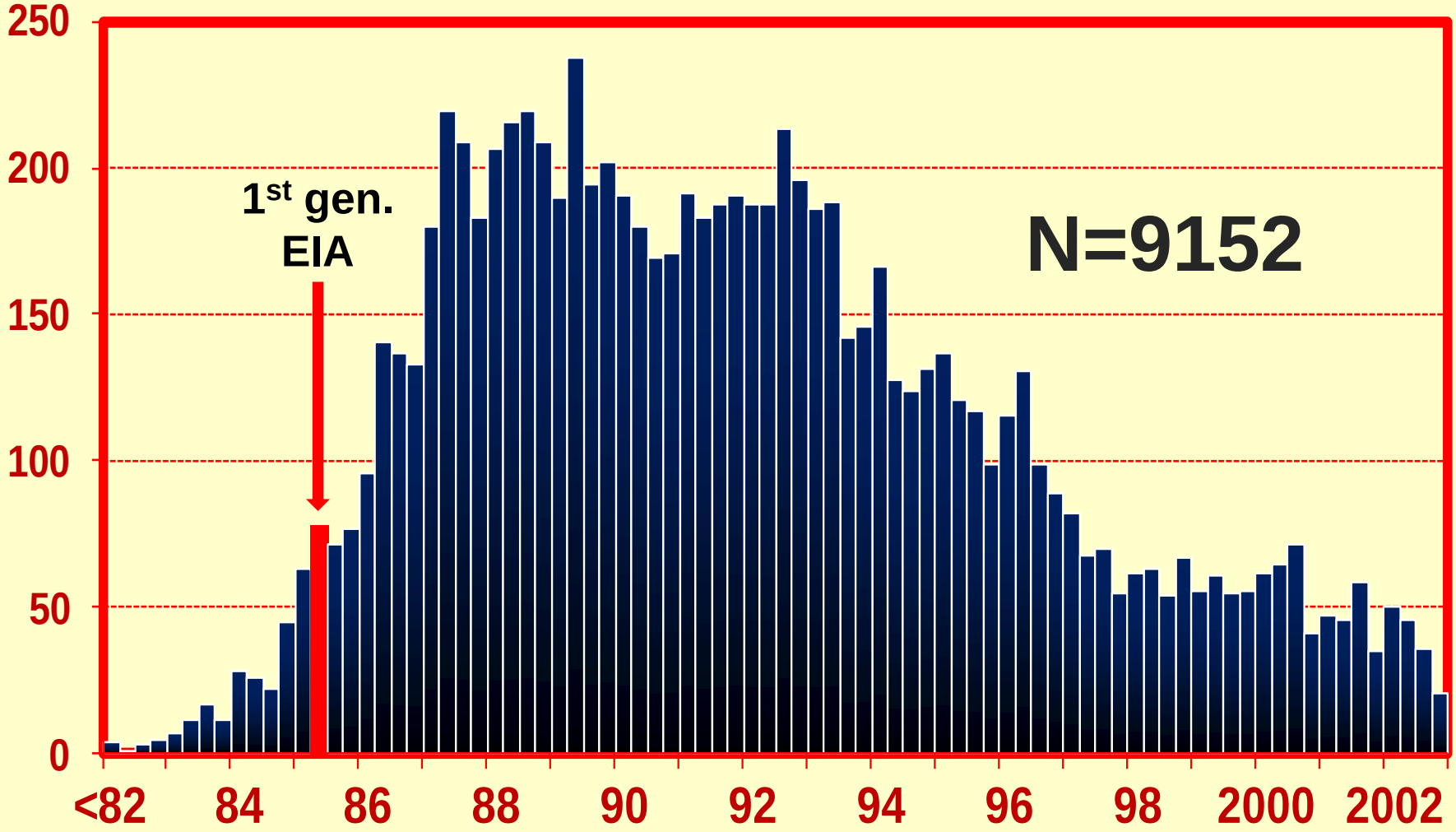
Louis M. Katz MD

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

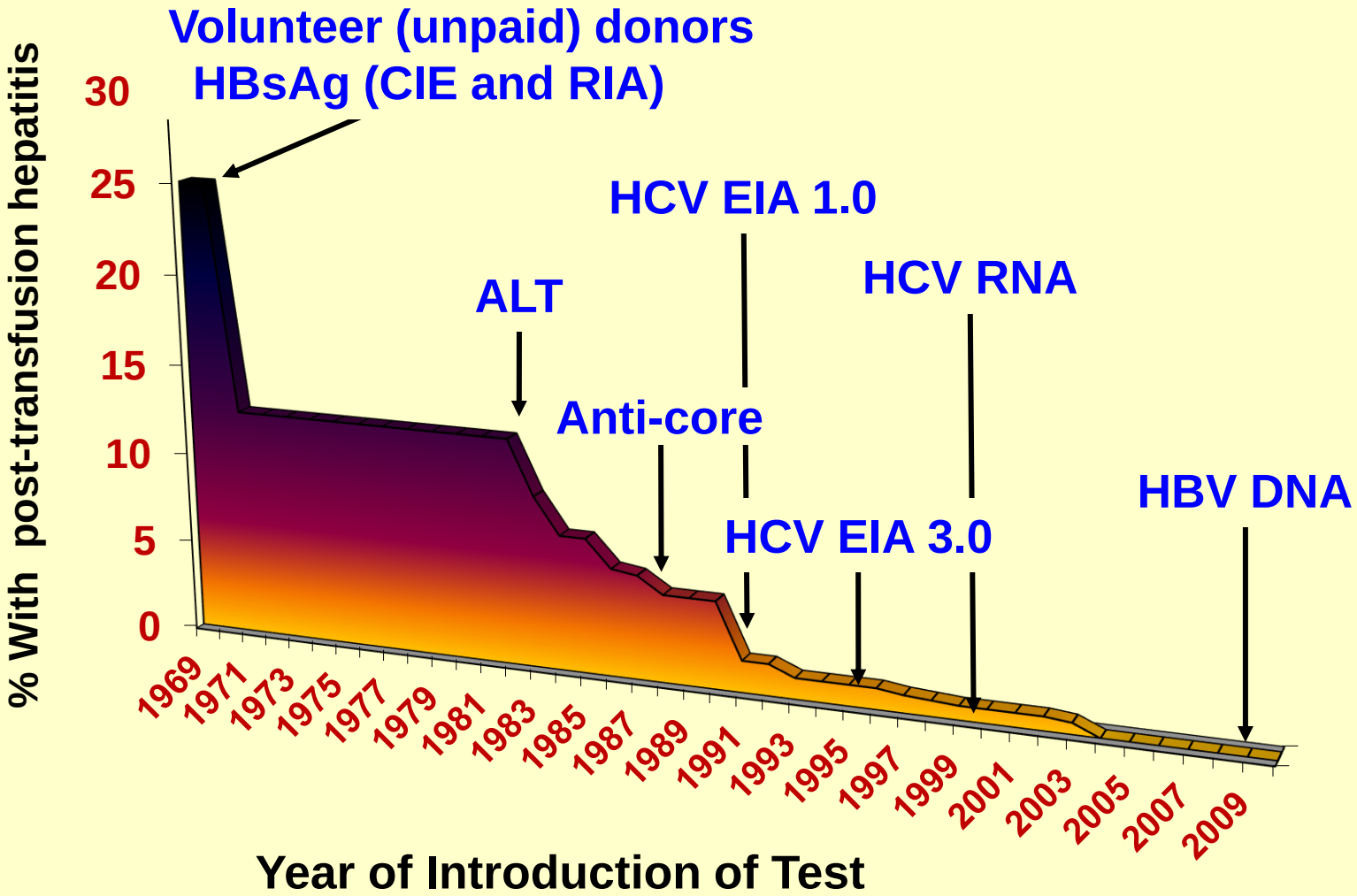


CDC: AIDS public use data file

"You wonder where the yellow went"

Post-transfusion hepatitis risk: 1969-2005

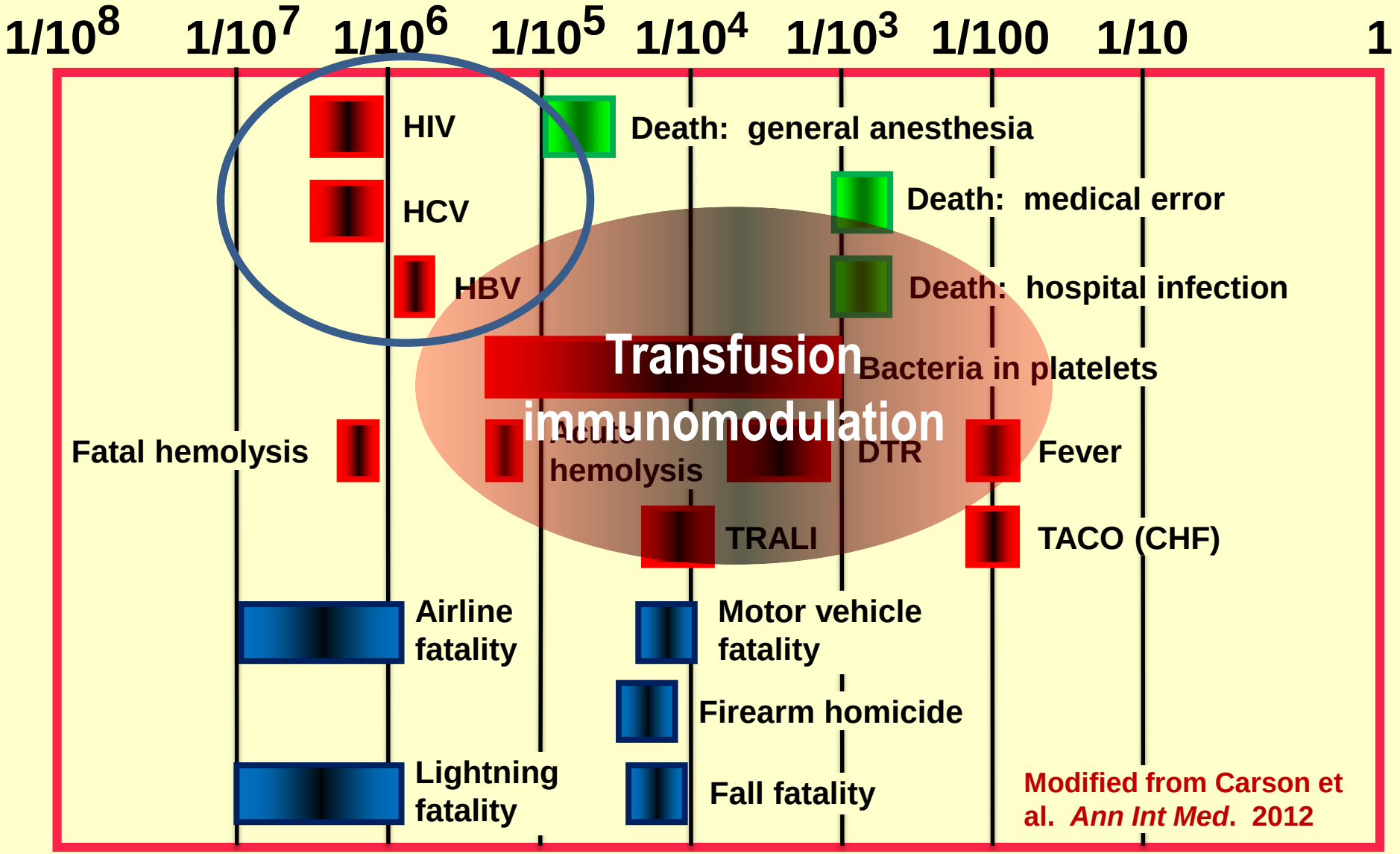
NIH Clinical Center



Courtesy Harvey Alter. DTM. NIH.

Relative risks in life:

Probability of event/unit transfused



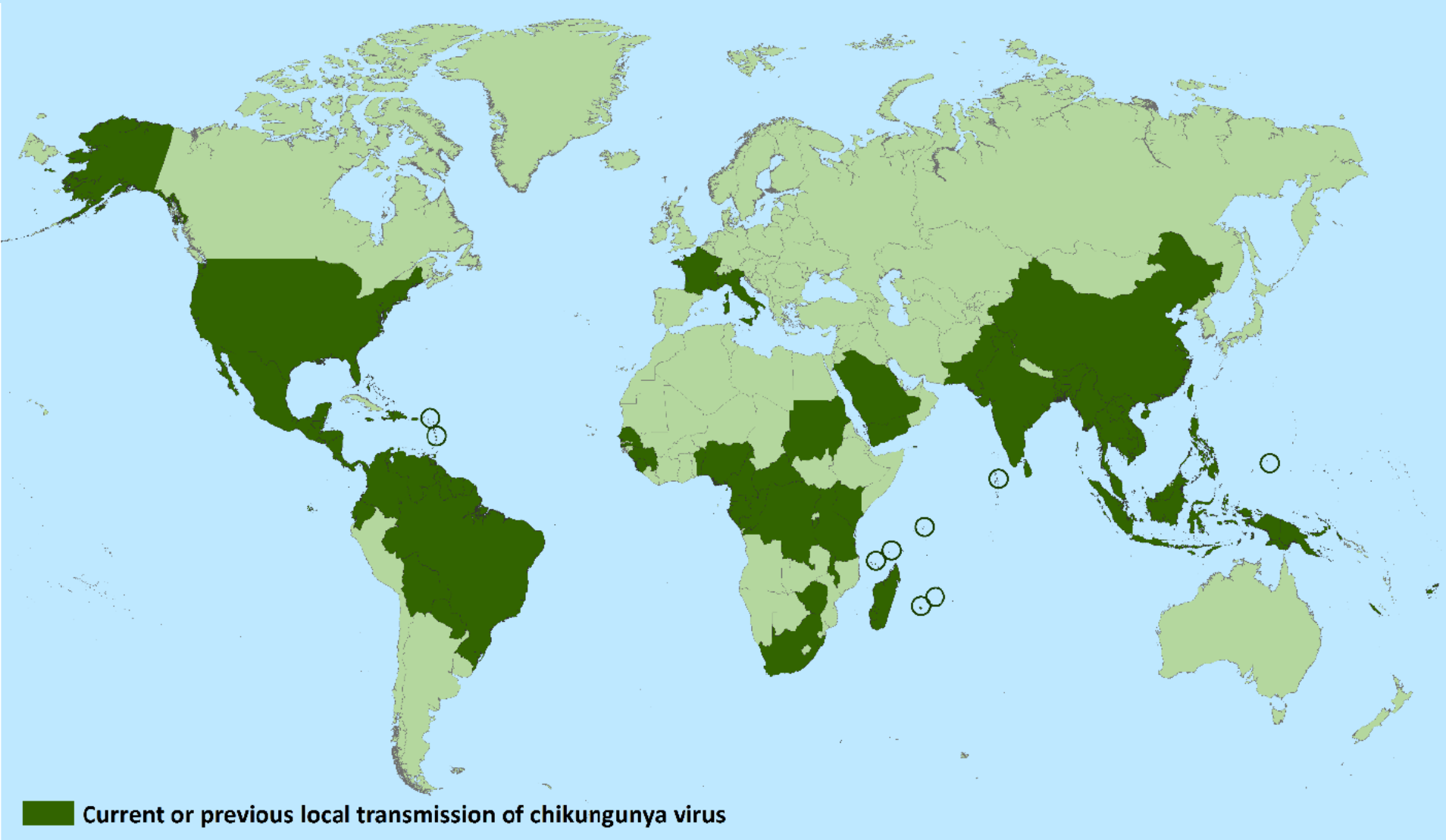
Yay us! TT-WNV in US

- **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 → ID NAT conversion**
- **2004-2014, 13 subsequent transmissions**

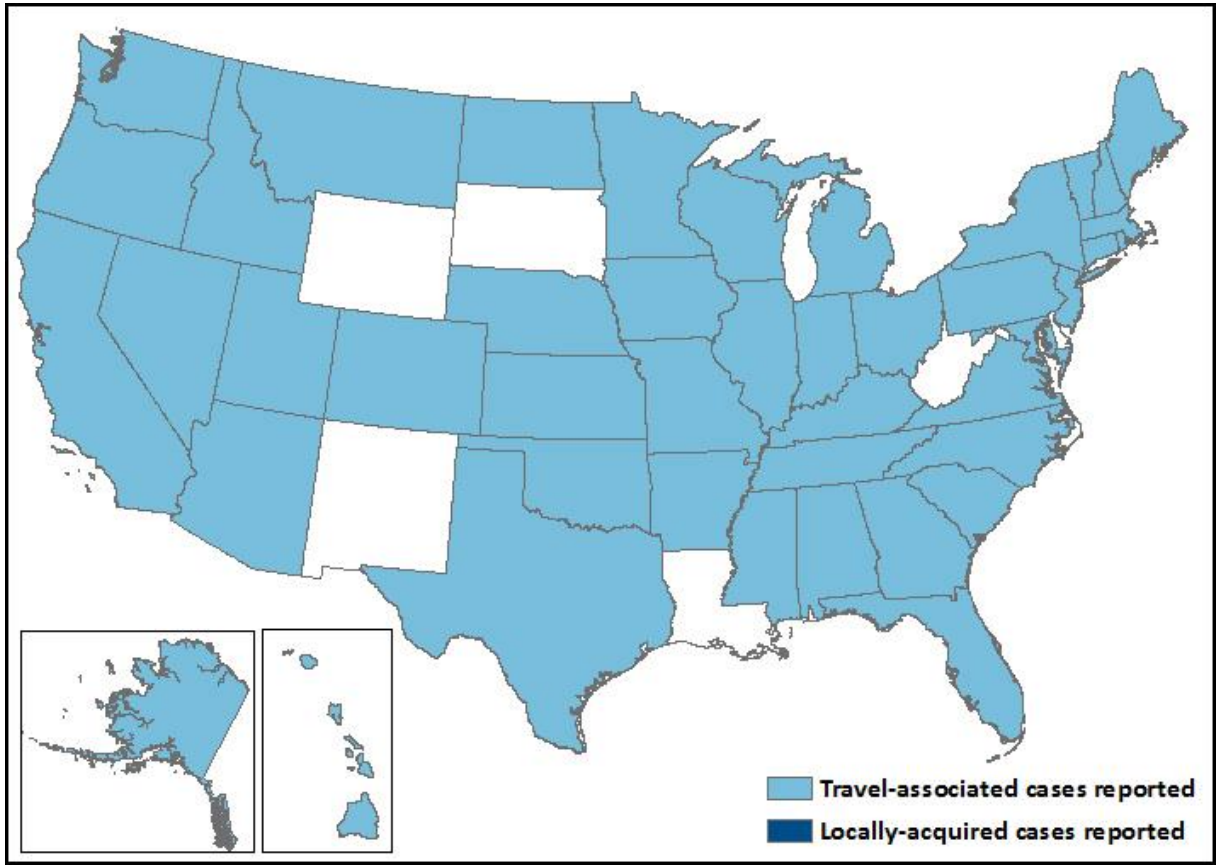
Lessons learned

- **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**
  - **~20% of infections asymptomatic, and *~2d. viremia before symptoms***
  - **4/2149 *well* donors PCR +: French West Indies 2014 (Gallian P et al. Blood. 2014.)**
  - **3/557 *well* donors TMA +: Puerto Rico (ARC) 2014 (Chiu et al. EID. 2015)**
- **Agent infectious by parenteral inoculation**
  - **Lab accidents & macaque model (Labadie et al. JCI. 2010)**
- **Survives modern blood processing and storage**
  - **Limited understanding**
- **Clinically recognizable morbidity by this route**
  - **Limited understanding**

***Stramer et al. *Transfusion*. 2009.**

ChikV by transfusion
model results from 3 studies

	Incidence	Duration viremia (days)		Percent without symptoms	Est. viremia prevalence/100,000 donations	
		Before symptoms	After symptoms		Mean	At epidemic peak
Thailand[1]	5.3%	1.5	8.0	10%	38	237
Reunion[2]	35%	1.5	6.0	15%	132	1500
No. Italy[3]	.03%	2.0	6.0	15%	NA	1

[1]Appassakij, *Transfusion*. 2014.

[2]Brouard, *Transfusion*. 2008.

[3]Liumbruno, *Blood Transfusion*. 2008. (Region wide modelling).

Est. weekly ChikV transfusion risk

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

	Peak population incidence/wk	Peak risk/10^5 donations
Palm Beach 1 case	0.0000007	0.03
Palm Beach 2 cases	0.0000015	0.06
Palm Beach 5 cases	0.0000037	0.16
Palm Beach 10 cases	0.0000074	0.32
Palm Beach 100 cases	0.0000737	3.21

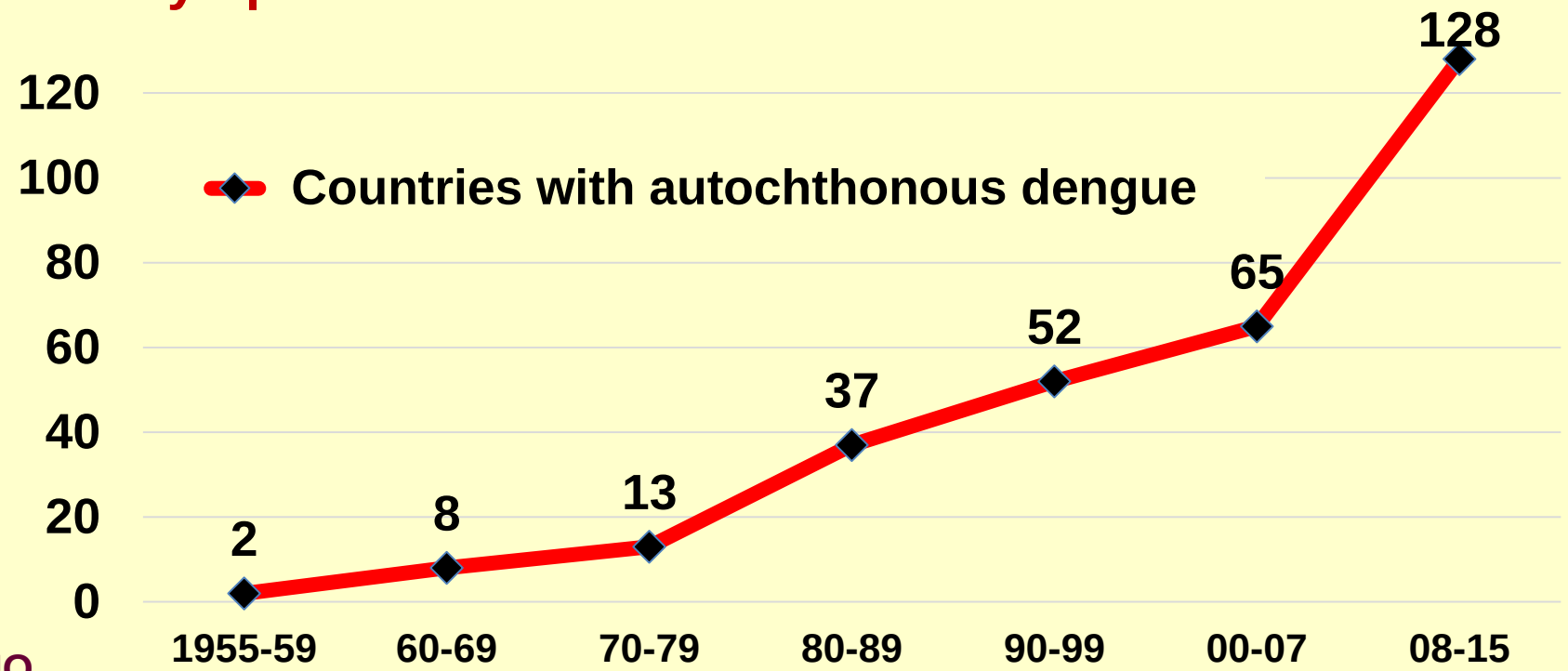
Lyle Petersen, CDC/DVBD, for TTD 09-15-14

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")?***

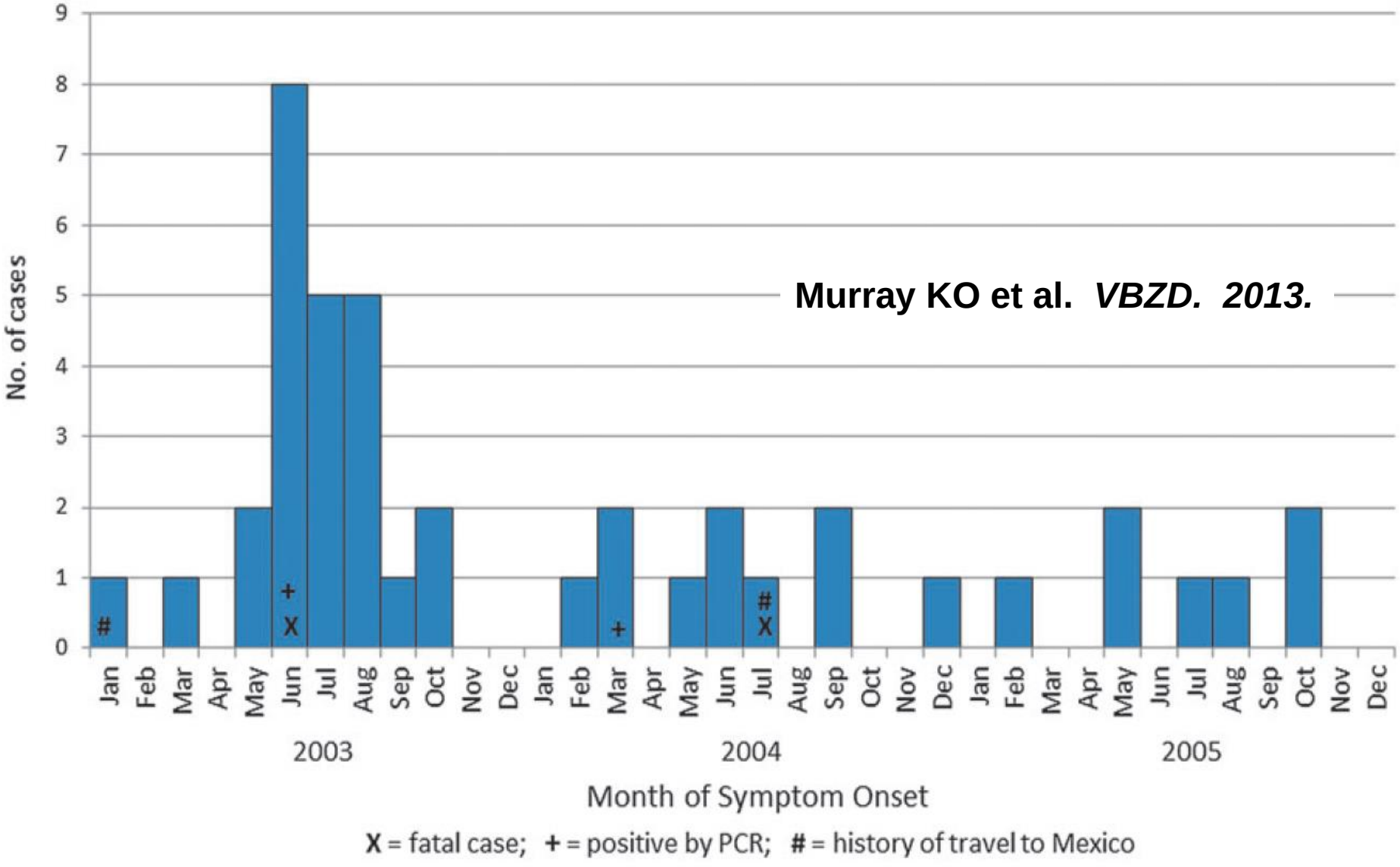
Dengue (re)emergence

- *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



WHO

Dengue in Houston

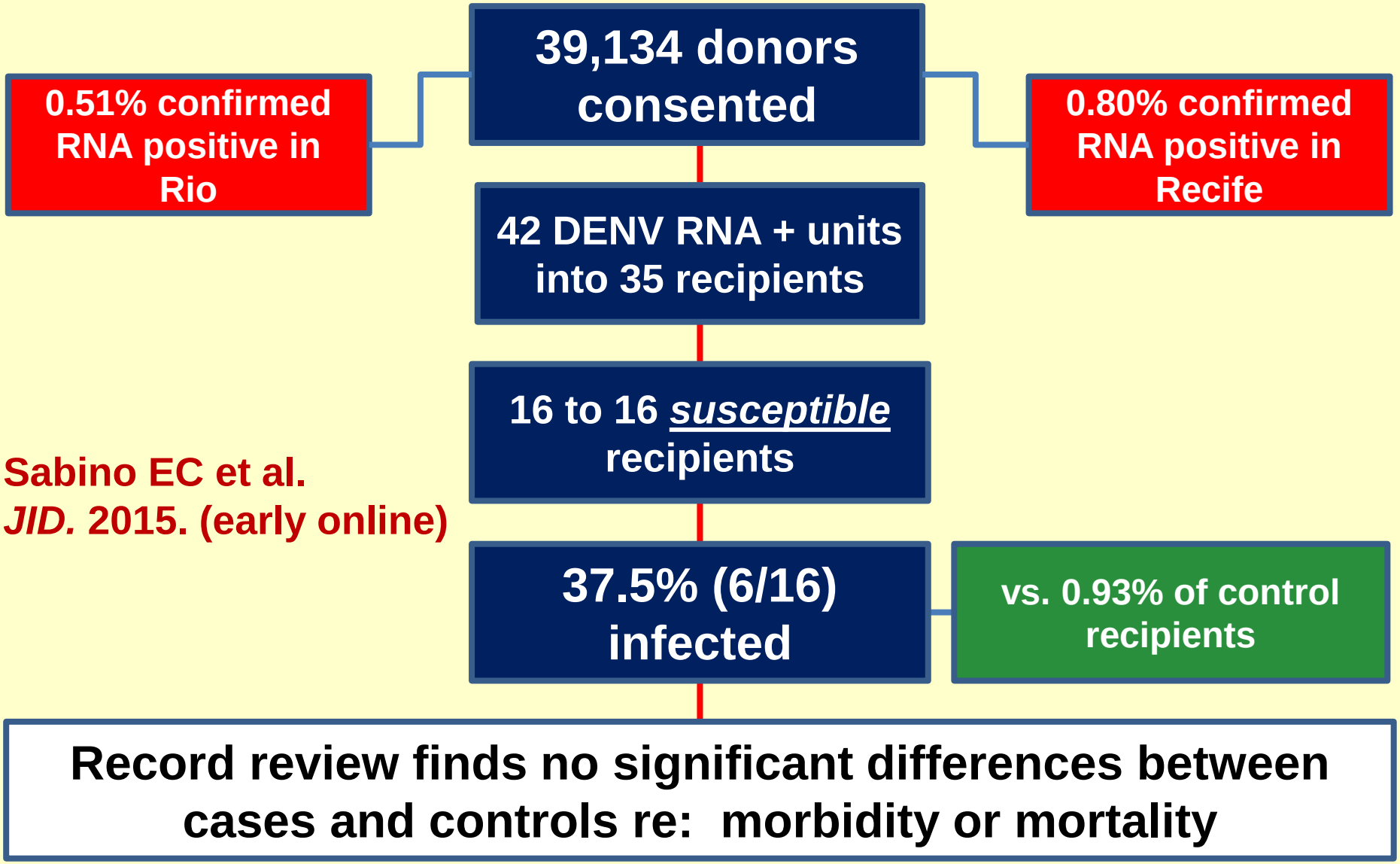


Murray KO et al. *VBZD. 2013.*

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

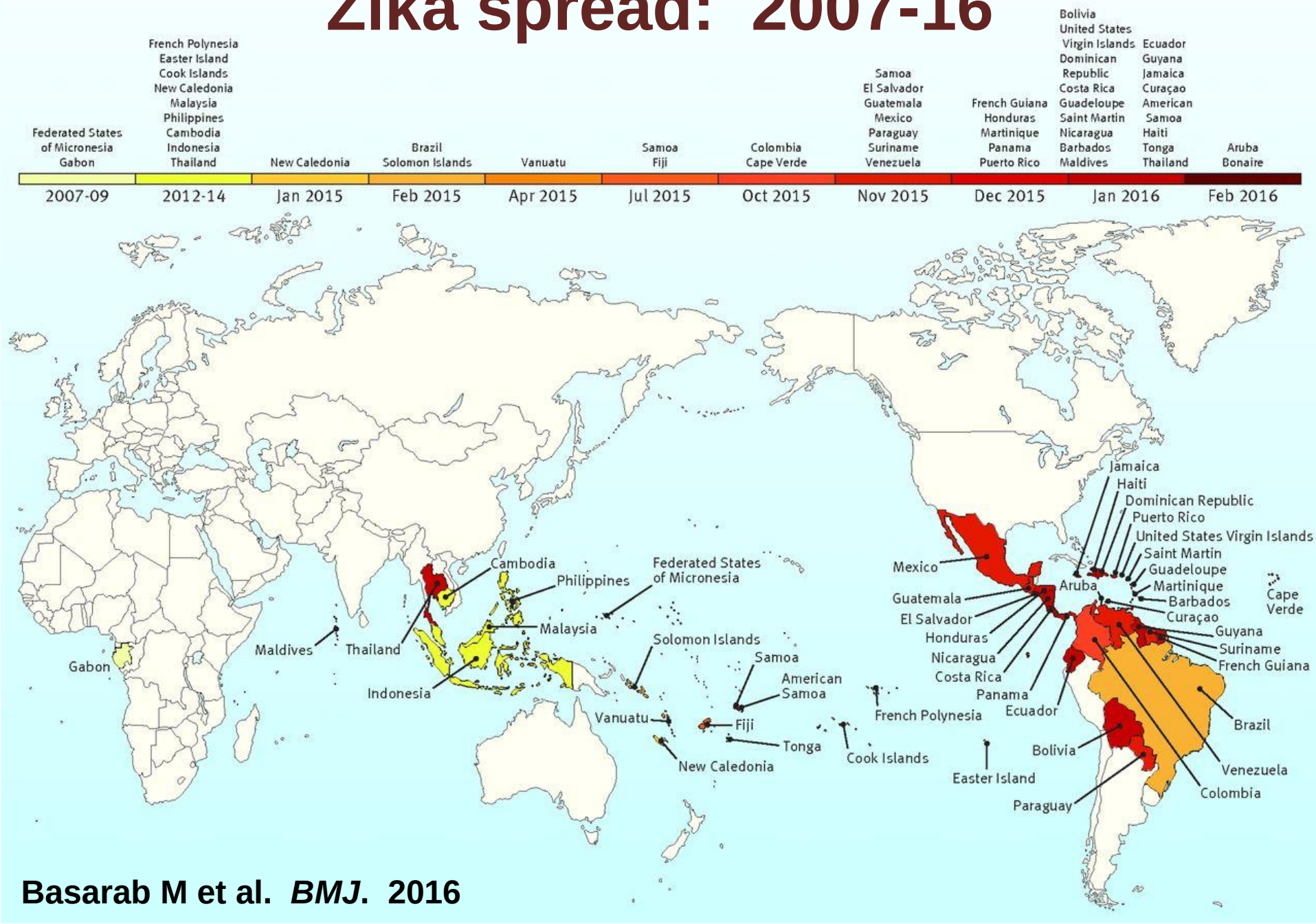
Dengue-4 in Brazilian donors:
a "*sheep in wolf's clothing*"??



Sabino EC et al.
JID. 2015. (early online)


ZIIKA FOREST
RESEARCH FIELD
STATION.
UGANDA VIRUS RESEARCH
INSTITUTE (UVRI)
P.O.BOX 49 ENTEBBE.
TEL: 0414-320631
FUN all
the TIME

Zika spread: 2007-16

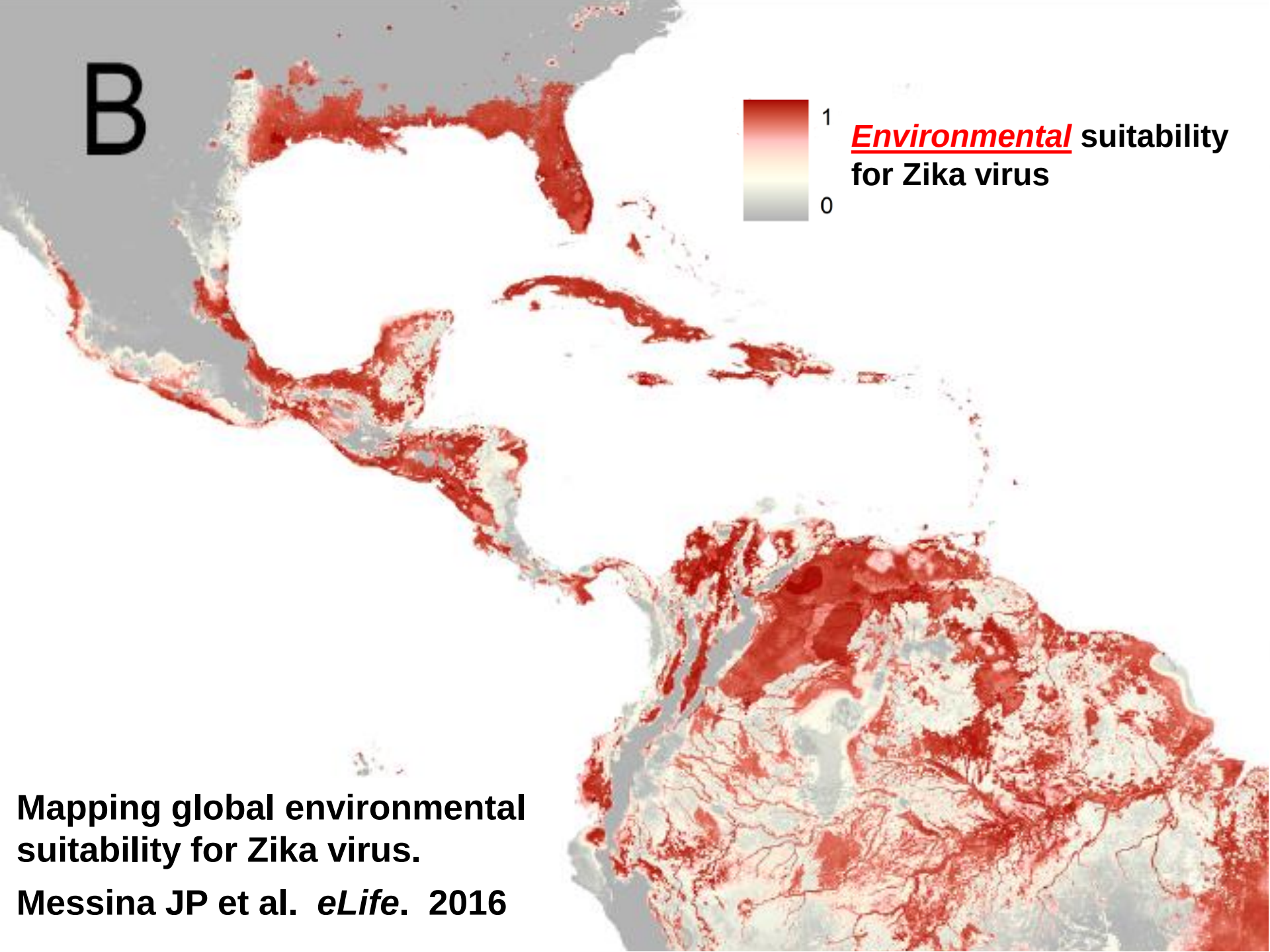


Basarab M et al. *BMJ*. 2016

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.

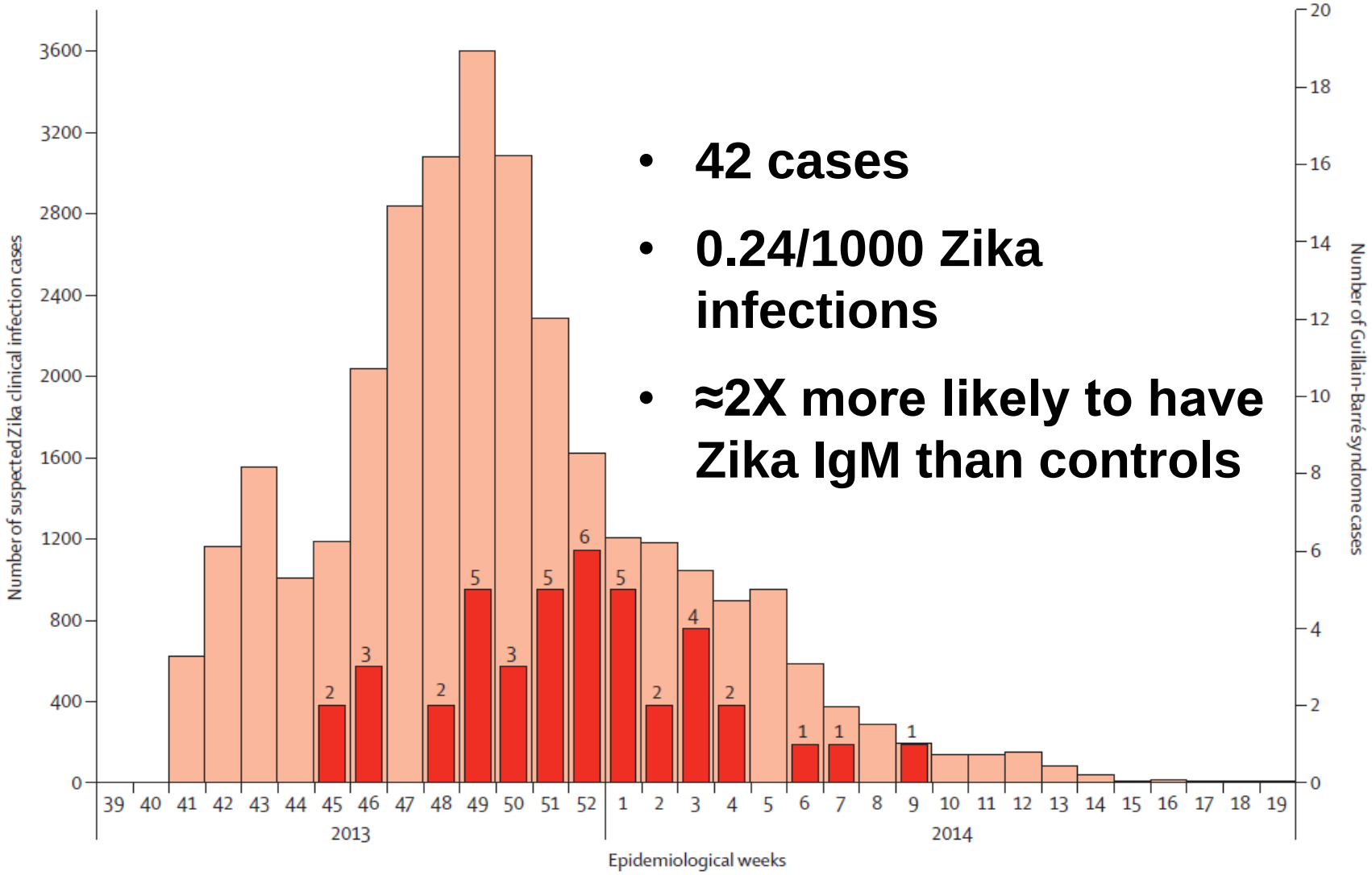
2. April 2015, transfusion recipient, (died from gunshot wounds after 3 mos. in ICU), lab abnormalities suggesting infection led to trace-back revealing he had received blood from a donor with retention sample positive for ZIKV. Donor reported illness c/w Zika 3 days after donating.



Mapping global environmental suitability for Zika virus.

Messina JP et al. *eLife*. 2016

Zika and GBS: French Polynesia



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

Cao-Lormeau V-M et al. *Lancet*. 2016.

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".

Brasil P et al. *NEJM*. 2016.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Zika Virus and Birth Defects — Reviewing the Evidence for Causality

Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H.,
Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.

- **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

***NEJM*. 2016.**

FDA (final) Guidance

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*

	Summer-14d	Summer-28d	Winter-14d	Winter-28d
Mexico	0.19%	0.52%	0.40%	0.92%
Caribbean	0.16	0.48	0.48	1.16
C. America	0.02	0.06	0.13	0.26
S. America	0.03	0.07	0.07	0.20
Total "Americas"	0.39	1.17	0.96	2.23
Total ex-US & Canada	NA	2.64	1.35	4.02

*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**

$P_{viremic\ donation}$ =	1:312,500	no deferral
	1:22,000,000	@ 14d deferral
	≤1:200,000,000	@ ≥21 day deferral

Pers. Comm. Germain M and Gregoire Y.

FDA (final) Guidance

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

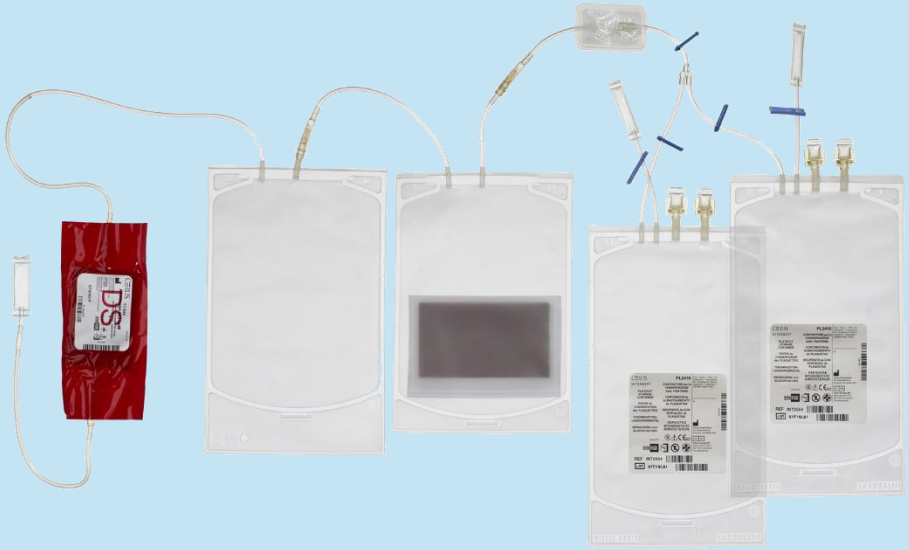
- **Assume 100% infectivity of viremic donation**
- **Assume 80% of infected donors asymptomatic**
- **Assume 1% of transfusion to obstetrics**
- **Assume bad fetal outcome in 50%**

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

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

PLT

1

Transfer product to Illumination bag

2

Add Riboflavin

3

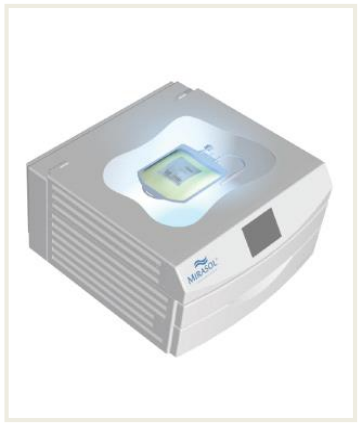
Illuminate for 6-10 min.

Ready to store or transfuse!

4

Transfer to Pls storage bag

PLS



Bugs making us nervous
log_{10} reductions in titer

	Intercept	Mirasol
WNV	>6.0	≥5.1
Denguevirus	≥4.3	1.6
Chikungunya	≥5.7	≥3.7
Zika virus*	≥6.0	Pending
Babesia microti	≥4.9	>5.0
Staph. Epi.	≥6.1	≥4.2
E. coli	≥6.3	>4.4

*FFP only.

Source: Cerus Inc. Intercept PI. Ray Goodrich (Terumo). AABB. 2014. Stramer et al. *Transfusion*. 2009. Aubrey M. et al. *Transfusion*. 2015

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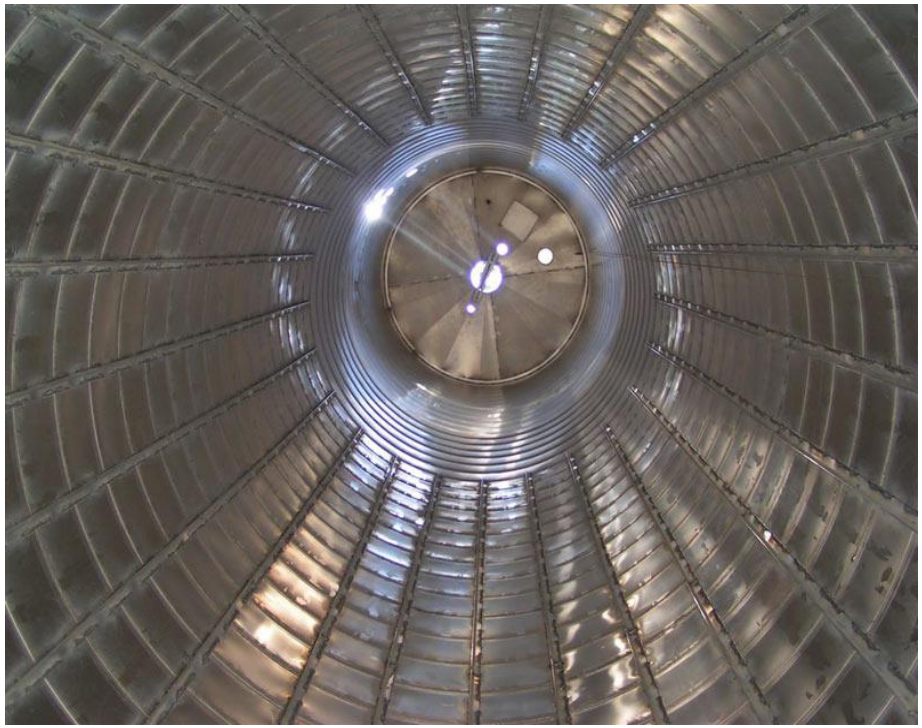
“We now have the means to protect patients from existing & emerging bloodborne threats—all we need is the will.”



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.

April 22. DOI: 10.1056/NEJMp1500154

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 ≅ $750,000-1,000,000/QALY**
- **Active surveillance for bacterial contamination and stopping cultures, 7-days ≅ $200,000/QALY**
  - **Does not consider emerging TTIs**
  - **Does not consider lost revenue from irradiation and CMV screening**

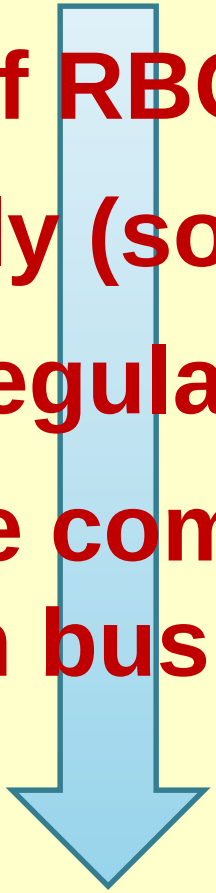
Custer, B. AABB PR Symposium. April 2015

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?

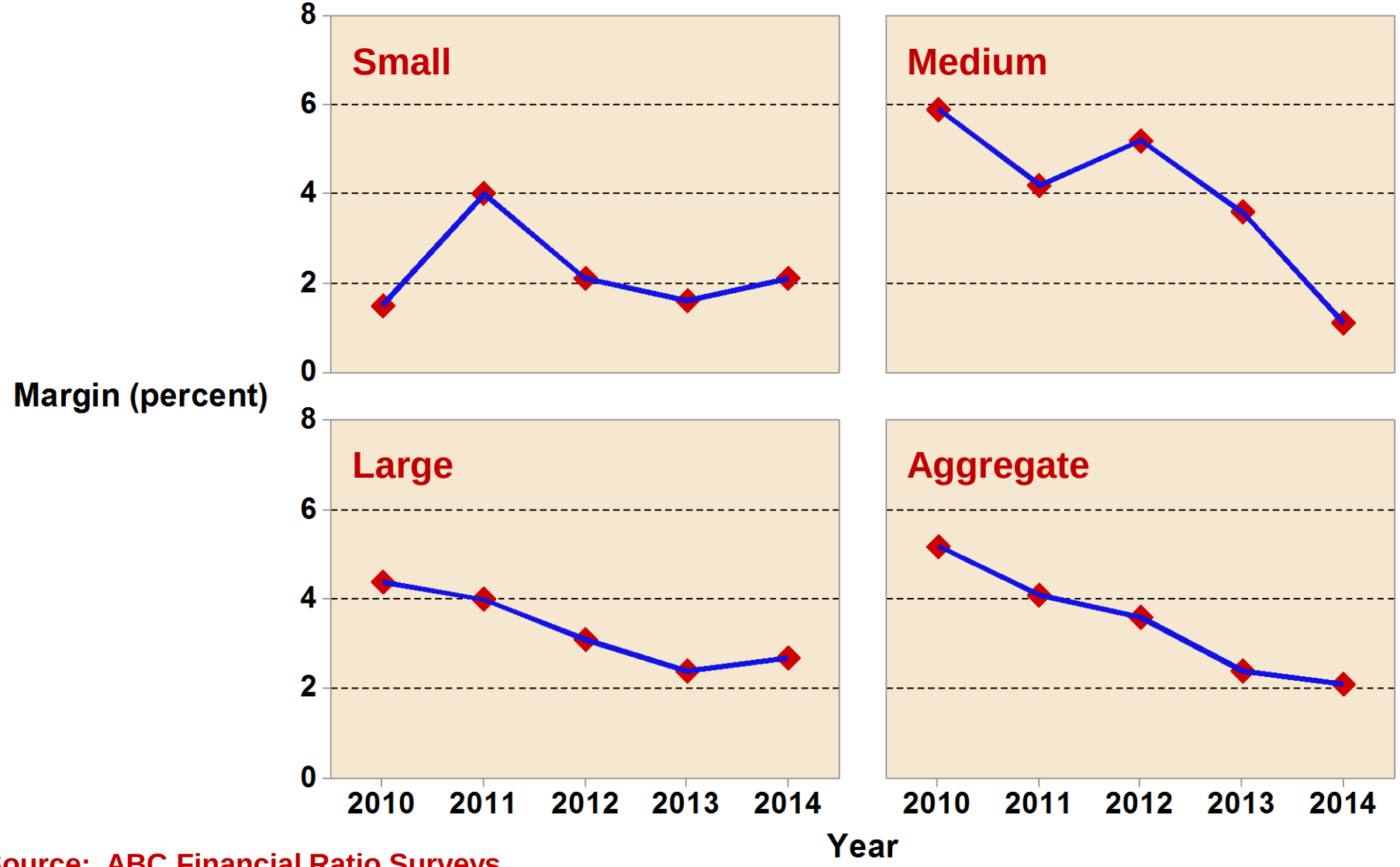
- **Declining use of RBCs. Rest flat.**
- **Adequate supply (sorta)**
- **Safety/quality/regulatory burden ↑ ↑ ↑**
- **Increasing price competition for hospital/system business**



Commoditization of blood

No Δ fixed costs=declining margins

Margins at ABC centers 2010-14



Source: ABC Financial Ratio Surveys

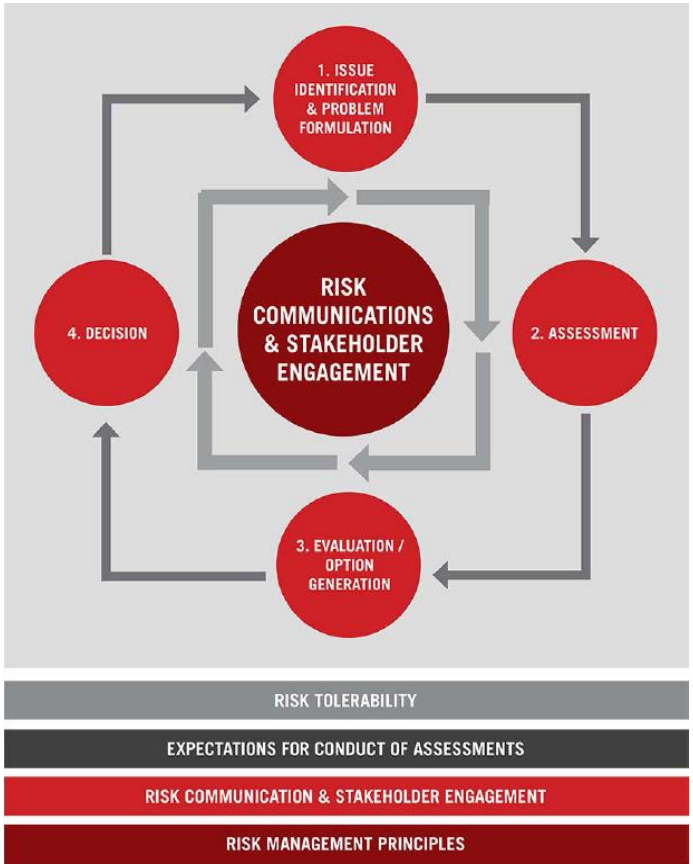
47th ACTBSA Nov. 2015

- **"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. Katz[4]



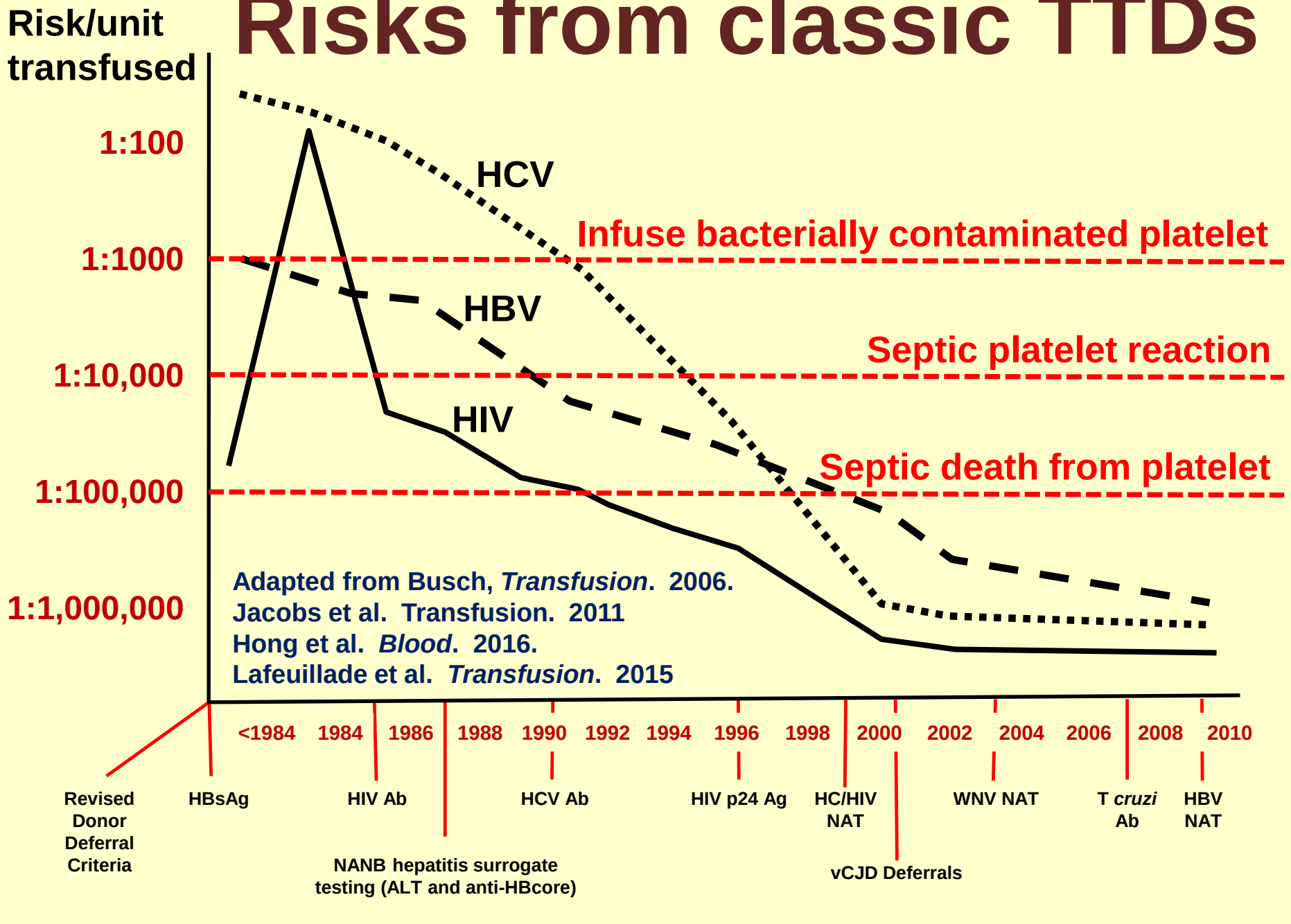
- **Explicit policy foundations**
- **Systematic consideration of relevant information *from a societal perspective***
- **Decision support tools provided, expected outputs are explicit**
- **Iterative as new information is developed**

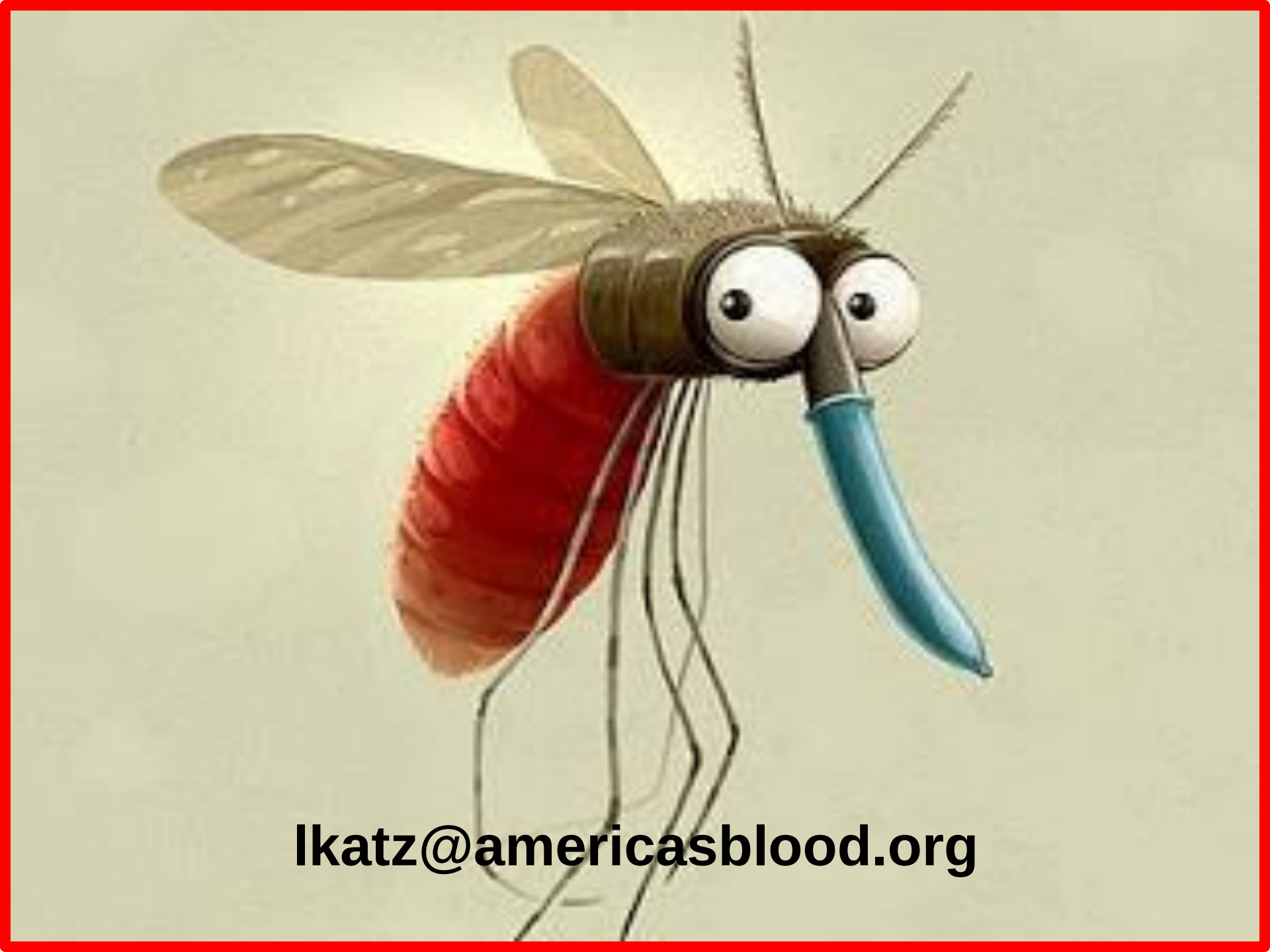
https://allianceofbloodoperators.org/abo-resources/risk-based-decision-making.aspx

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




lkatz@americasblood.org