Update on Transfusion-Transmitted Infectious Diseases

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I have no conflicts of interest to disclose.

Global changes and the spread of disease

- Changing environmental dynamics provide opportunities for new niches for vectors
  - Diseases previously identified as being geographically-restricted are emerging in new areas
- Travel has increased both in frequency, distance and numbers of individuals
- Global trade has increased
  - Including items such as used tires

Vector-Borne and Zoonotic Diseases. April 2007, 7(1): 76-85.

Transfusion-Transmitted Infection

- Bacteria, viruses, parasites or prions present in blood products that can cause disease in a recipient when transfused

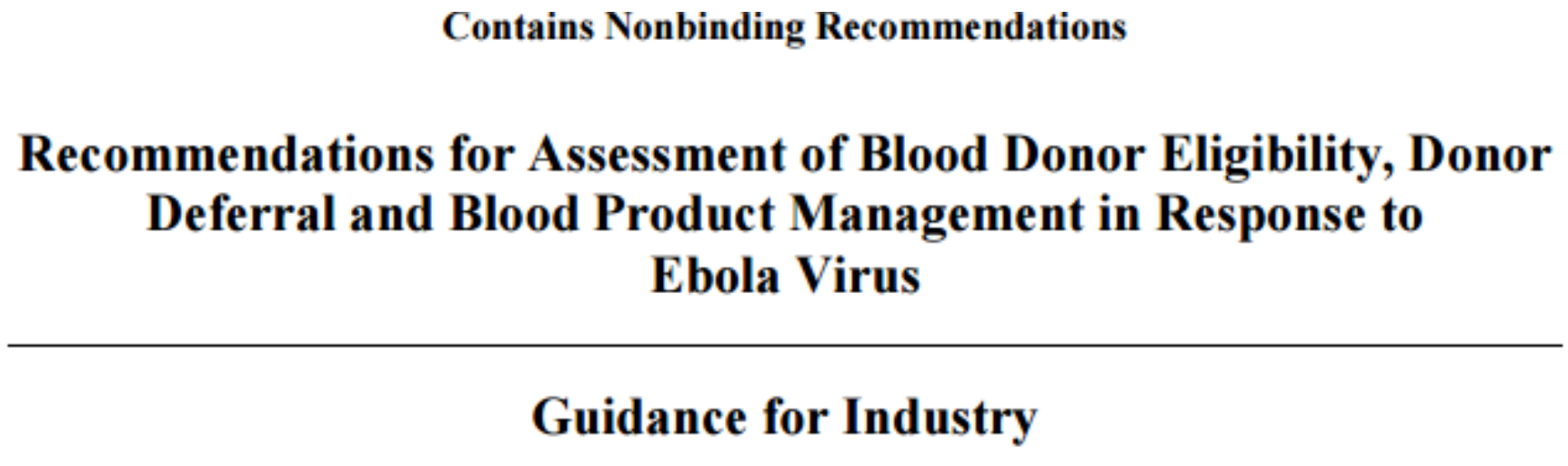
- Traditionally, blood supply protected by several mechanisms:
  - Donor history and physical exam
  - Screening tests (nucleic acid, serologic, culture, POC)
  - Pathogen reduction
  - Leukoreduction
  - Failure to survive storage conditions

Transfusion-Transmitted Infection: Donor questions

- Utility of donor screening questions versus donor education material
- Though new questions and material can be rapidly developed, implementation at blood centers can be cumbersome
- Travel questions can be nebulous
  - Travel to an endemic area – does airport connections count?
- Areas of disease activity can change or be unfamiliar to the donor
- Some questions are simply unknown
  - Have you had sexual contact with someone who has travelled to an area with…

Transfusion-Transmitted Infection: Donor Questions

- Utility of donor screening questions versus donor education material
  - Recent guidance from the FDA (1-2017) regarding Ebola
    - Recommends adding to the education materials that donors with a history of Ebola virus infection do not donate blood
    - Recommends updating donor history questionnaire to assess travel and contact history should areas with widespread transmission of the virus develop



Contains Nonbinding Recommendations

Recommendations for Assessment of Blood Donor Eligibility, Donor Deferral and Blood Product Management in Response to Ebola Virus

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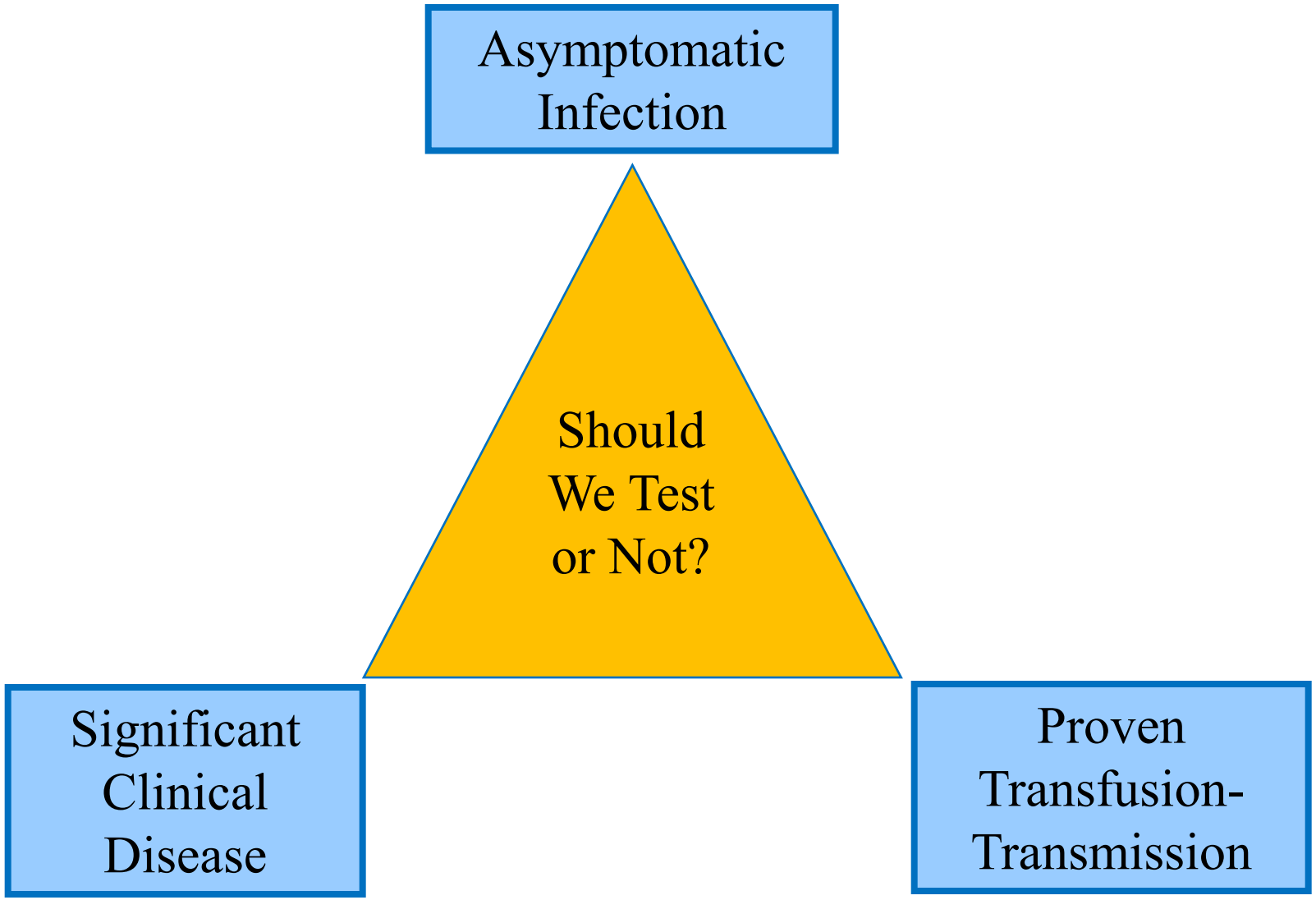
Guidance for Industry

Transfusion-Transmitted Infection: Screening tests

- Development and licensing of approved screening tests for infectious diseases takes significant time and capital
  - FDA licenses diagnostic and screening tests differently
- Serologic and nucleic acid testing are used for virus detection
- Culture and POC testing are used for bacterial detection
- Cost

Triangle of Transfusion Testing



(Adapted from Harvey Alter, M.D.)

Pathogen reduction

- FDA approved technology that reduces (but not eliminates) the viability and infectivity of infectious agents in platelets and plasma
- Not approved for RBCs in the United States
- Cost
- Availability
- If fully implemented, capacity issues may arise

Arboviruses

- Any virus transmitted by an arthropod (insects and ticks)
- Wide variety of diseases and risks
- Most immediate challenge facing the United States' blood supply today

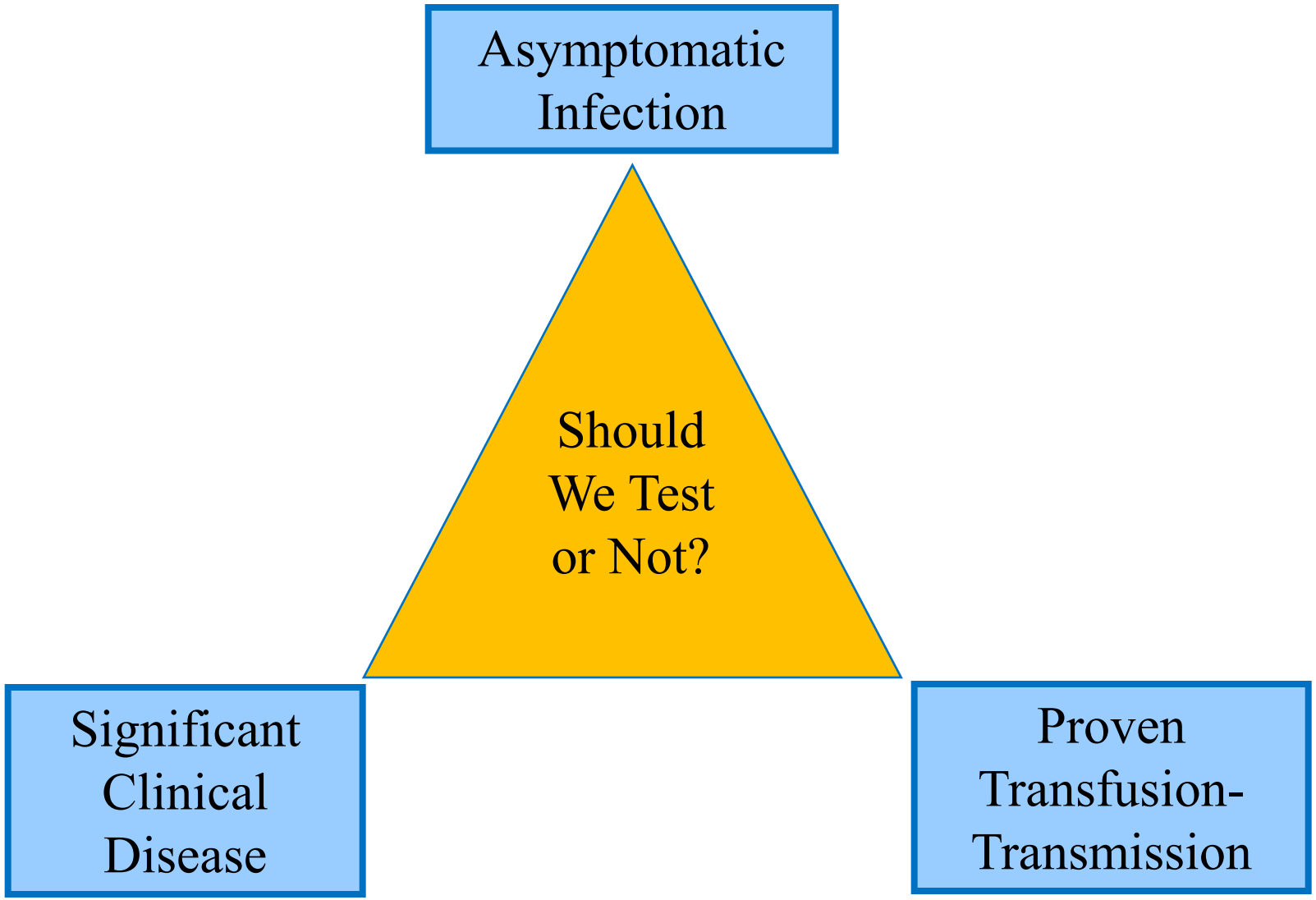
Emerging Diseases: Zika

- *Flaviviridae* family, genus *Flavivirus*
  - Same as WNV
- May cause asymptomatic virema or present with fever, rash and athralgias
- Transmitted through mosquito bites, perinatal exposure, sexual contact, transfusion
- Potentially transmissible up to 6 months after infection

Emerging Diseases: Zika

http://www.sciencemag.org/news/2016/05/zika-causes-microcephaly-mice

Triangle of Transfusion Testing



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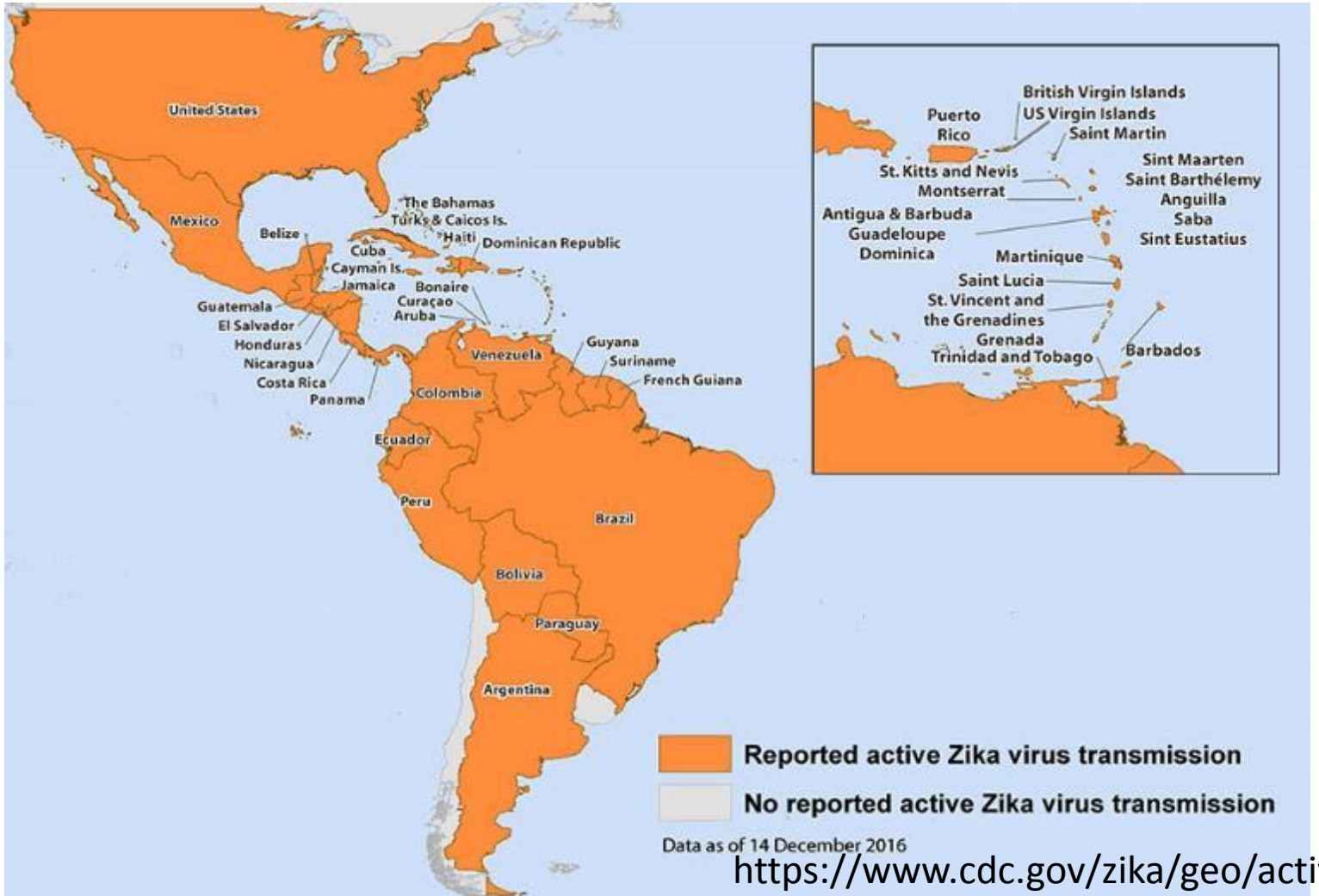
Emerging Diseases: Zika

- Challenge for blood collections centers



https://www.cdc.gov/zika/geo/active-countries.html

Emerging Diseases: Zika

- Challenge for blood collections centers

Aedes aegypti

Aedes albopictus

Emerging Diseases: Zika

- 1947 Discovered, with cases reported in equatorial Africa and Asia
- 2007 Spread to island of Yap in Pacific
- 2013-14 Outbreak in French Polynesia
- 2015 First report in Brazil in March
- 2016 FDA issues guidance on Transfusion Transmission in February with questionnaire guided restrictions
- 2016 FDA revises guidance in August that includes recommendations to test all donations collected in the US with individual donor nucleic acid testing (IND) or pathogen reduce all platelets/plasma

Emerging Diseases: Zika

- Roche cobas Zika ID-NAT has screening 358,789 donations
- 23 initially reactive, 14 confirmed positive (all from Florida)
- 10/14 travelled to Zika endemic areas (Caribbean or Miami)
- When a minipool testing was simulated, 7/14 were not detected

Galel, S. A., et al. Transfusion. doi:10.1111/trf.14029

Emerging Diseases: Zika

- Procleix ID-NAT has screening 466,834 donations
- 5 confirmed positive (all from non-endemic areas)
- Estimated 1:93,000 units in non-endemic areas

Williamson PC et al. Transfusion. doi:10.1111/trf.14041

Emerging Diseases: Zika

- Currently, PR is not available for red blood cells, so ID-NAT is used by most major blood suppliers to screen donations for Zika
- Neither available ID-NAT test is licensed and both are currently used under IND exemption
- Unknowns
  - Is testing units permanent?
  - Does PCR positivity correlate with infectivity?
  - What are the performance characteristics of these tests?
  - Will the FDA use this model to approach other diseases?

Arboviruses to watch

- Dengue fever
  - Up to 87% of infected individuals can be asymptomatic
  - During a large epidemic in Brazil, up to 0.8% of donations tested positive for viremia, with 1/3 of these transmitting disease by transfusion
  - Reported in Brazil, Figi, Saint Lucia, Belize, Grenada, Argentina

Teo et al. Transfu Med 2009
Sabino et al. J Infect Dis 2016

Arboviruses to watch

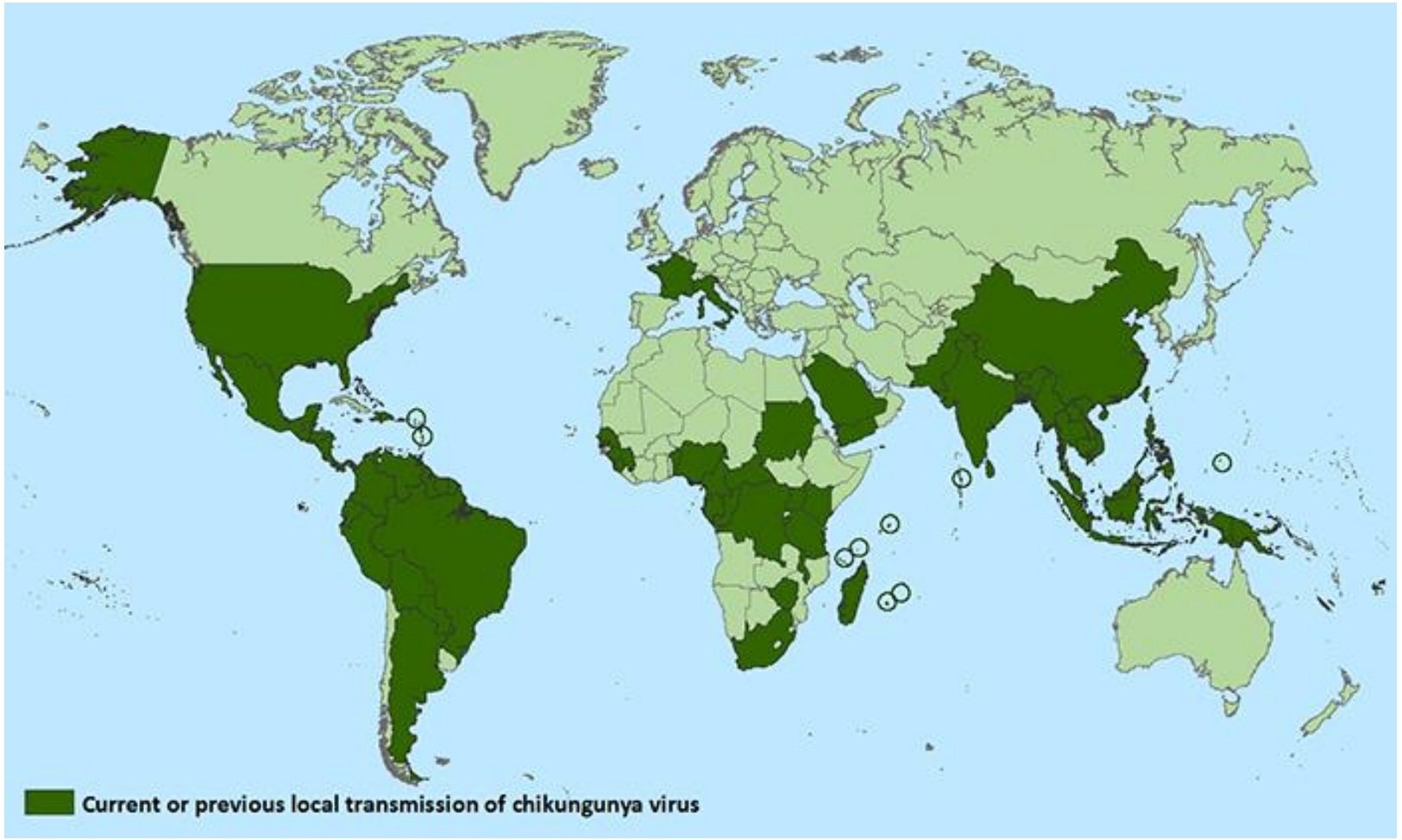
- Yellow fever
- Vaccinated individuals can donate blood that contains vaccine virus

MMWR 2010 59(02);34-37

CDC

Arboviruses to watch

- Chikungunya



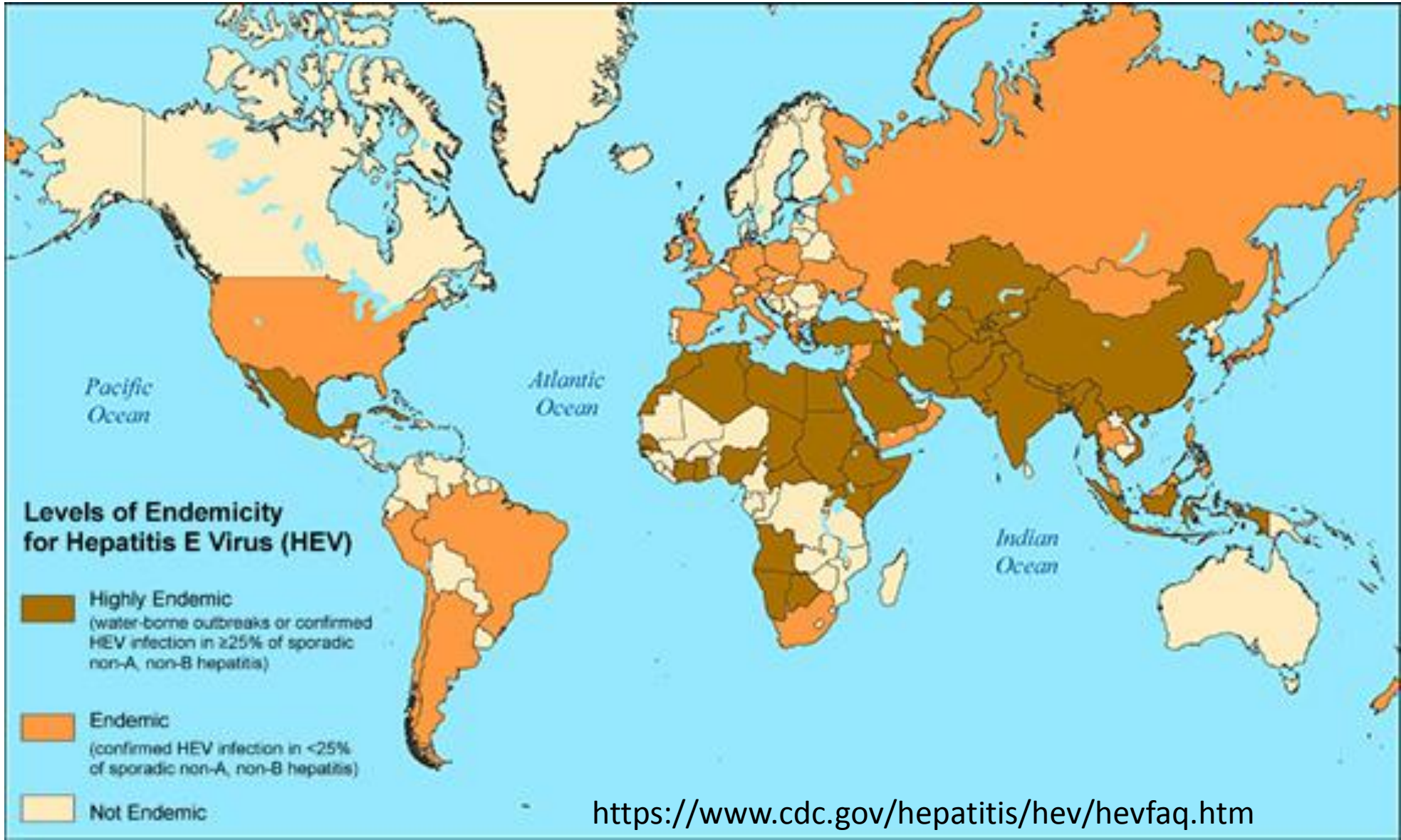
CDC

Arboviruses

- Likely a continual issue
  - Climate
  - Travel
  - Population density
- Zika is unusual in its association with microcephaly
- Yellow Fever, Dengue, Chikungunya have the potential for transfusion transmission

Hepatitis E

- Positive-sense single-stranded non-enveloped RNA virus
- Four Genotypes (Type 3 is common in North America)



https://www.cdc.gov/hepatitis/hev/hevfaq.htm

Hepatitis E

- Transmission is mostly food-borne or fecal-oral
- Usually asymptomatic, with some patients have usual hepatitis symptoms (fever, nausea, vomiting, jaundice)
- Self-limited unless immunocompromised or pregnant
- Worldwide, 56,600 deaths per year
- Potentially treatable with ribavarin

https://www.cdc.gov/hepatitis/hev/hevfaq.htm

Hepatitis E

- Transmission from transfusion has been documented in Europe, Japan and the middle east

- Transplant recipients can develop fatal complications from transfusion-transmitted HEV
  - Liver abnormalities (elevated AST/ALT) can lead to a misdiagnosis of GVHD in allogeneic hematopoietic stem cell transplant recipients

- Patients with compensated liver failure

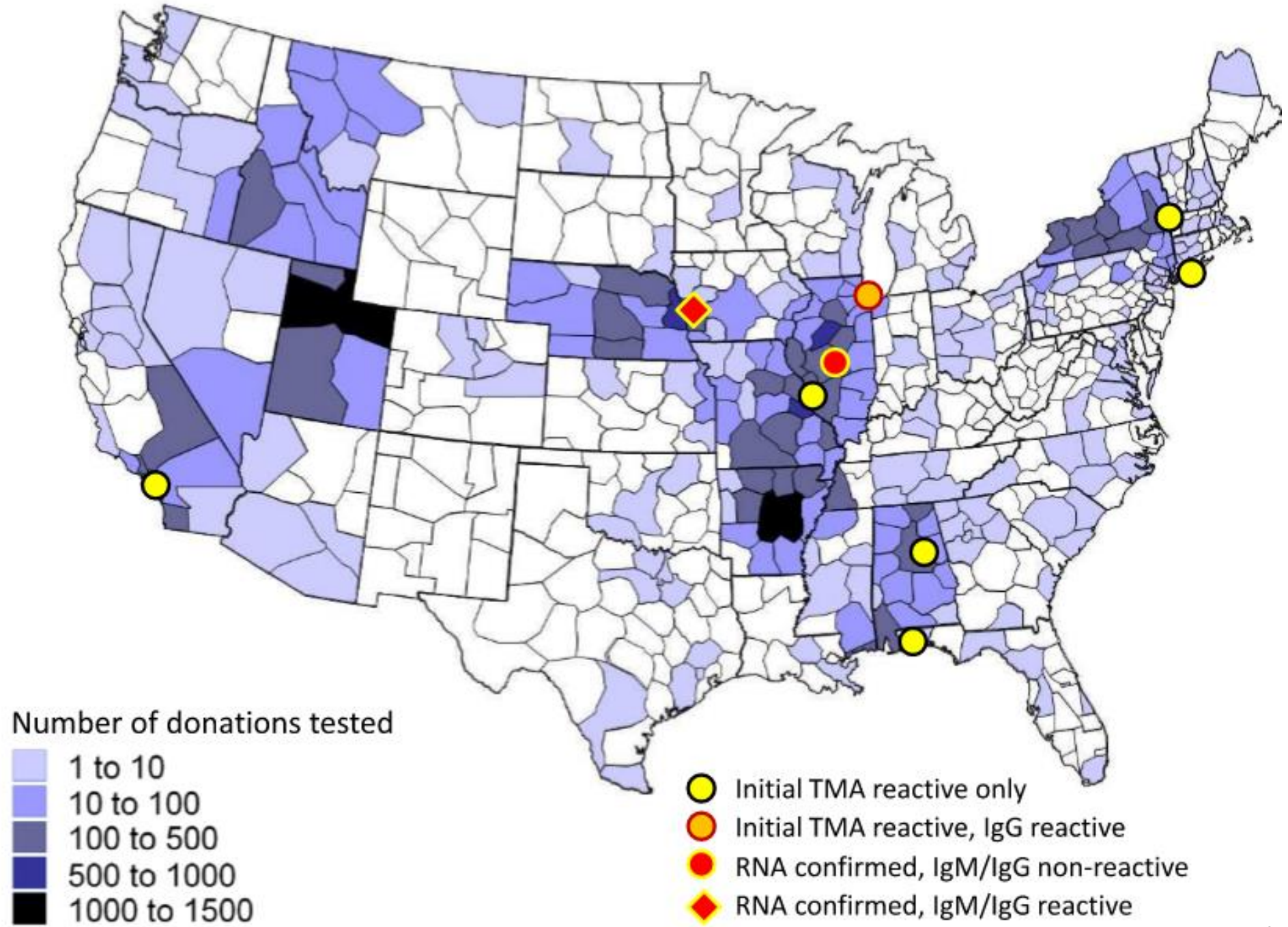
Blood 2013 122:1079-1086

HEV RNA and confirmatory results

#	US Region	Procleix HEV Assay Results (S/CO)				Sanquin PCR Results			Antibody Results (S/CO)		
		Initial	Test 2	Test 3	Test 4	Test 1	Test 2	IU/mL Estimate	HEV ELISA 4.0 (total)	HEV IgM ELISA 3.0	HEV ELISA (IgG only)
1	Northeast	4.29	0	0	NT	Neg	Neg	--	0.206	0.191	0.112
2	Los Angeles	1.96	0	0.06	NT	Neg	Neg	--	0.020	0.558	0.106
3	Southeast	1.14	0	0.05	0.06	Neg	Neg	--	0.025	0.116	0.237
4	Southeast	33.94	0	0.2	0	Neg	Neg	--	0.022	0.255	0.216
5	**Midwest**	**1.59**	**3.24**	**9.15**	**0.05**	**Pos**	**Pos**	**14**	**0.017**	**0.151**	**0.049**
6	**Midwest**	**6.27**	**0**	**0**	**0**	**Neg**	**Neg**	**--**	**9.651**	**0.141**	**3.564**
7	Northeast	3.24	0	0	0	Neg	Neg	--	0.017	0.142	0.088
8	**Midwest**	**6.36**	**0**	**0.23**	**0**	**Pos**	**Neg**	**--**	**10.152**	**10.096**	**6.313**
9	Midwest	1.03	0	0	0	Neg	Neg	--	0.017	0.046	0.033

18,829 donations TMA screened (Procleix HEV Assay) from six different regions of the US with 9 TMA initial reactives and two confirmed positive (i.e., 1 TMA repeat reactive and PCR positive, and 1 initially TMA reactive and PCR positive in 1 of 2 replicates).

Prevalence is based on the two confirmed positives and equals 1:9500 (95%CI:1:2850-1:56,180). One additional TMA initial reactive was IgG reactive. Stramer et al. Transfusion 2016



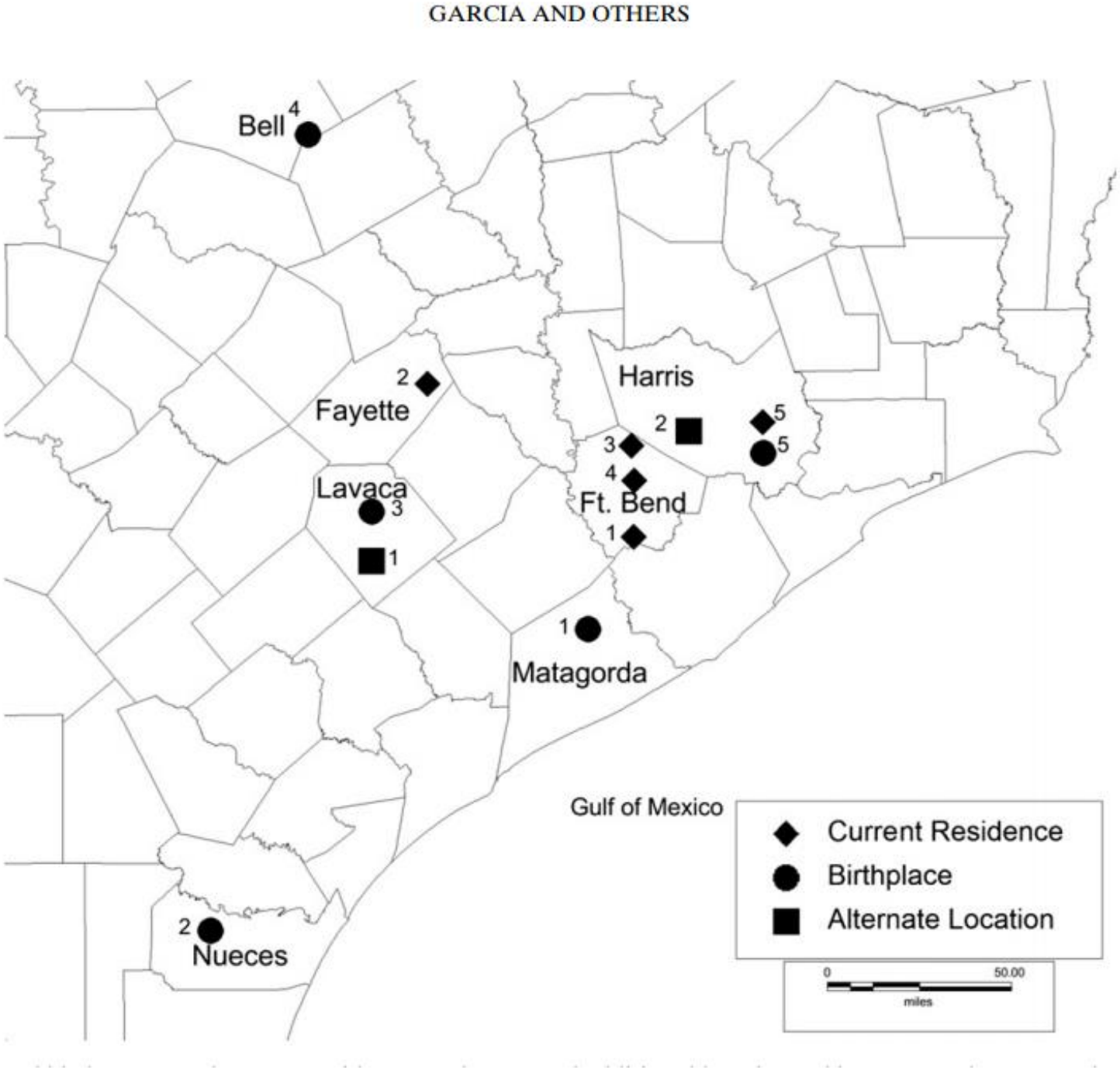
Stramer et al Transfusion 2016

Hepatitis E

- Present in blood donations, with an estimated 544 to 952 donations with Hepatitis E viremia in the USA
- No licensed screening test
- No licensed diagnostic test
  - Under-recognized clinically
- Not effectively inactivated with pathogen reduction techniques

Chagas disease

- Possible autochthonous Chagas disease in Texas?
- Testing the first donation for Chagas antibodies relies on no autochthonous transmission of disease

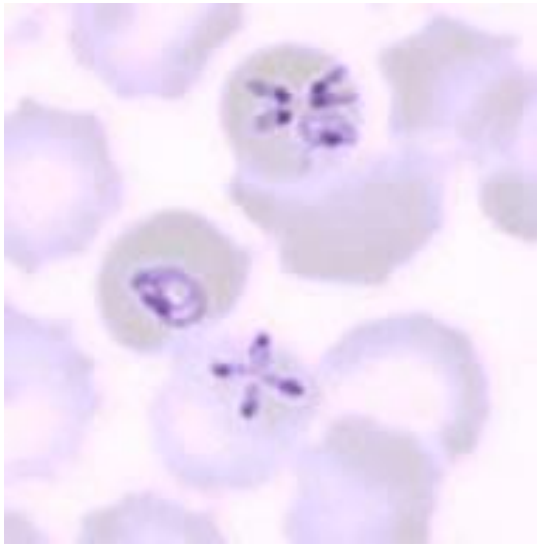


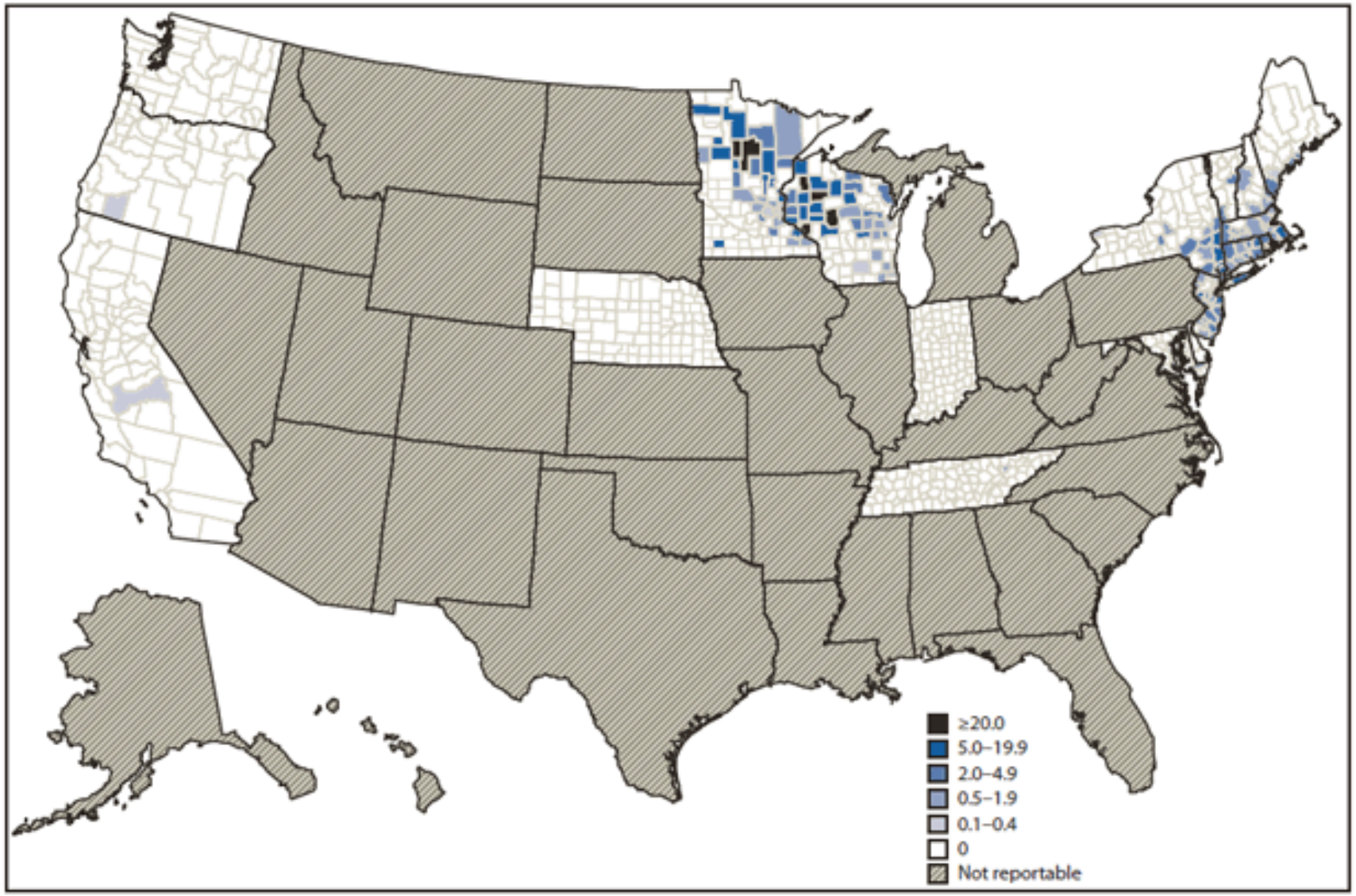
Am J Trop Hyg 2015

Chagas disease

- In 11-2016, FDA issued an Amendment to Guidance for Industry on Chagas
  - Recommends that one time testing alone is sufficient to protect blood supply
  - No questions of donor are needed
    - Most donors did not know their status and the question proved to be of very low yield
- Should autochthonous transmission become a reality, more frequent testing may be required

Babesia





Babesia

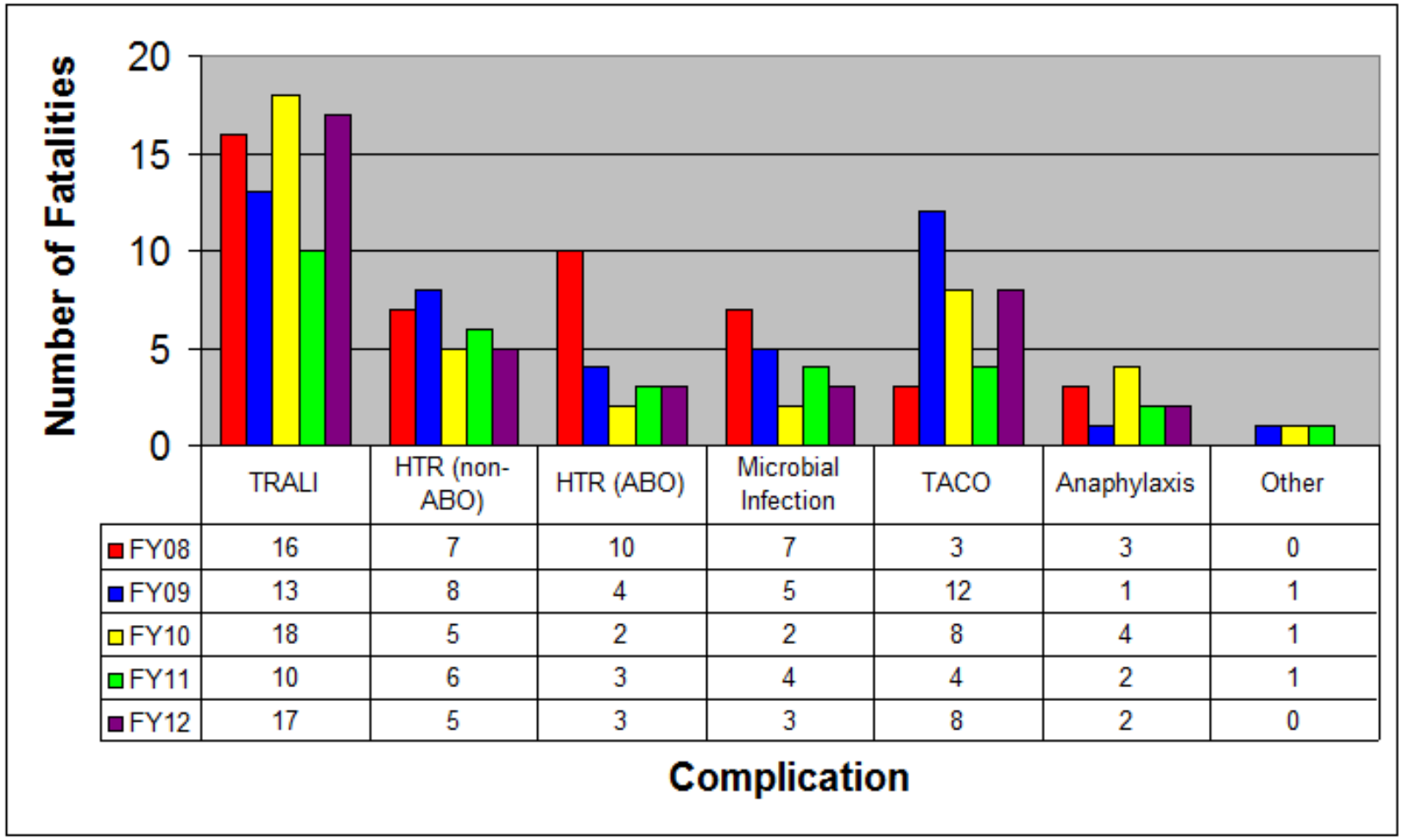
- 165 reported cases of transfusion-transmitted babesiosis
  - Hematologic (19%), neonate (10%), Cardiovascular (8%), GI (6%)
  - 32/165 died, 25 of which was due to Babesiosis
  - Usually due to RBC transfusions

Transfus Med Rev 2016

Babesia

- FDA Blood Product Advisory Committee recommended nationwide year-round antibody screening in addition to NAT screening in high-risk states
- No licensed tests available
- Regional disadvantages for some blood suppliers

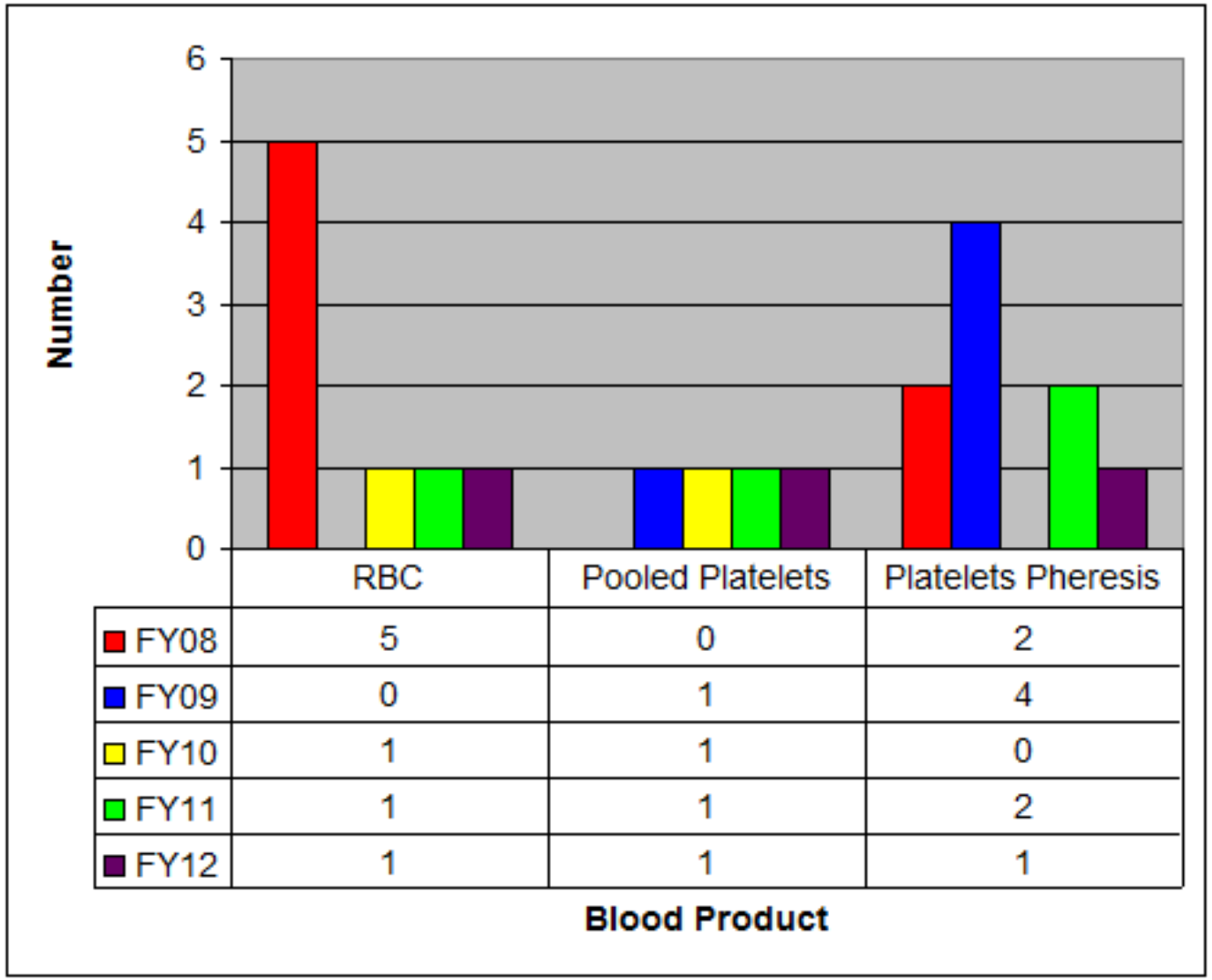
Tranfusion-related fatalities



	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY08	16	7	10	7	3	3	0
FY09	13	8	4	5	12	1	1
FY10	18	5	2	2	8	4	1
FY11	10	6	3	4	4	2	1
FY12	17	5	3	3	8	2	0

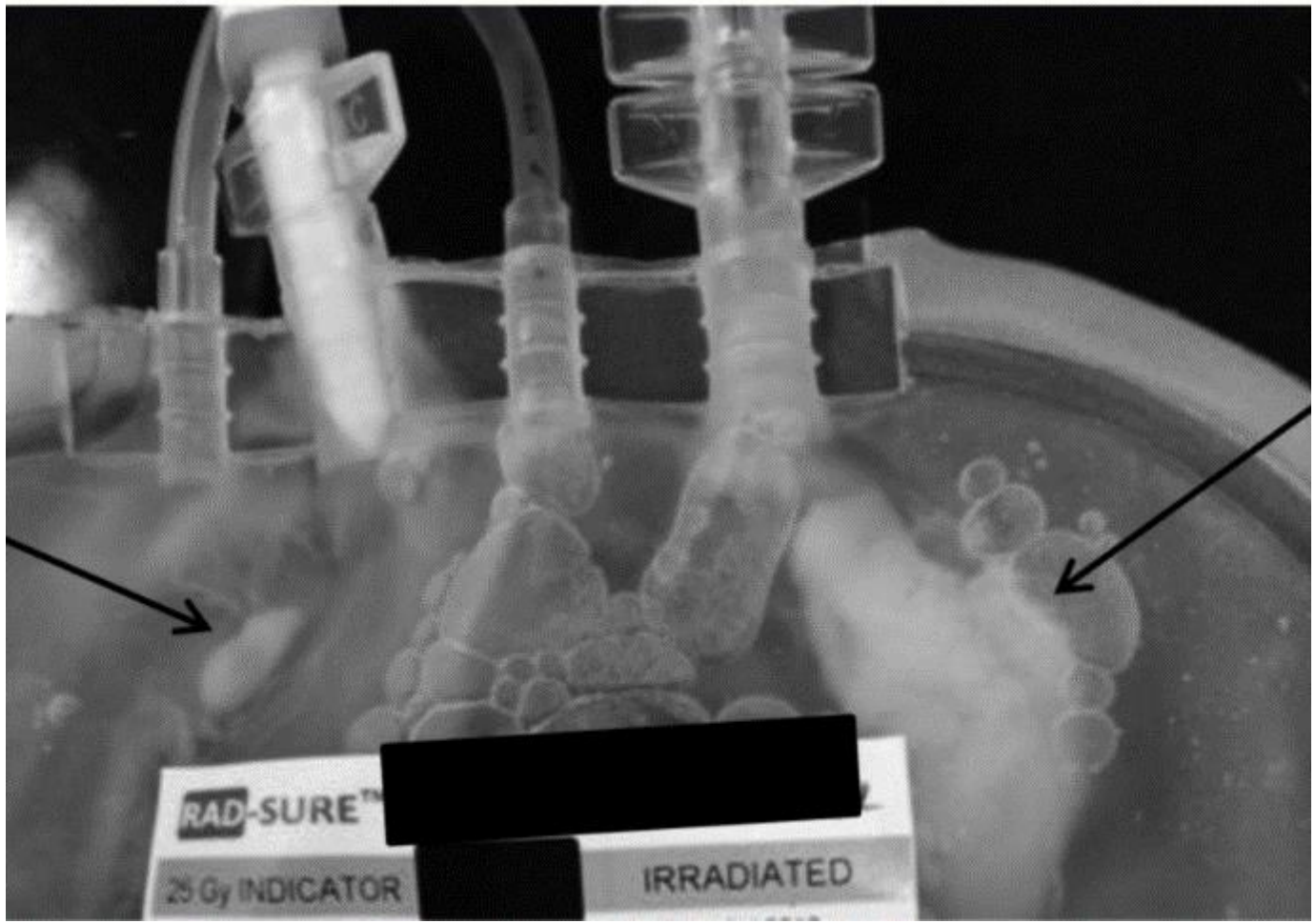
FDA

TTD bacterial deaths



	RBC	Pooled Platelets	Platelets Pheresis
FY08	5	0	2
FY09	0	1	4
FY10	1	1	0
FY11	1	1	2
FY12	1	1	1

Bacteria



Loza-Correa et al. Transfusion 2017

Bacteria

- FDA guidance for apheresis platelets for blood collection services
  - Pathogen reduction
  - Culture-based testing
    - Cx no sooner than 24 hours after collection
- FDA guidance for apheresis platelets for transfusion services
  - Purchase PR platelets
  - For cultured platelets
    - On day 4 or 5, perform rapid testing of unit or
    - Culture platelet on day 4, for at least 12 hours

FDA

Summary

- Global factors are changing transfusion-transmitted disease risk
- The FDA has reacted to emerging threats with zero-tolerance approaches with major economic implications
- New technologies and tests are being developed and implemented to keep our blood supply safe

Blood Suppliers

- Donor education material and donor health questions require updates and can initially be the first response to a new infectious threat
  - Questionably efficacy

- Adding new screening tests is costly, time consuming, and requires significant workflow changes/validation

- The FDA has required unlicensed testing with Zika

Blood Suppliers

- Educating clients
- Blood supply is not always local with significant movement of products at the regional/national level
- To PR or not to PR? Limiting collection to double units?
- Should we have a universal travel deferral?

Transfusion Services

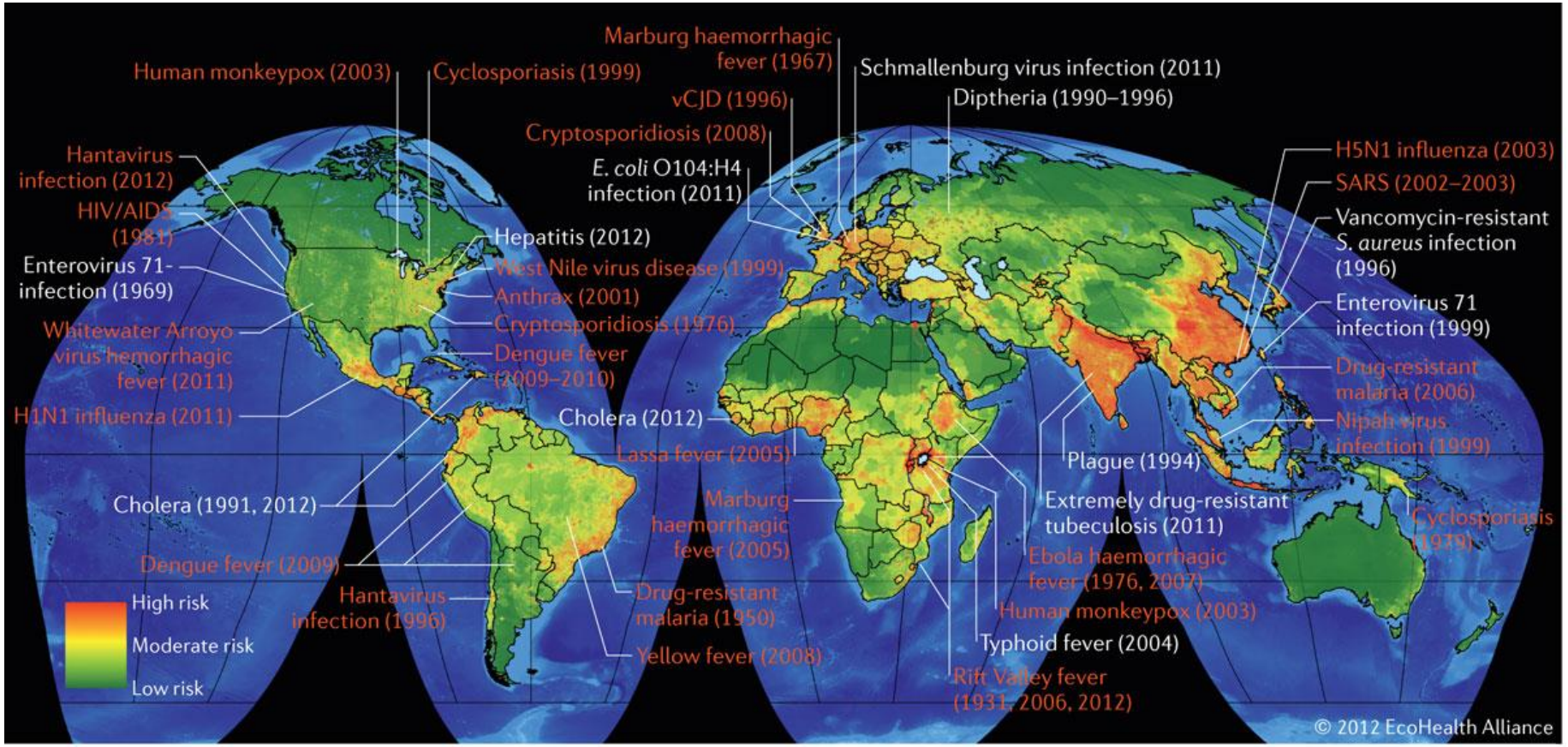
- Added testing or pathogen reduction strategies affect budget
- Pathogen reduction may be useful to combat emerging diseases, but is there a trade off in efficacy or reactions?
  - No licensed RBC technology yet
- Complex FDA guidance like issued for bacteria can present significant challenges in terms of workload and budget

Transfusion Services

- Little or no information for clinicians who consent recipients
  - Education is important

- Suspected transfusion-transmitted diseases cannot always be routinely tested
  - Zika and Hep E

Questions?



Nature Reviews | Microbiology