



**American
Red Cross**

**Reducing Babesia and Malaria Risks:
*Testing, Donor Selection, Inactivation***

Susan L. Stramer PhD

IPFA 23rd Meeting

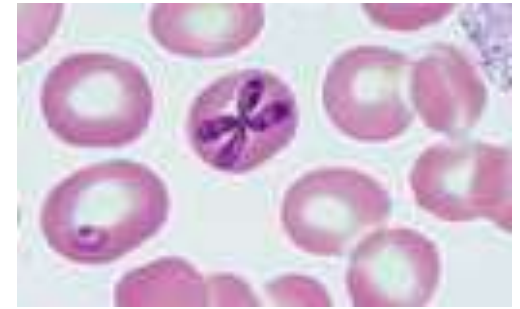
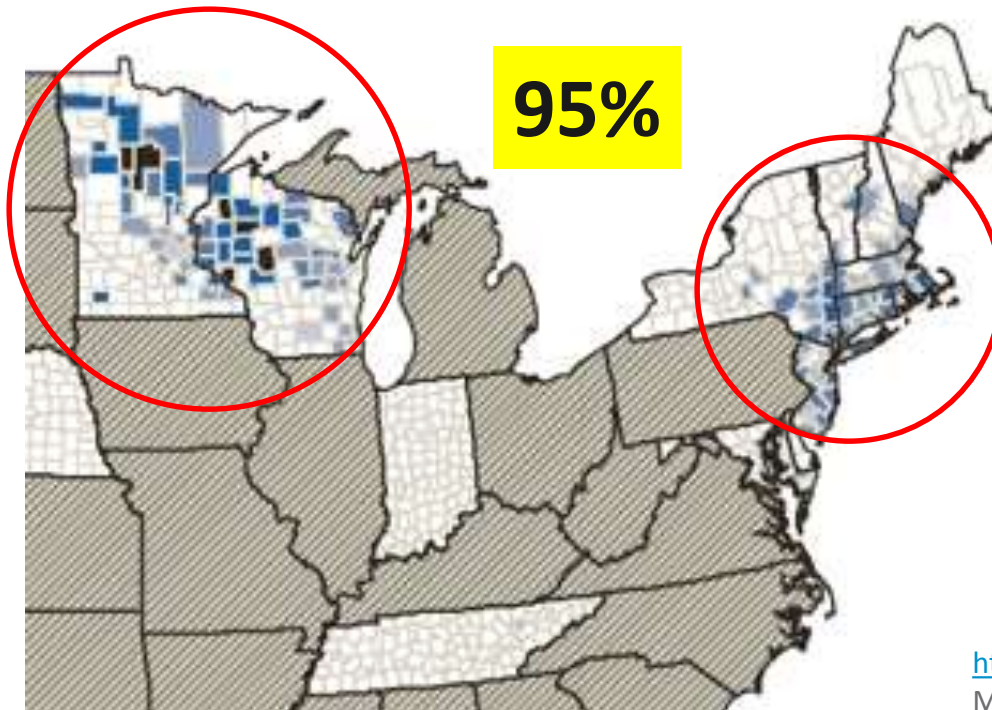
May 26 2016

Babesiosis

- **Malaria-like illness caused by babesia spp.**
 - Asymptomatic → fatal
 - Non-specific symptoms (malaise, fever, etc.)
 - Hemolytic anemia
 - Onset 1-9 weeks after exposure
- **General mortality 5-9%**
 - 21% immunocompromised
- **At risk:** infants, elderly, immunocompromised, asplenic, red cell disorders
- **However, risk groups not limited to above**

Babesia microti

- *B. microti*
 - Intraerythrocytic parasite
 - Tick-borne; transfusion-transmitted
 - Most frequent cause of TT fatalities reported to FDA
- **7 endemic states:** CT, MA, MN, NJ, NY, RI, and WI



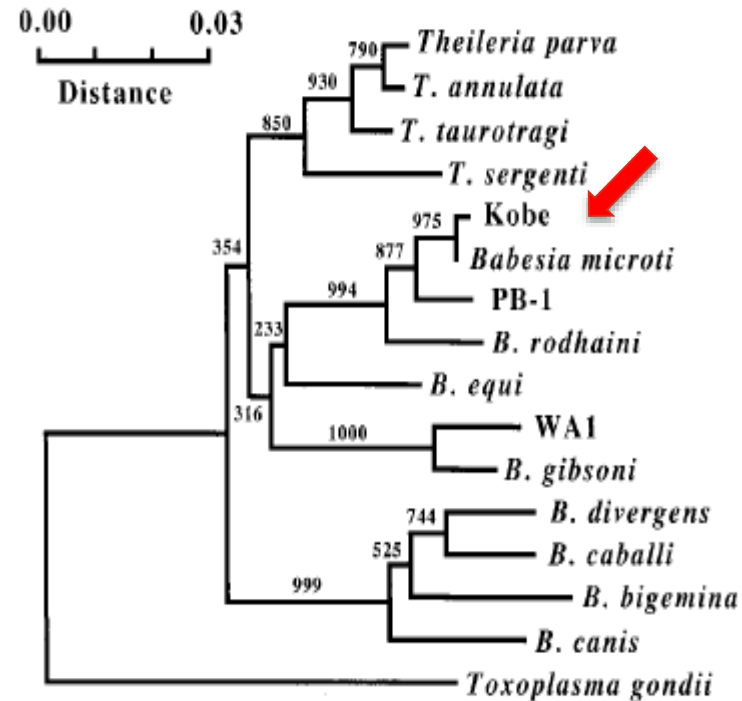
http://www.cdc.gov/parasites/babesiosis/gen_info/index.html

MMWR, Babesiosis Surveillance, 18 states

Incidence of reported cases of babesiosis by county of residence (2011)

Outside of the US

- Reports of babesiosis worldwide (>100 babesia spp):
 - Japan, China, Taiwan, Europe, S Africa, S America, Australia
 - 39 human cases published in Europe; all clinically severe and involved immunocompromised patients
 - *B. divergens* (mainly a bovine parasite)
 - *B. venatorum* (EU1), and *B. microti*
 - *Babesia* variants Korea (KO1), Taiwan (TW1)
 - ***B. microti*-like transfusion transmission** in Japan - donor presumably infected in Japan
- 
- Canada – 1999 first reported case babesiosis; in 2001, TTB case reported;
 - RBCs transfused @ 6 mos following the implicated donor's travel to Cape Cod, MA
 - Donor PCR pos/Ab pos (IFA 1:1024) at follow-up



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
 - Asymptomatic or mild in healthy individuals (e.g., blood donors)
- **Potential screening: questions re tick exposures**
 - Up to 9% of donors regionally report tick bites*
 - No difference in positive donors vs controls
 - Infected patients often do not recall tick bites
- **Potential screening: laboratory testing**
 - Antibody and DNA

*Leiby et al. Transfusion 2002;42

The tick that gives you Lyme Disease is smaller than a poppyseed.

www.TickEncounter.org



Deer tick nymphs



Think TICK...
Take ACTION!

TickEncounter Resource Center

Possible Results – Infectious Stages

- **PCR pos/Ab neg:** Early stage infection
 - “Window period”
 - Parasite is present; no immune response yet; **infectious**
- **PCR pos/Ab pos:** Active infection
 - Parasite is present; body has mounted immune response; **infectious**
- **Ab pos/PCR neg:** Resolved infection
 - Parasite has been cleared; antibody remains; **infectivity unknown => likely non-infectious**

Linked Retrospective Testing Results

Aug-Oct 2010 and May-Sept 2011

Moritz et al. Transfusion 2014

Region	No. Screened	No. (%) PCR pos/Ab neg	No. (%) PCR pos/Ab pos	No. (%) PCR neg/Ab pos	Total No. (%) pos
AZ/OK	4022	0	0	1 (0.025)	1 (0.025; 95%CI:0.00-0.14)
MN/WI	4167	0	2 (0.048)	3 (0.072)	5 (0.12; 95%CI:0.04-0.28)
CT/MA	5080	0	5 (0.072)	33 (0.65)	38 (0.75; 95%CI:0.53-1.03)
Total	13,269	0	7 (0.098)	37 (0.28)	44 (0.33)

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

Specificity:

At 1:128, 99.98% (99.86 – 100%)

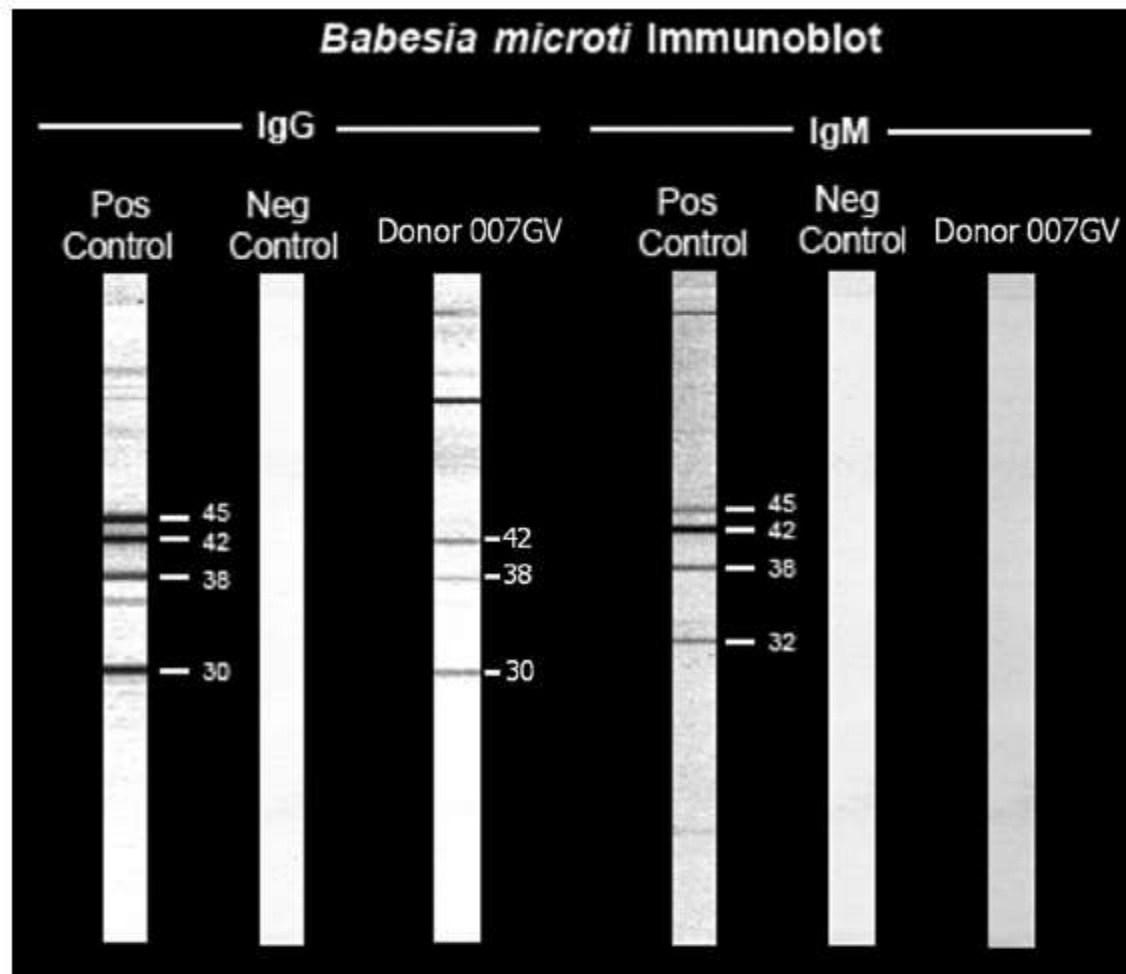


Fig. 4. IgG and IgM WBs of positive and negative controls and the index sample from Donor 007GV. To be considered positive on WB, reactivity to the 30-kDa protein was required in addition to reactivity to two additional proteins of 38, 42, or 45 kDa. The origin of this donor's reactivity is unclear: he lived in New York from 1955 to 1970 and spent time in Pennsylvania and New Jersey in 1968, but did not recall spending time in wooded or grassy areas or finding a tick on his body. He was stationed in Germany from 1975 to 1976, where he reported tick bites. Currently, he reports spending substantial amounts of time outdoors in AZ and owning three "outdoor" dogs and reported flulike symptoms in the past 2 years. Neg = negative; Pos = positive.

ARC Prospective Donor Prevalence to 9/30/14

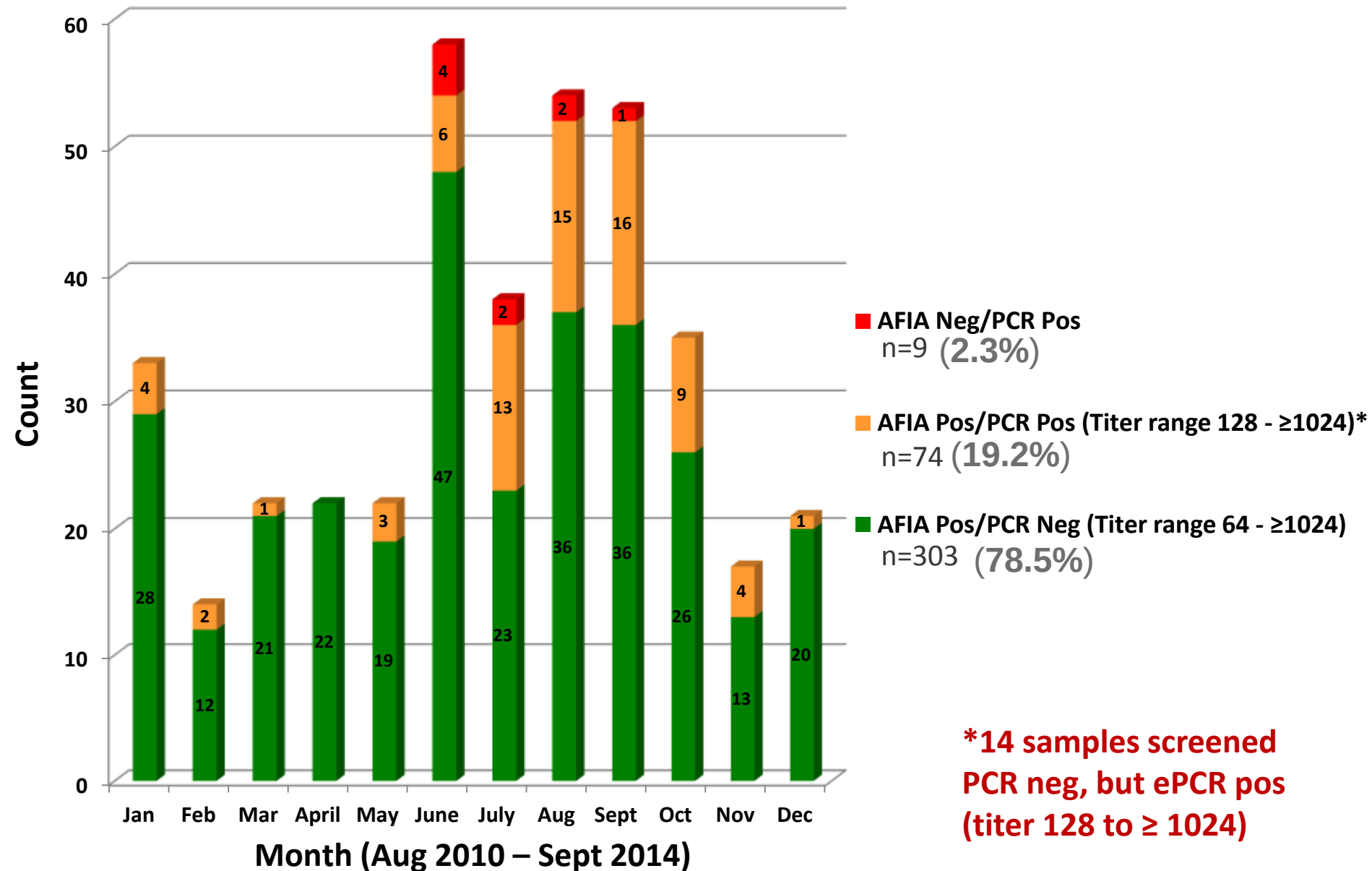
- 339 reactive/89,141 donations screened
 - **0.38%** (95% CI 0.34 – 0.42%)
 - 9 window-period units (0.01%; **1:9,905**)
 - Note: 100-fold higher window-period yield than HIV and HBV; 20-fold higher than HCV
- Minn/Wisc: 13/13,822
 - **0.094%** (95% CI 0.04 – 0.15%)
- Massachusetts: 75/36,266
 - **0.21%** (95% CI 0.16 - 0.26%)
- Connecticut: 251/39,065
 - **0.64%** (95% CI 0.57 - 0.73%)

IND Test Results: 4 endemic states June 2012 – Sept 30 2014

**89,141 donations screened
339 (0.38%) reactive**

~4 of every 1,000 donations are positive for *B. microti*

Number of *B. microti*-Positive Samples by Month (n=386; Retro + Prospective to 9/30/14)



Positive Predictive Value (9/30/14)

Infectious stage	No. confirmed/ No. tested	Confirmation Method	% Positive Predictive Value
Window period (PCR pos/Ab neg)	9/9	Ab seroconversion (AFIA, IgM/IgG WB); repeat qPCR	100
Acute (PCR pos/Ab pos)	74/74*	IgM/IgG WB; repeat qPCR	100
Early resolving (PCR neg/Ab pos ≥512)	72/72	IgM/IgG WB; Ab pos index plasma	100
Late resolving (PCR neg/Ab pos <512)	226/228	IgM/IgG WB; Ab pos index plasma	99
Overall	381/383		99.48

*Includes 14 ePCR pos

Figure 1: Time to First DNA-Negative F/U Sample

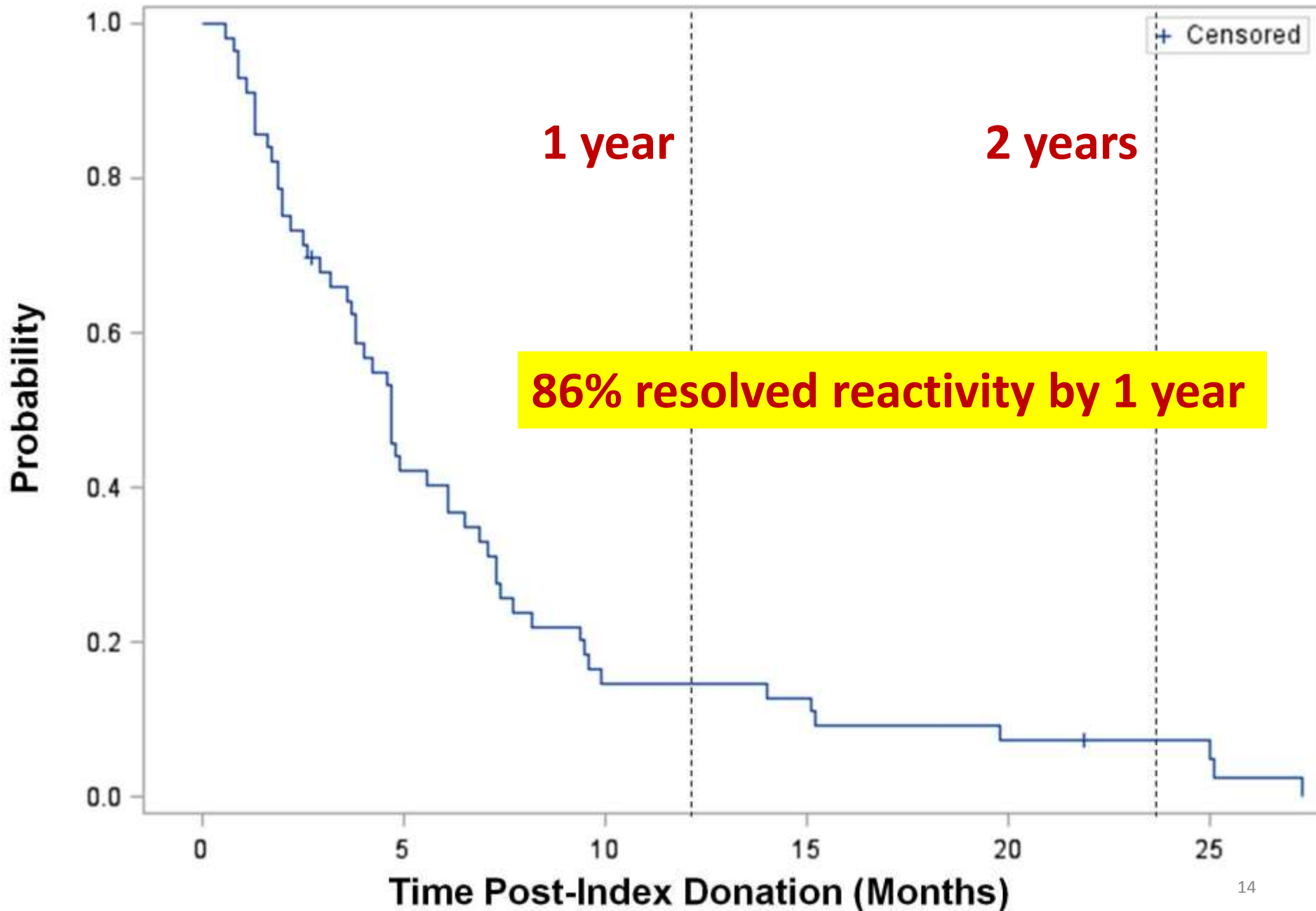
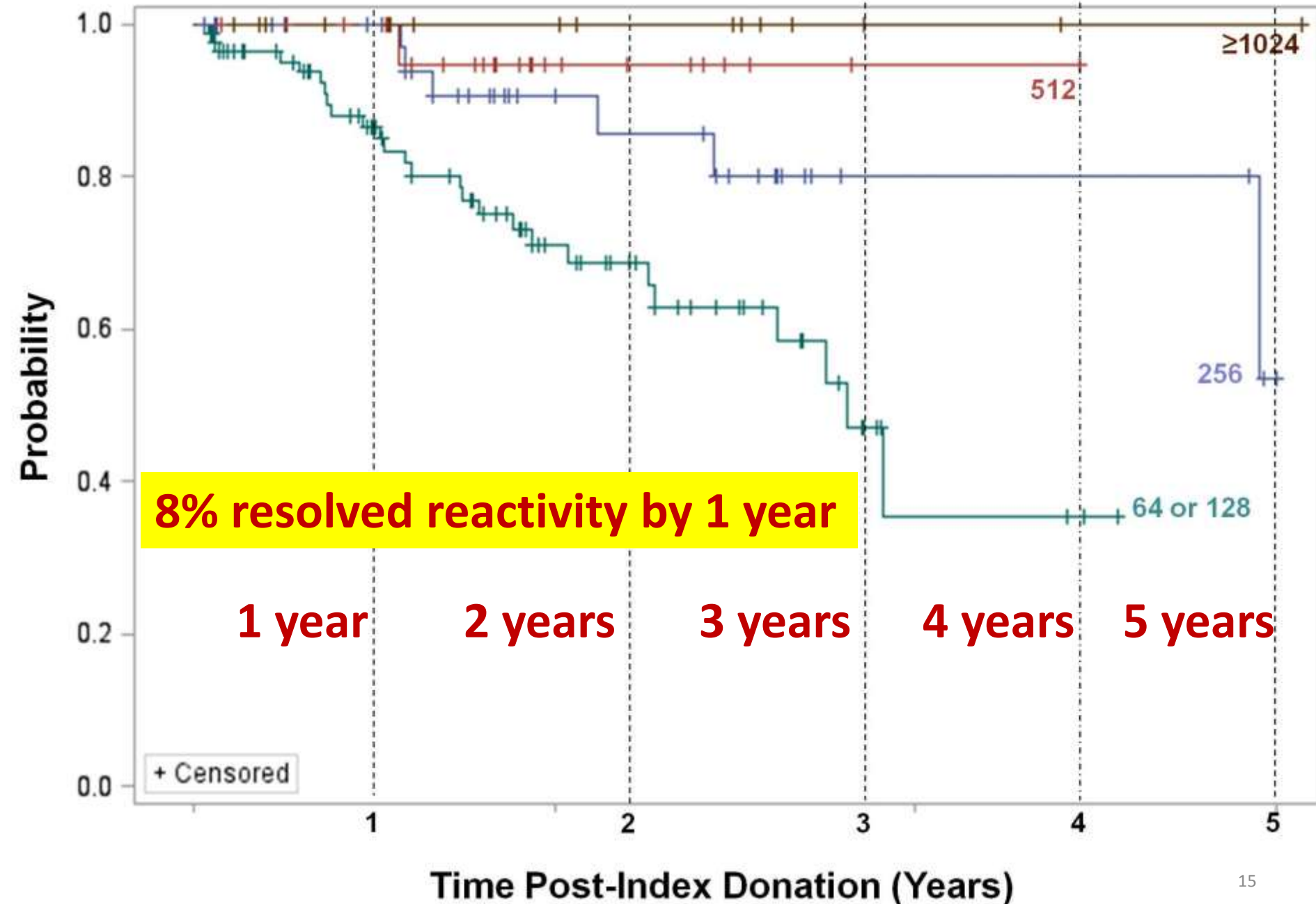
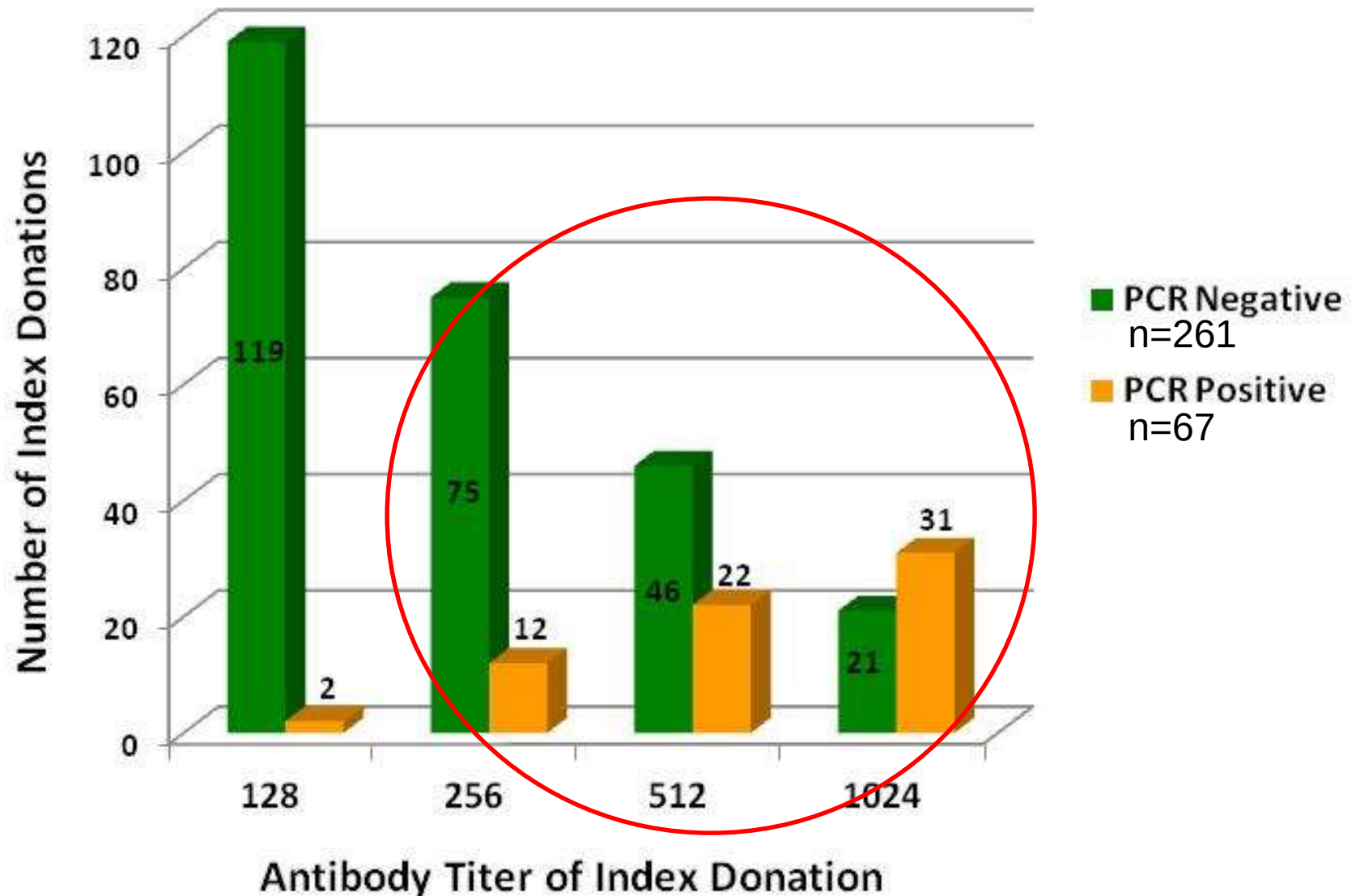


Figure 2: Time to First Antibody-Negative F/U Sample



Number of PCR Positive vs. PCR Negative Donations by Titer



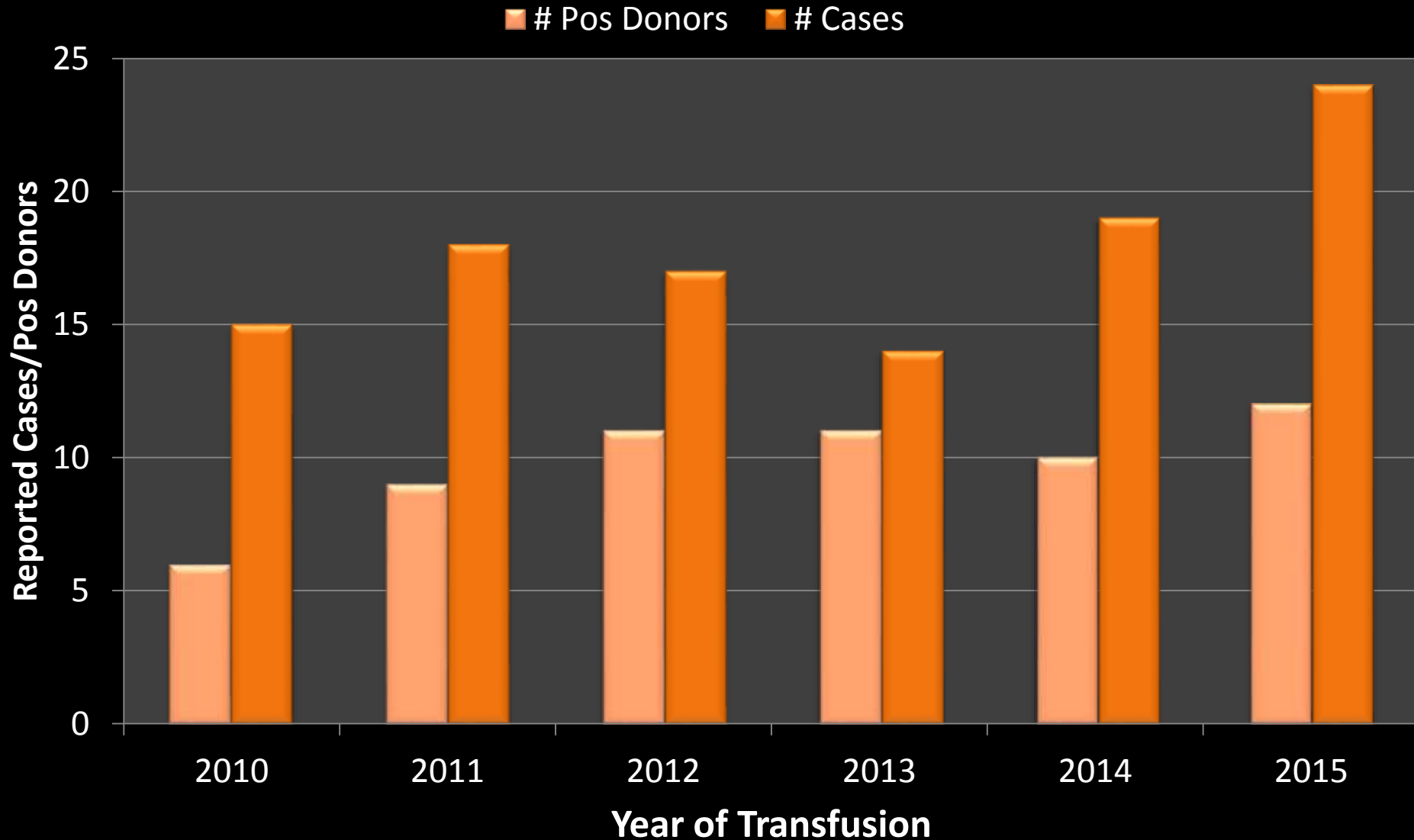
Donations screening PCR neg, ePCR pos: n=1 (titer 128), n=4 (256), n=4 (512), and n=5 (≥ 1024)

Correlation to Infectivity

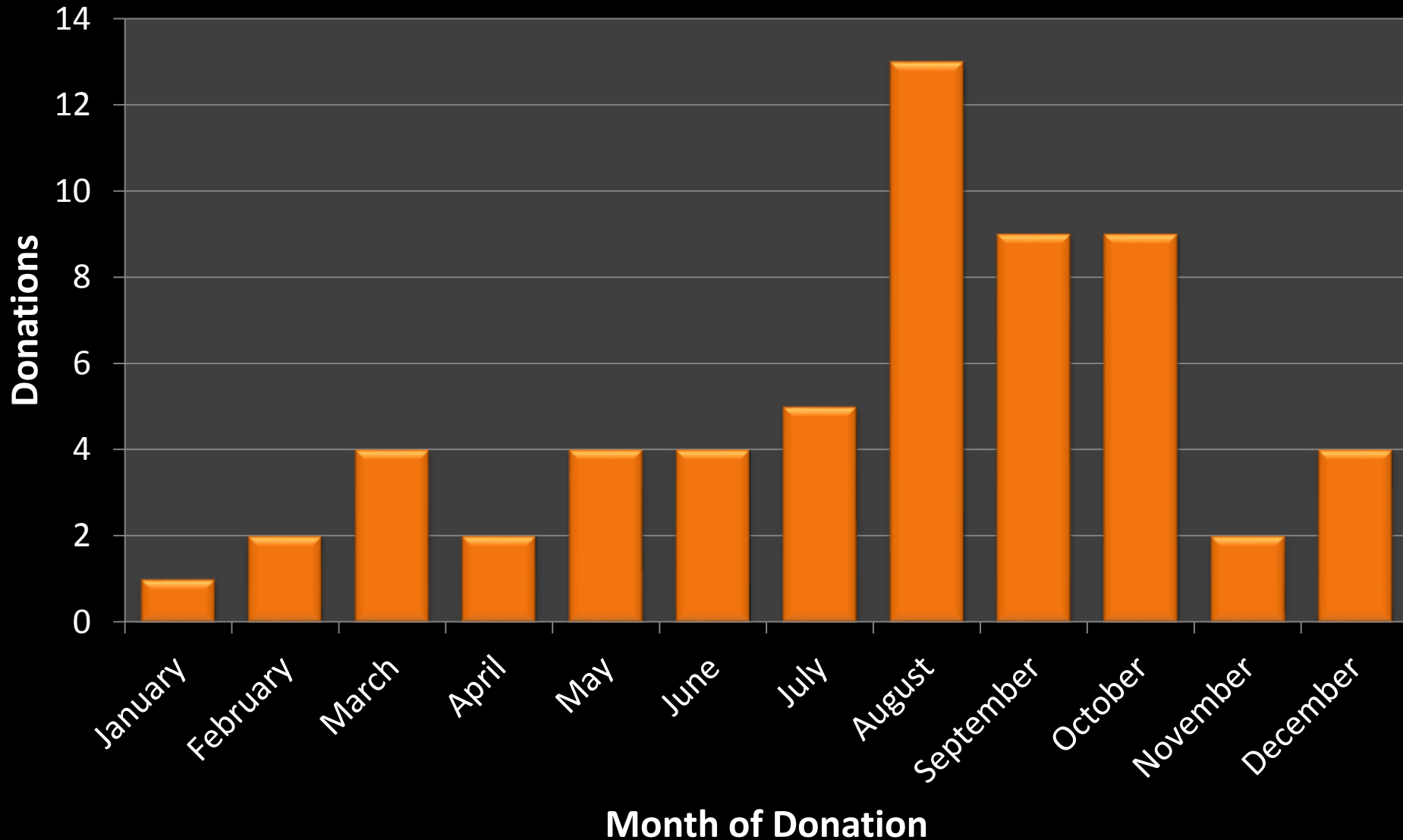
- Hamster inoculation results
 - 27/93 (29%) units infectious in hamsters
 - 25/46 (**54%**) PCR-pos units infectious
 - 7-34 day RBC age (vs 11-55 days noninfectious; $p=0.01$)
 - **2/47** (4%) PCR-neg, Ab high-titer units infectious
 - 9-21 day RBC age (vs 6-69 days noninfectious; $p=0.01$)

AFIA Results	PCR Result	Estimated Parasite/mL	Hamster Infectivity
<1:128	Pos	400	Positive
<1:128	Pos	1,100	Positive
1:512	Neg	N/A	Positive
≥1:1024	Neg	40	Positive

107 suspect TTB cases of which 56 (52%) cases involved 59 confirmed-positive donors; 2010-2015

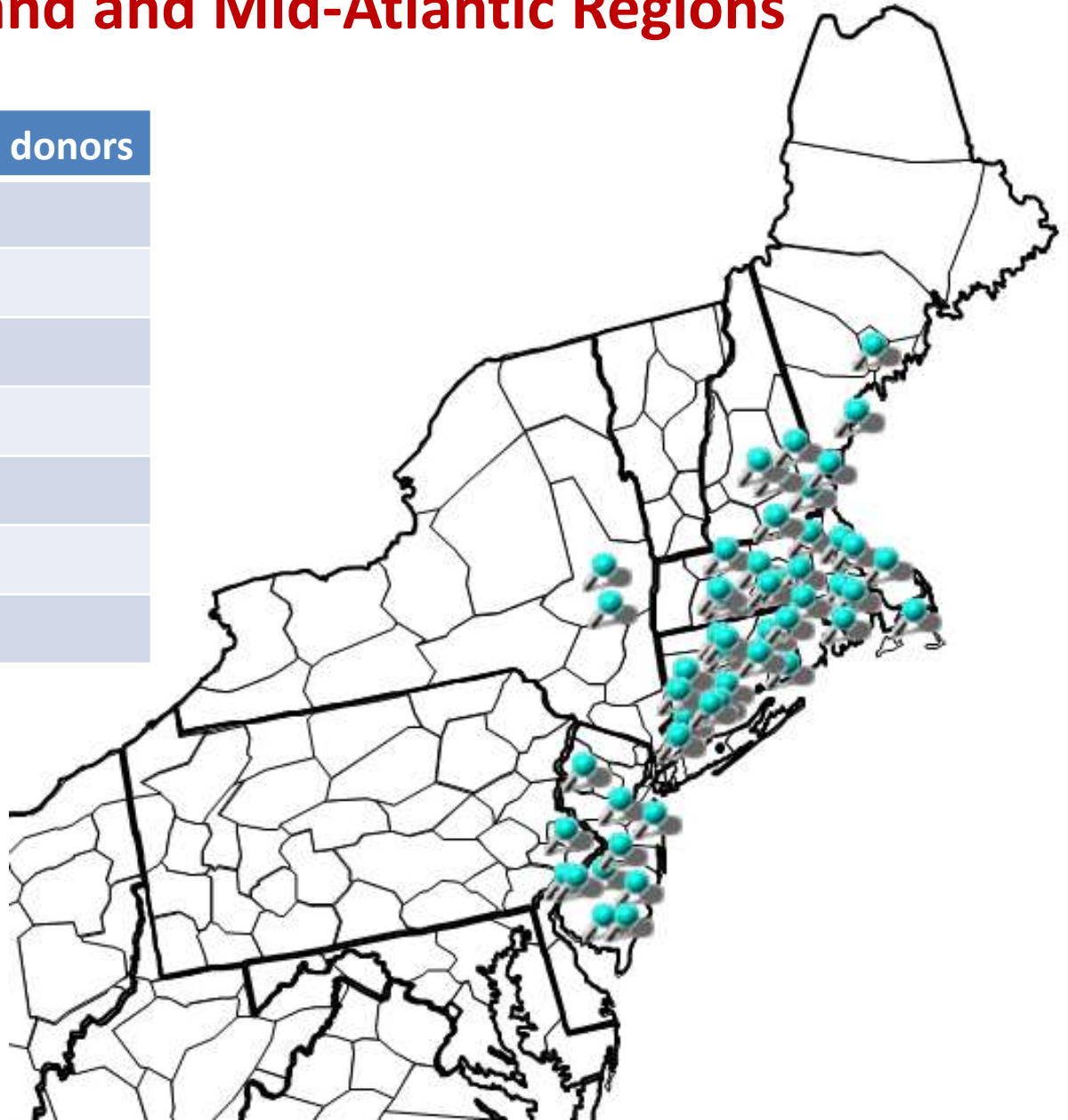


Distribution by month of the blood donation collection dates associated with *B. microti* transfusion cases (N=56) 2010-2015



53 of 59 (90%) Babesia-positive donors with residence in New England and Mid-Atlantic Regions

State	# Positive donors
Connecticut	18
Massachusetts	15
Maine	3
New Hampshire	4
New Jersey	8
New York	2
Pennsylvania	3



TTB Risks – Unscreened Blood

- Based on ARC collections over 28 months (thru Sept 30 2014):
- Within 7 endemic states = 22/2,526,518 or **1/114,387**
- Outside of 7 endemic states = 7/10,359,192 or **1/1,479,885**
- Within 9 endemic states = 28/2,825,414 or **1/100,908 (including NH, ME)**
- Outside of 9 states = **1/10,359,192**

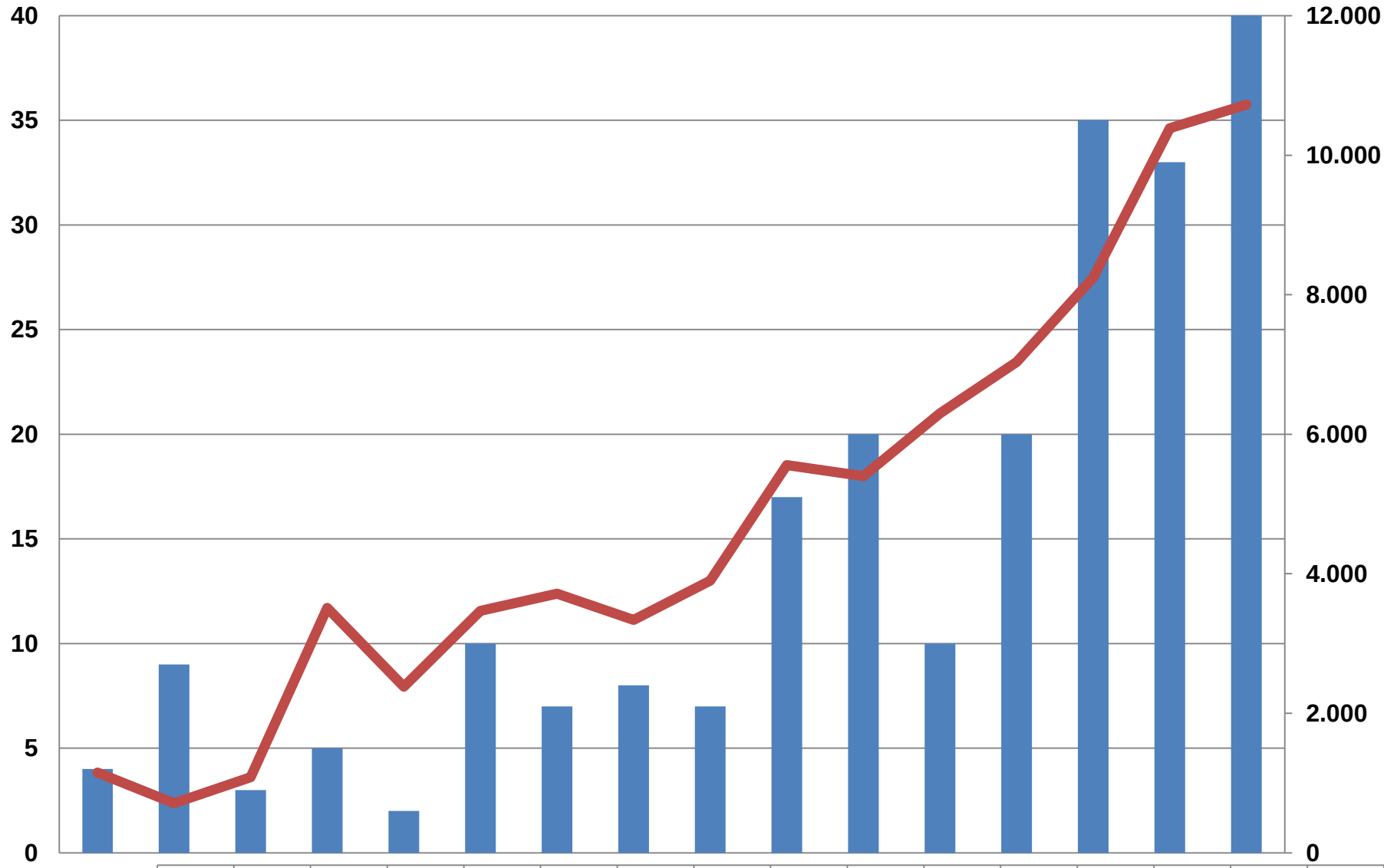
Summary

- Prospective blood donor screening for *B. microti* is feasible and has resulted in **339** units being removed from the blood supply (to 9/30/14)
 - **67** PCR/Ab pos; **9** window units (1:9,905) Ab neg
- Screening has likely prevented TTB
 - **54%** PCR-pos infected hamsters
 - **41** probable TTB cases where/when no screening occurred
 - Same counties/time period: 0/75,331 vs 14/253,031
 - OR: 8.6 [95% CI 0.51-14.4]; p=0.05
 - TTB cases from unscreened blood = all RBCs (8-42 days)
- IND goal: Qualify testing approach to reduce TTB in the blood supply appears to be successful

Current Status

- From June 4 2012 – April 30 2016
 - 598 positive/169,810 samples tested (**0.35%**); CT, MA, MN, WI
 - 553 positive/122,528 samples tested (**0.45%**); CT and MA

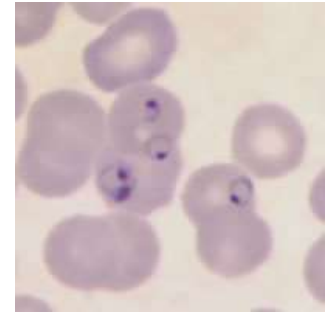
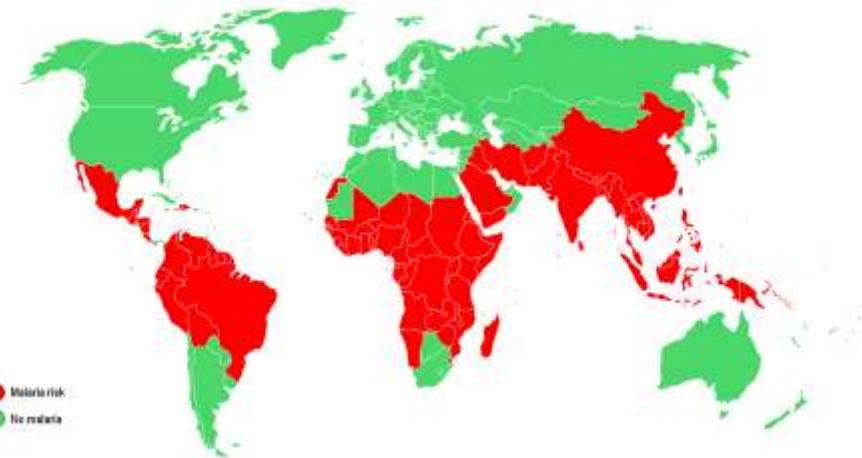
Babesia Testing, Jan 2015 Forward



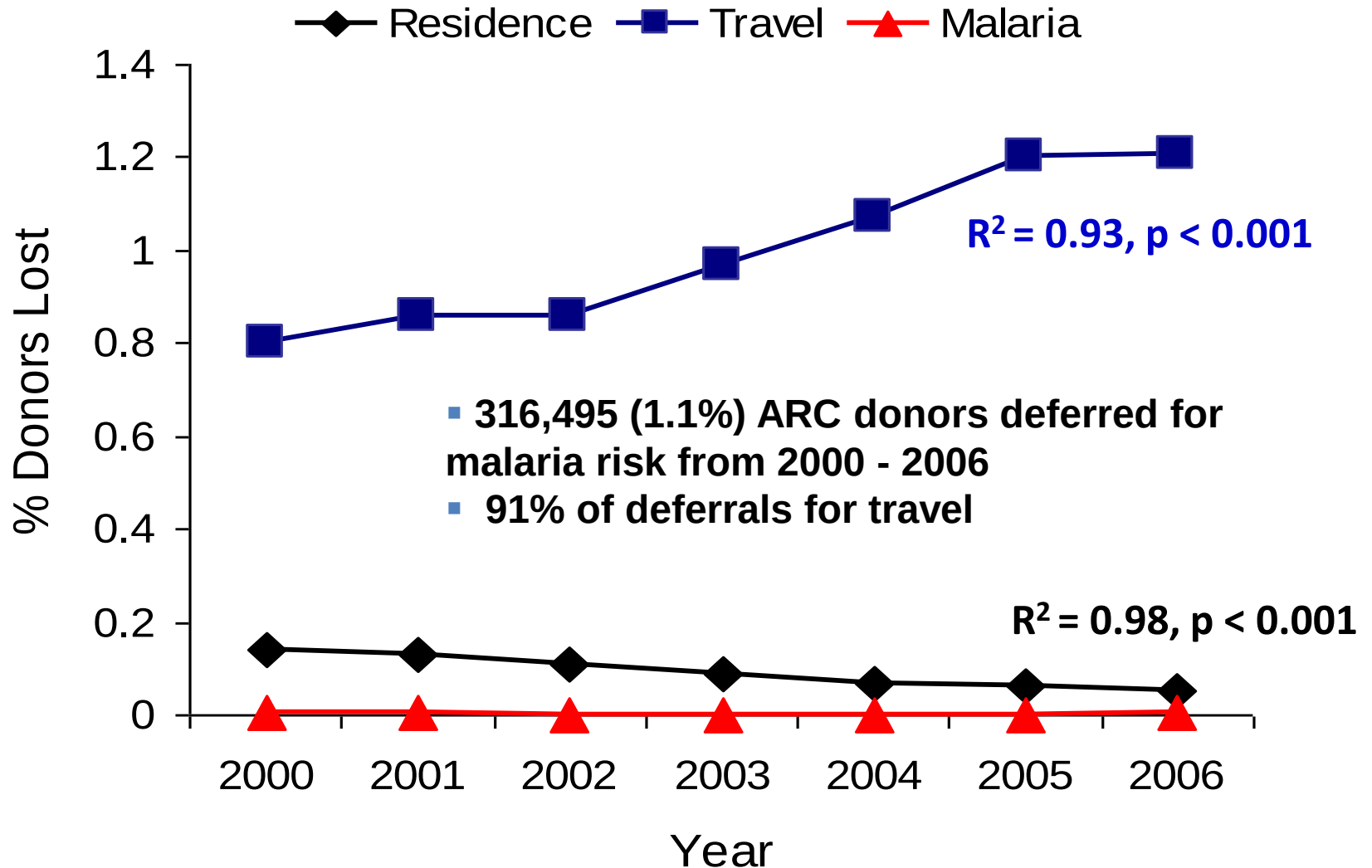
	Jan-15	Feb-15	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16
No. Rx	4	9	3	5	2	10	7	8	7	17	20	10	20	35	33	46
No. Tested	1151	710	1085	3510	2381	3470	3715	3339	3901	5559	5401	6299	7035	8245	10386	10724

Plasmodium spp.

- Agents of human malaria
 - *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* & *P. knowlesi*
- Found inside red and liver cells
- Transmitted by female anopholene mosquitoes
- Usually found in tropical or subtropical areas
 - >200 million cases/year
 - 665,000 to 1.24 million deaths/year
 - > 80% occur in sub-Saharan Africa
 - 90% is *P. falciparum*
 - Periods of fever & chills
- Blood banks
 - challenges differ by country
 - blood safety vs. availability



Donors Lost to Malaria Deferrals



Malaria Deferrals in the US

- Few travelers visit high risk areas of Africa (3.7%)
- Travel to Africa 1,100-fold higher risk than travel to Mexico where most US travel occurs (38%)
 - Relative malaria risks at the end of 12 months after return:
 - 1 per 109,000 Africa
 - 1 per 33 million Mexico
 - Quintana Roo – estimated rate of donor infection:
 - 1 per every 125 years
 - *Spencer et al., Transfusion 2009;49:2335-45*

US Resident Outbound Travel Abroad: 2005-2014

International Trade Administration

Top 5 destinations (travel/million residents):

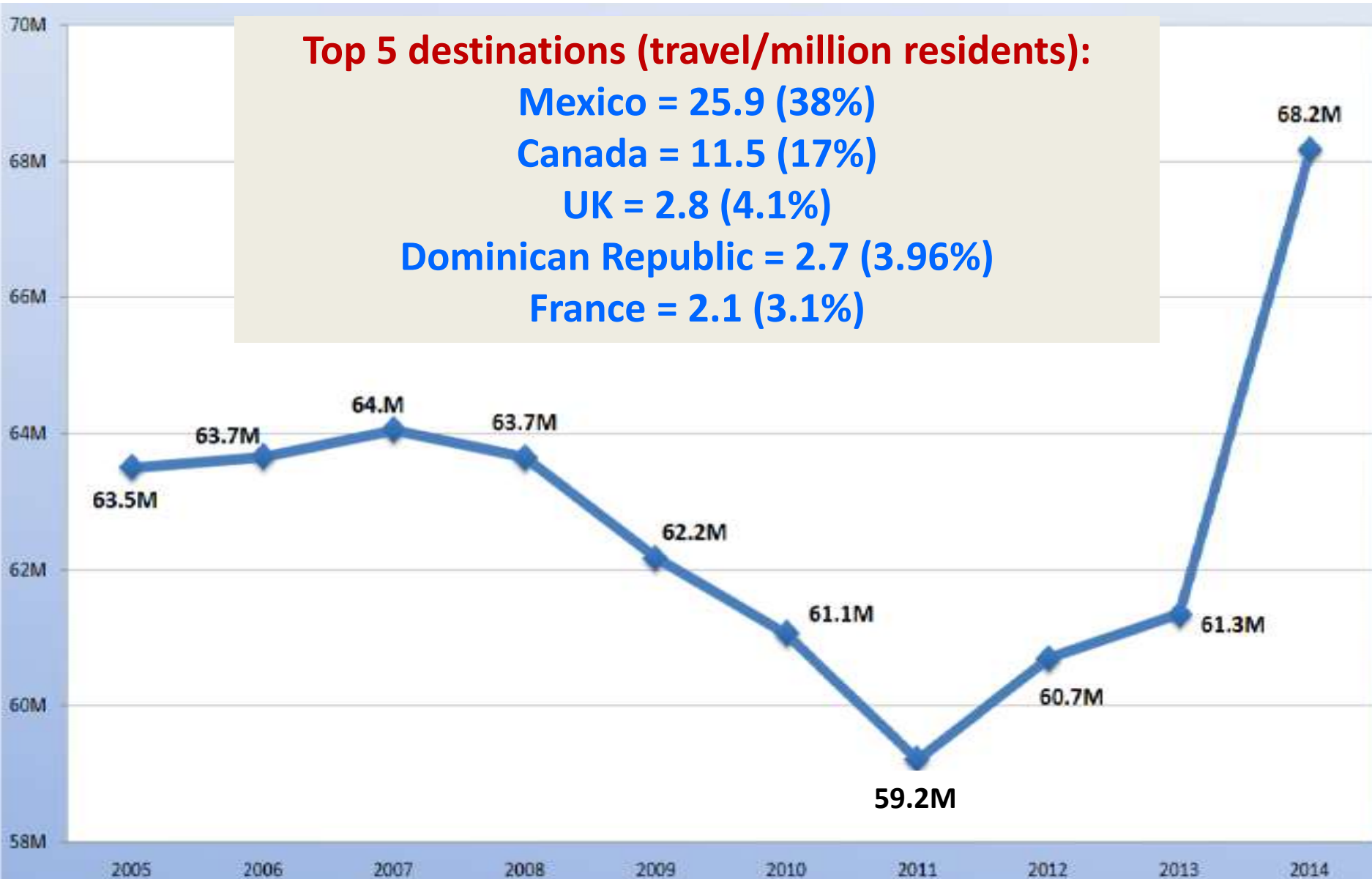
Mexico = 25.9 (38%)

Canada = 11.5 (17%)

UK = 2.8 (4.1%)

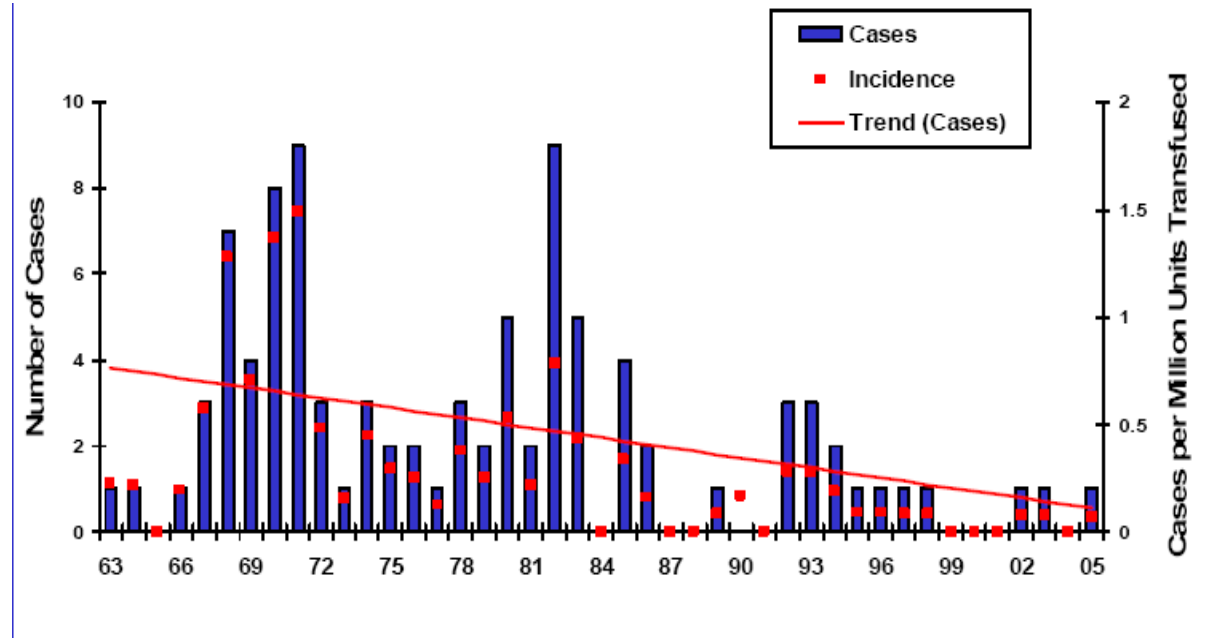
Dominican Republic = 2.7 (3.96%)

France = 2.1 (3.1%)



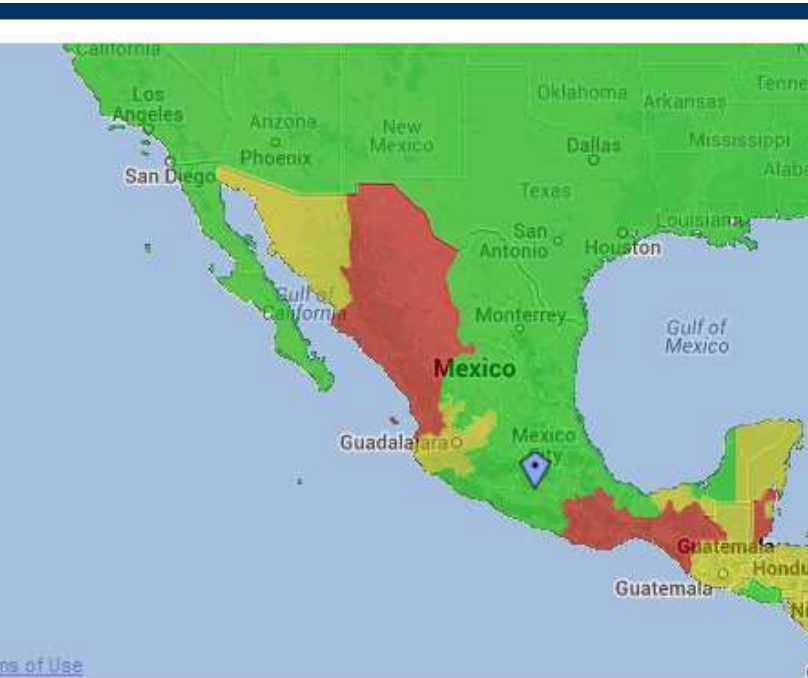
Transfusion-Transmitted Malaria (TTM) in the US

- 93 cases 1963-99*
 - WB:63%
 - RBCs:31%
 - Platelets:6%
- Since: TTM is rare
- Only 7 cases since 2002



- $\geq 2/3^{\text{rd}}$'s of cases attributed to donors with a previous history of malaria (i.e., semi-immune)
 - associated with residence in an endemic country
 - military service in Vietnam

**Mexico endemic areas: according to the CDC
and used by Spencer et al. (*Transfusion* 2011;51:2398-410)
to develop risk modeling based on locally derived malaria risk**



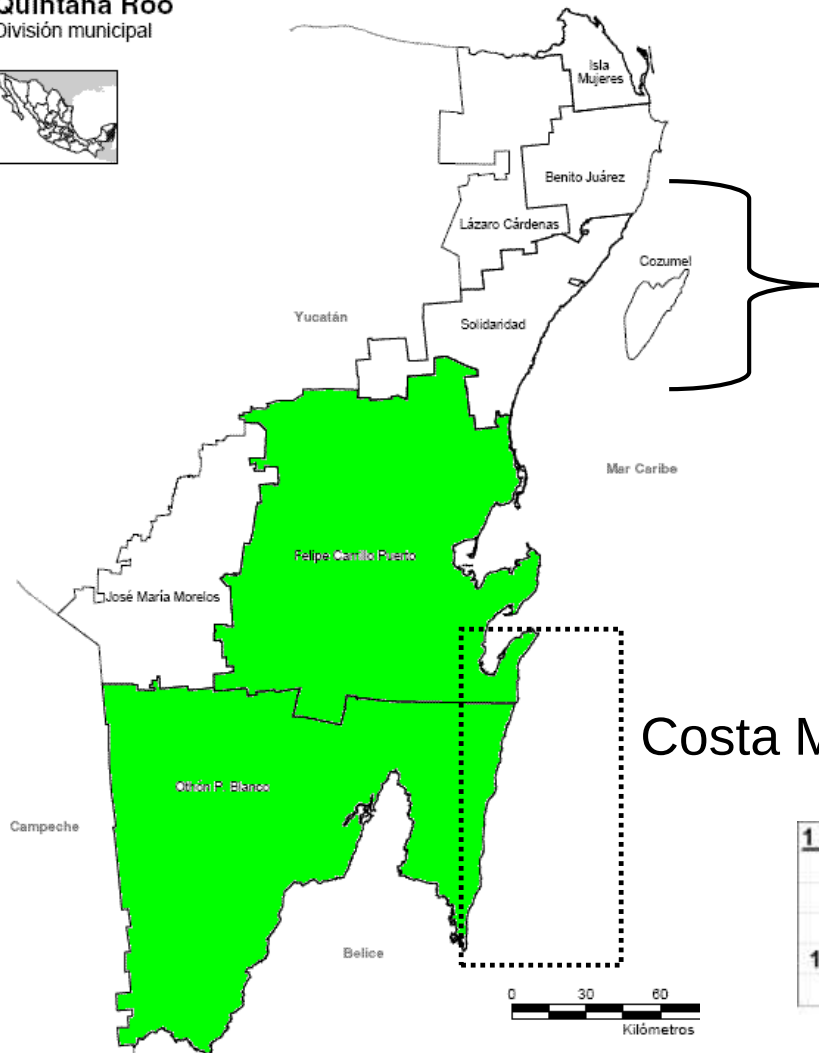
**Malaria chemoprophylaxis recommended for
Chihuahua, Durango, Sinaloa, Nayarit, Oaxaca, Chiapas**

**Most travel (72% deferrals) => Quintana Roo; area w/ very low malaria tx
Eliminating the travel requirement for all but Oaxaca may result in the rescue of
65,000 donors (of a projected 161,000 due to travel in 2006 in the US) and a risk
of ~1 contaminated unit collected every 20 years**

Quintana Roo – Resident risk 2005

72% of total Mexico deferrals for US donors

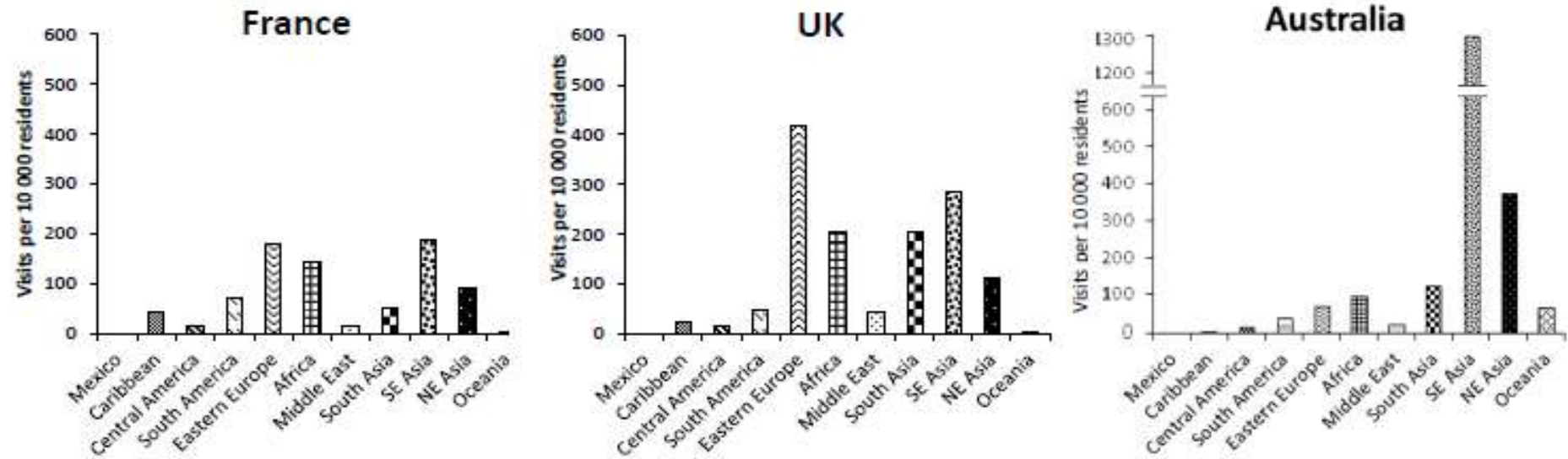
Quintana Roo
División municipal



81% travel deferrals; no malaria cases in 2005

Costa Maya = 17%

1 Case per <i>N</i> residents	
≤ 100	Red
100 to 1,000	Orange
1,000 to 10,000	Yellow
10,000 to 100,000	Green
≥ 100,000	Blue



Travel to malaria risk regions/10,000: 5 different countries (WTO) 2011

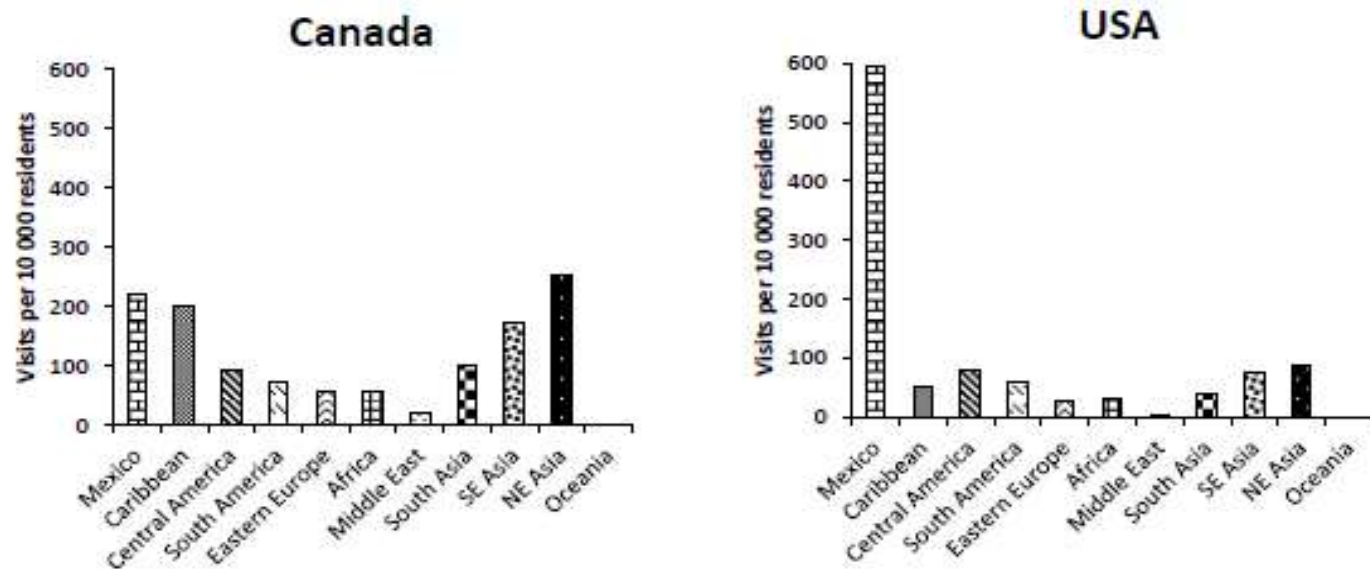
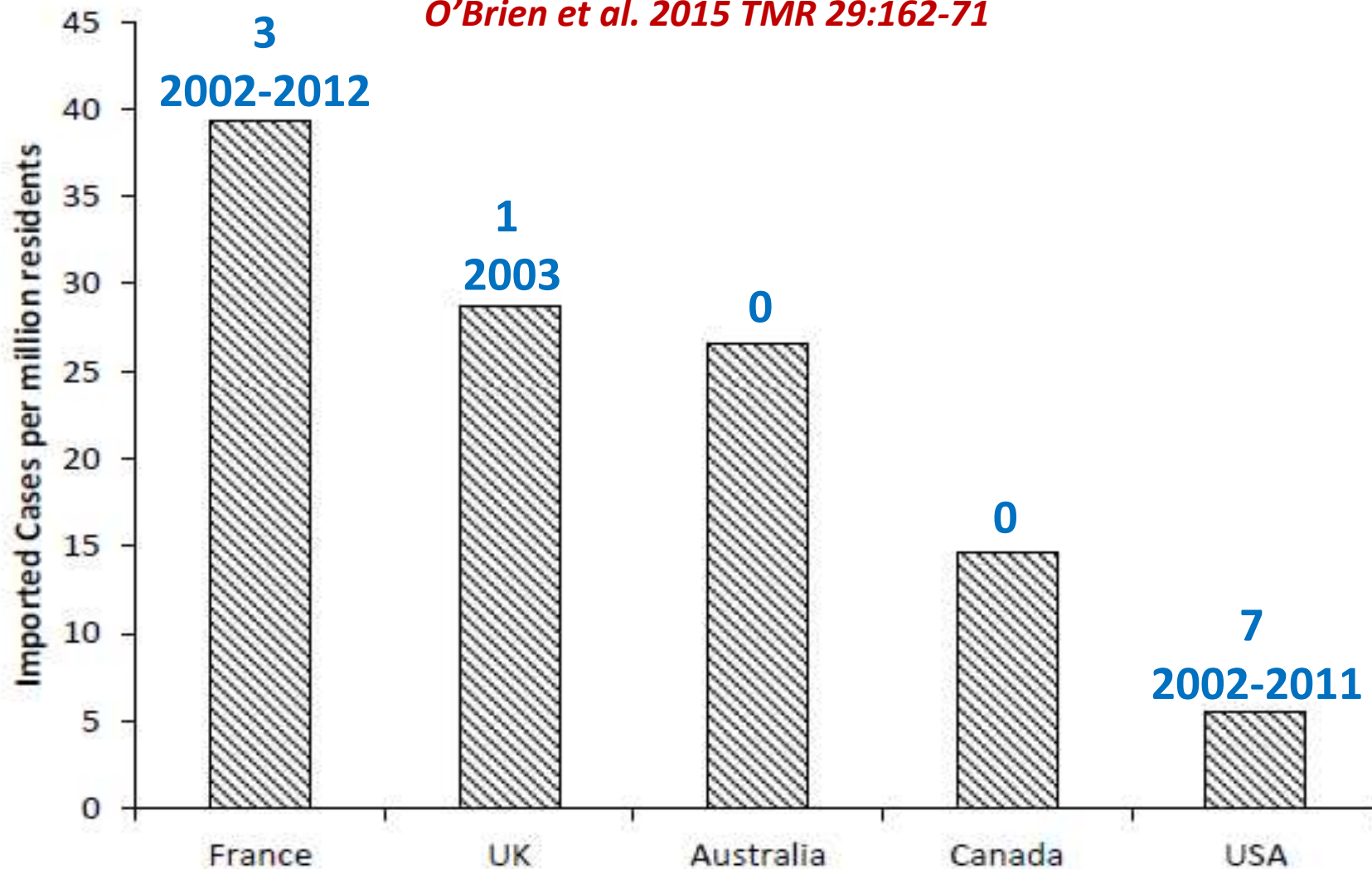


Figure 2 Number of visits to malaria risk regions per 10,000 residents in France, the UK, Australia, Canada and the USA. Travel data from World Tourism Organization (2011) [16] expressed per 10,000 residents [18].

Imported malaria cases by country and TTM

TTM: 11 all from West Africa, 10 *P. falciparum* (1 *P. malariae*)
10 emigrated, 5 had or had been treated for malaria

O'Brien et al. 2015 TMR 29:162-71



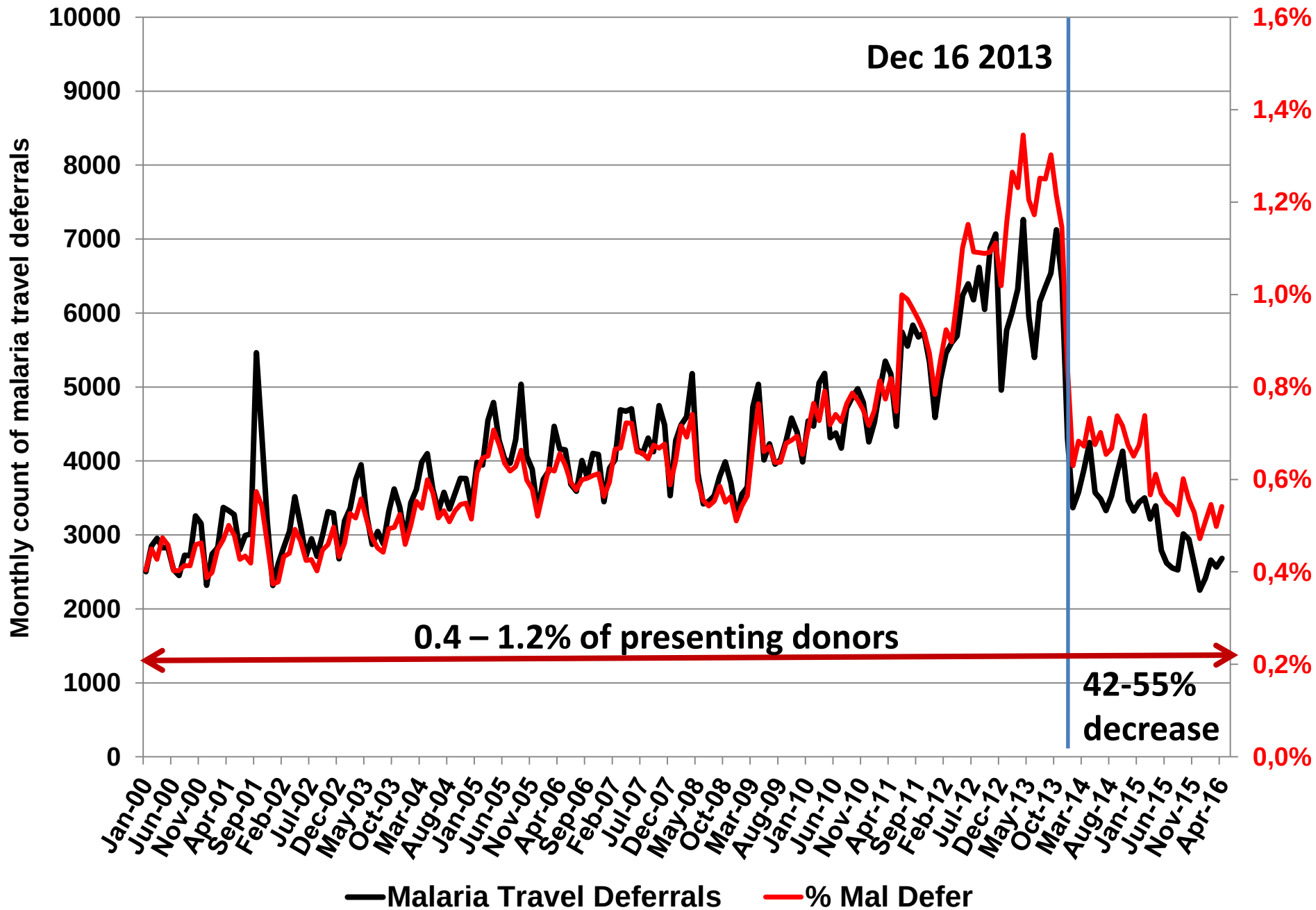
Guidance for Industry

Recommendations for Donor Questioning, Deferral, Reentry and Product Management to Reduce the Risk of Transfusion-Transmitted Malaria

Released Aug 2013 updated Aug 2014

- **FDA does not currently recommend donor deferral for the Mexican states of Quintana Roo (QR) and Jalisco (J)**
- **FDA's risk assessment w/o deferral from QR+J yields an absolute increase = 0.0166 blood units from inf'd individuals/yr, or 1/60 yrs Donor pool would increase by 45,000 (79,000 units)/yr excluding self deferrals**

Number and Percent Malaria Deferrals in Presenting Donors



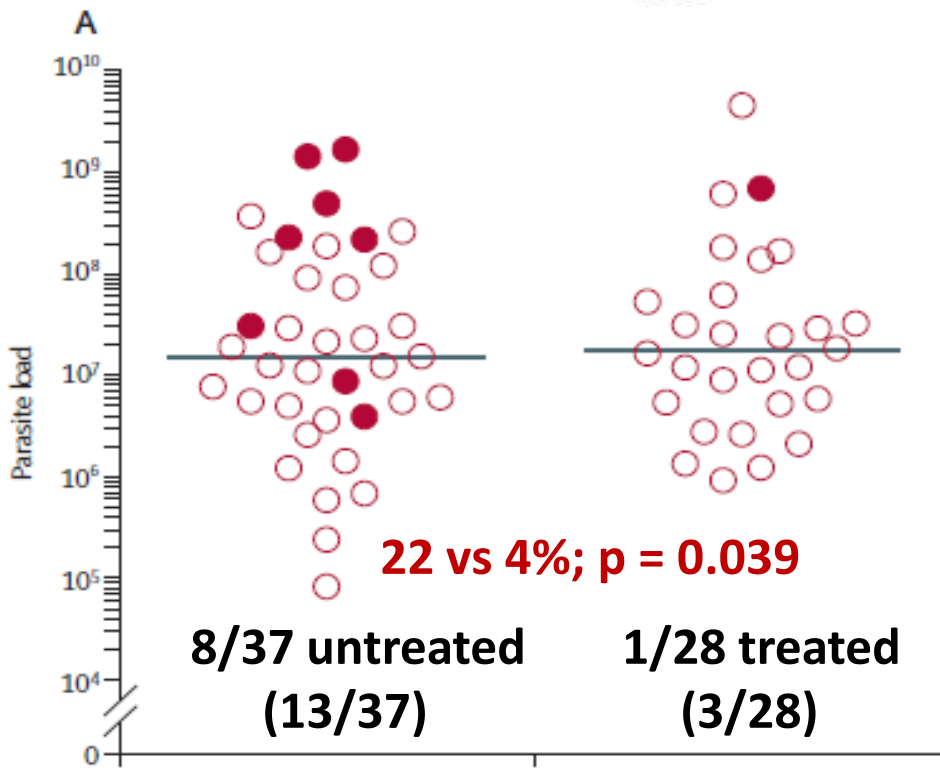
Effect of *Plasmodium* inactivation in whole blood on the incidence of blood transfusion-transmitted malaria in endemic regions: the African Investigation of the Mirasol System (AIMS) randomised controlled trial

Jean-Pierre Allain, Alex K Owusu-Ofori, Sonny Michael Assennato, Susanne Marschner, Raymond P Goodrich, Shirley Owusu-Ofori

Summary

Lancet 2016; 387: 1753–61

Background Transfusion-transmitted malaria is a frequent but neglected adverse event in Ghana. We did a randomised controlled clinical trial to assess the efficacy and safety of a whole blood pathogen reduction technology at preventing transfusion transmission of *Plasmodium* spp parasites.



111 patients rec'd treated WB and 112 rec'd untreated WB...

Parasitemia in 65; closed circles show TTM cases when allelic discrimination was used in the definition of TTM (TTM w/o allelic discrimination)