

Policies for Modifying Deferral and Testing after Pathogen Inactivation (Reduction)

Susan L. Stramer, PhD



IPFA/PEI 25TH INTERNATIONAL WORKSHOP ON
“SURVEILLANCE AND SCREENING OF BLOOD-BORNE PATHOGENS”

May 16-17, 2018



Pathogen inactivation or pathogen reduction: proposal for standardization of nomenclature

Miguel Lozano, MD, PhD¹

e-mail: mlozano@clinic.ub.es

Joan Cid, MD, PhD¹

Chris Prowse, MA, DPhil, FRCPathol²

Jeffrey McCullough, MD, PhD³

Harvey G. Klein, MD⁴

James P. Aubuchon, MD, PhD⁵

690 TRANSFUSION Volume 55, March 2015

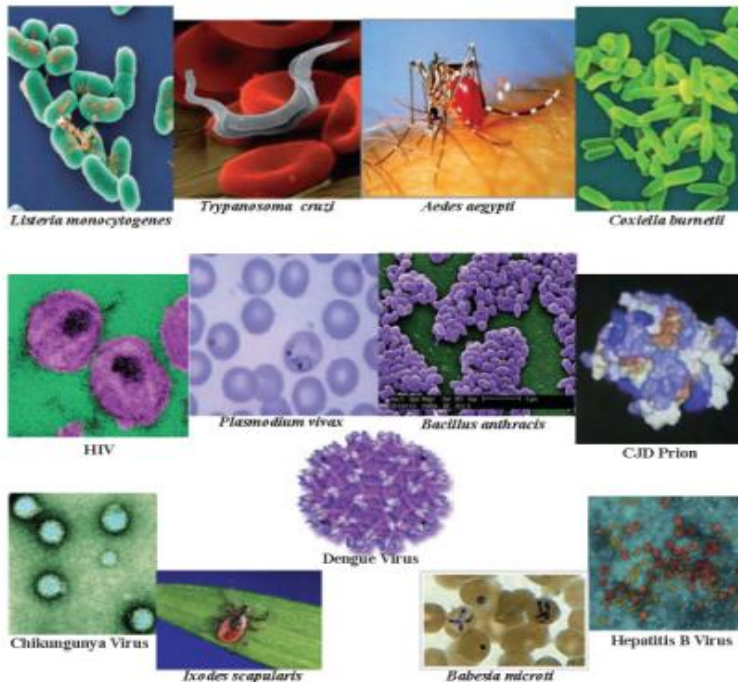
In our opinion, the differences in the terminology are provoking some misunderstandings and lack of standardization in the transfusion medicine community.

To avoid that, we propose to group those technologies aimed at damaging the infectious capacity of the pathogens into what can be referred to as “pathogen inactivation methods,” as has been the practice in the case of plasma derivatives and as was recently used in a review in *TRANSFUSION*.⁴ However, since none of the currently available methods can guarantee the complete sterility of the treated blood components, we suggest using the term “pathogen-reduced blood component” to refer to the treated unit itself.

Background

- Despite best efforts, recipient risk from transfusion persists
 - Chronic disease/age increases risk due to ↑ # of transfused units
 - Initiatives to ↓ risk by ↓ the number of transfused units or evaluating whether transfusion is indicated
- Risk derives from both known and unknown pathogens
- Blood safety currently relies on multiple overlapping measures that include donor health/risk history => deferrals, and donation testing => deferrals
- The testing approach requires the continued addition of tests (NAT and serology), increasing complexity and cost
- Deferrals and complicated reentry algorithms reduce the pool of available donors
- If sufficiently robust, Pathogen Inactivation can
 - Help eliminate some gaps and replace some of the safety procedures
 - Reduce the risk of emerging viruses
 - Reduce/eliminate bacterial risk in platelets
 - Reduce/eliminate some non-infectious risks

TRANSFUSION



- List and prioritize EIDs lacking a current effective intervention & posing a potential threat to transfusion safety
- 68 agents identified and Fact Sheets developed
- New Fact Sheets added; others updated

Highest Priority Agents:

Dengue viruses

Babesia

vCJD

<http://www.aabb.org/resources/bct/eid/Pages/default.aspx>

Emerging Infectious Disease Agents and their Potential Threat to Transfusion Safety



August 2009;99:1S-29S

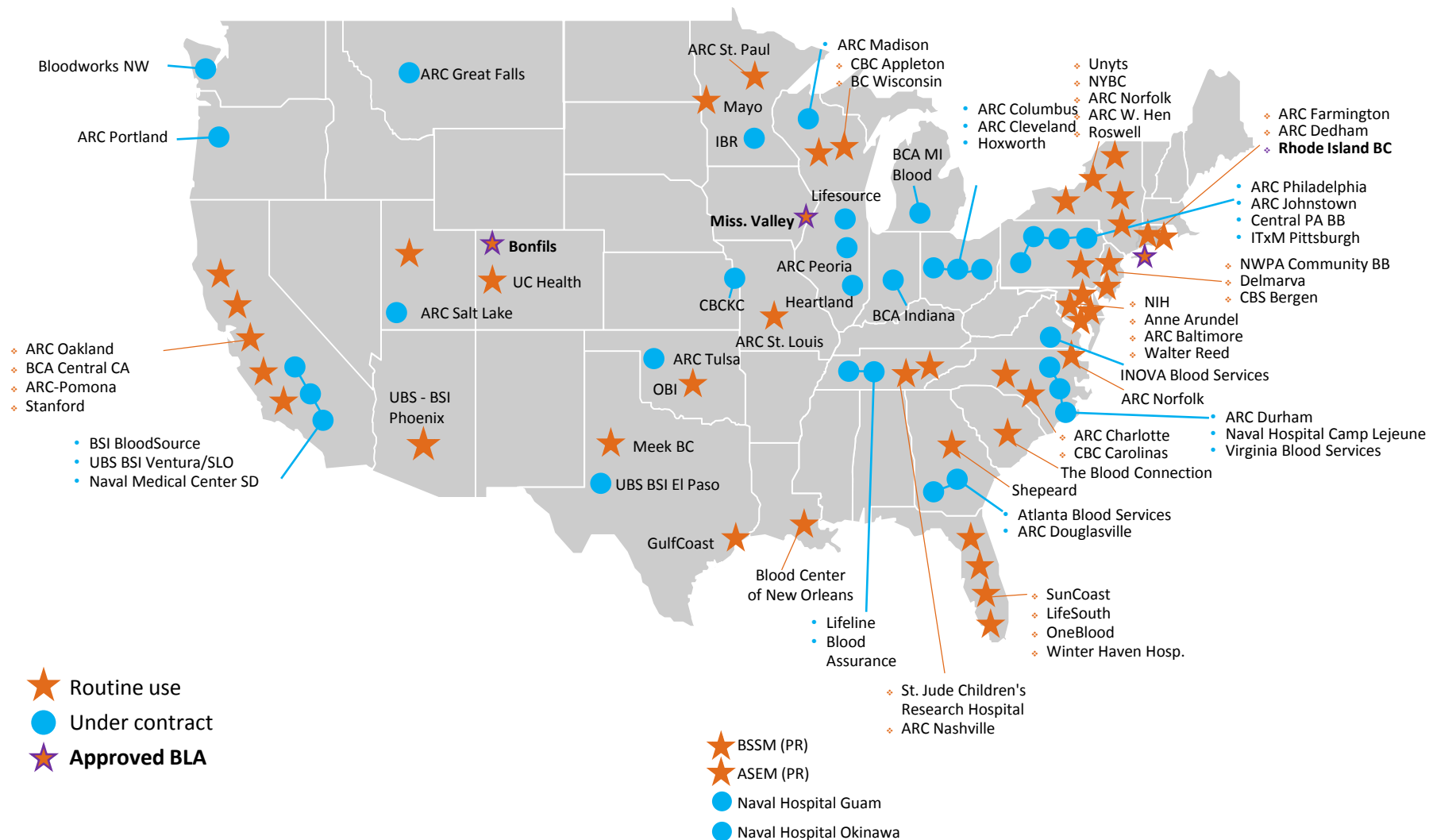
Updated Pathogen Inactivation (Supplement 2013-Jan 2018)

- Clinical Trial tables and listing of countries where PR products are in routine use
- E.g., INTERCEPT Blood System (e.g., platelets) in routine use in >30 countries (Jan 18) with approved indications of:
 - Inactivate broad spectrum - viruses, bacteria, parasites
 - Inactivate contaminating donor leukocytes
 - **Used as an alternate to gamma irradiation**
 - **Used in place of serology and LR for TT-CMV**
 - **Also will reduce alloimmunization, FNHTRs**



January 2018

US INTERCEPT Blood System Use



Donor/Donation Screening (US Focus)

- Health histories related to ID risk
 - Can any donor screening questions be removed/modified/reduced in complexity with PI?
 - MSM from ever=>12 mos (US, Canada, other) =>3 mos (UK) =>behavior based ???
 - Other risk behaviors (IDU, STDs, sex for money/drugs)
 - *Hx of hepatitis after the age of 11 (eliminated)*; sensitive tests for HBV, HCV; no other causes of chronic TT-HBV (current: deferral for 1 year after disappearance of symptoms)
 - *Hx/dx of Chagas disease (eliminated; 0.4/billion)*, Babesia (licensed tests/should be able to eliminate)
 - Travel to a *Leishmania*-endemic area
 - Travel/residence or having had malaria
 - Other (country specific)
- Tests performed
 - What tests can be eliminated with PI?
 - Can algorithms for screening, donor deferral/reentry be modified?
 - Can we avoid adding new tests?

Donation ID Screening in the US (ARC)

Routine testing for 10 ID agents using 13 screening tests on 6 screening platforms and 19 supplemental platforms/tests

Infect Disease Agent	Serology-Based Screen + Suppl	Nucleic Acid-Based Screen + Suppl
HIV-1/2	1 (PRISM)+3 (IFA, EIA, rapid test)	1 (MP-TIGRIS) + 1 (PCR)
HCV	1 (PRISM) + 1 (EIA)	1 (MP-TIGRIS) + 1 (PCR)
HBV	2 (PRISM)+ 2 (neut [Ag], PCR [Ab])	1 (MP-TIGRIS) + 1 (PCR)
HTLV-I/II	1 (PRISM) + 2 (WB + EIA)	0
<i>T. pallidum</i>	1 (PK7300)+ 2 (EIA => RPR)	0
<i>T. cruzi</i>*	1 (PRISM) + 2 (ESA + EIA)	0
WNV	0	1 (MP=>ID-TIGRIS) + 2 (PCR+Ab)
ZIKV (IND)	0	1 (ID-Panther, MP?) +2 (PCR+Ab)
<i>Babesia</i>	1 (AFIA)	1 (PCR) MP-Panther (IND) +2 (PCR+Ab)
CMV*	1 (PK7300)	0
Total	9 + 12	4 + 7

*Not performed on all donations

Per Unit Residual Risk for ARC Donations

		Incidence Rate (/100,000 PY)	X	Infectious Window Period (days)*	=	Residual Risk
2008-2009	HIV	4.27		9.1		1:939,342
	HCV	6.18		7.4		1:798,128
	HBV	4.27		30.0		1:284,934
2014-2015	HIV	1.65		9.1		1:2,430,902
	HCV	1.84		7.4		1:2,680,670
	HBV	1.26		18.5		1:1,565,852

*Between the first and last time periods of the study, the infectious window period of HBV decreased.

Incident donors significantly more likely to be:

Male

Caucasian

Age 18-24 (HIV), 18-39 (HCV), ≥40 years (HBV)

A patient-oriented risk–benefit analysis of pathogen-inactivated blood components: application to apheresis platelets in the United States

Steven Kleinman, William Reed, and Adonis Stassinopoulos

TABLE 2. Comparison of infectious risk estimates for a transfusion recipient when calculated per unit or per patient exposure

Infection	Per-unit estimate (%)	Per-patient estimate (6 AP units) (%)	
Bacterial contamination	0.067	0.4	1:250
Clinical sepsis	0.016	0.096	
TT-CMV	0.1	0.3 (50% susceptible patients)*	1:833-1:1333
Emerging acute agent	0.007-0.075 (0.025)†	0.042-0.45 (0.15)†	1:333
Emerging chronic agent	0.01-0.08 (0.045)†	0.06-0.48 (0.27)†	1:370
Aggregate infectious risk estimates	Not calculated	0.4—Baseline (bacterial transmissic 0.1—Minimum (clinical sepsis only) 1.18—Maximum (bacteria, CMV, and highest EIA risk)‡§	1:667

* The per-patient CMV risk estimate that has been adjusted for recipient susceptibility based on only 50% of recipients being susceptible.

† The number in parentheses is the most likely value.

‡ The EIA risk used in this calculation is at the uppermost end of the estimated range for a chronic EIA (e.g., 0.48%).

§ The numbers can be tabulated to calculate a variety of other combinations of infectious risks; these might include an acute EIA rather than a chronic EIA, replacing bacterial contamination with clinical sepsis, and excluding CMV risk.

doi: 10.1111/j.1537-2995.2012.03928.x

TRANSFUSION **,**,**.*.

Cumulative Infectious Transfusion Risk

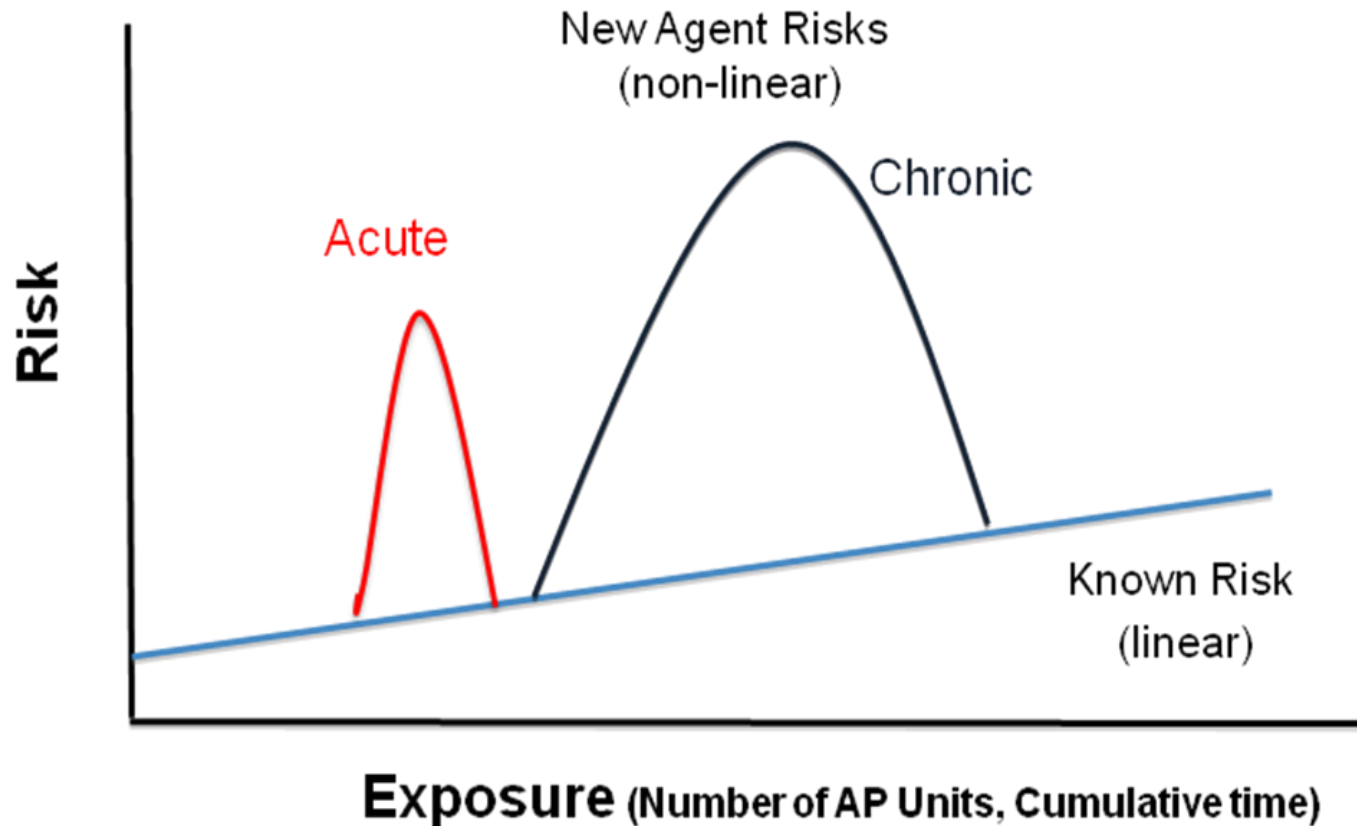
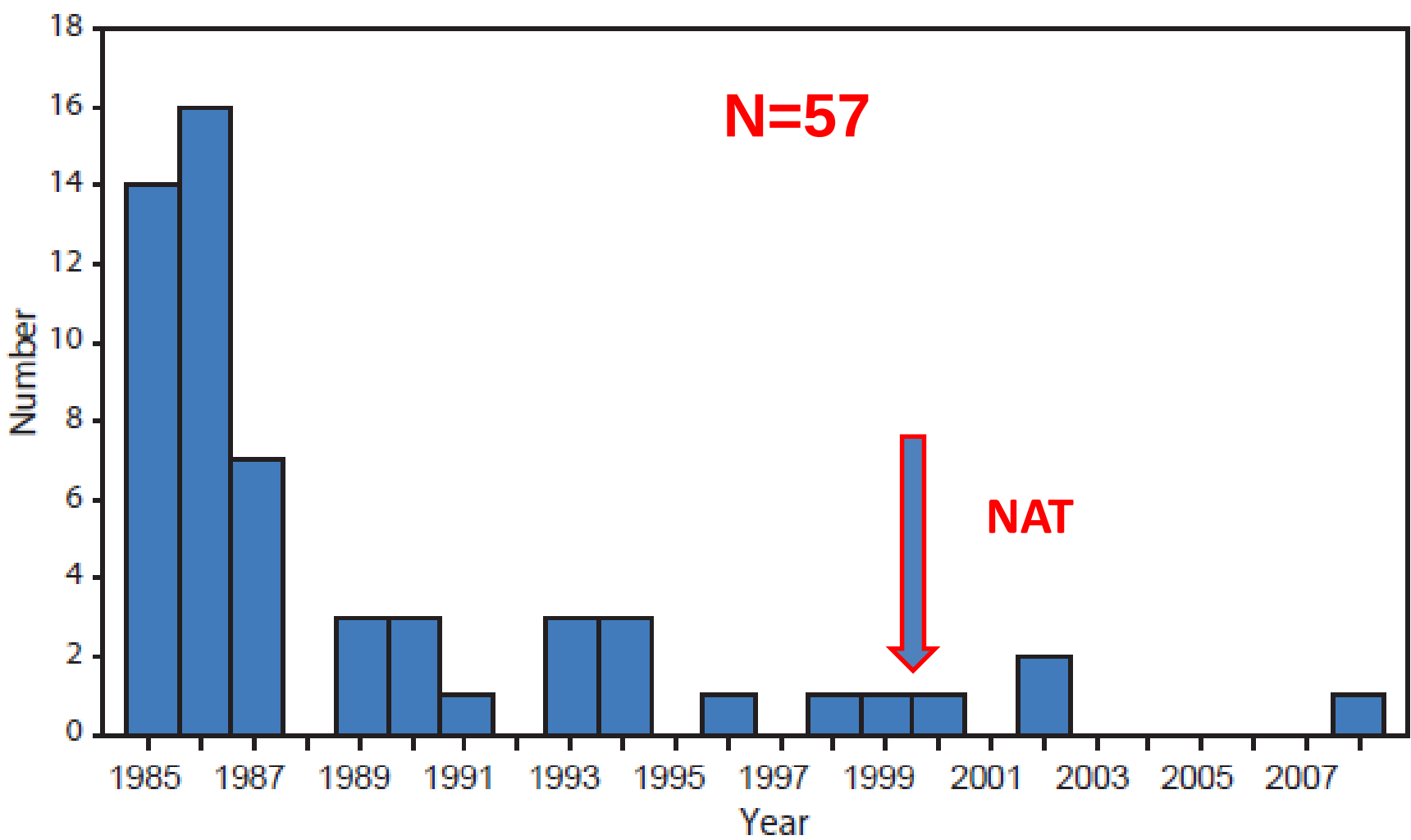


FIGURE 2. Number of cases of transfusion-transmitted HIV infection from contaminated blood products, by transfusion year — United States, 1985–2008



**HIV Window Period Transmissions in the US:
during the 9-day WP (with NAT)
All identified by Lookback**

Year	State	Component	No. Pos Recipients
2000	TX	RBC	1
2002	FL	RBC/FFP	1/1
2002	MD	RBC/FFP	0/1
2006	GA	RBC/FP24	0/1
2008	CO	FFP	1

Thus, in total there were **5 wp donors** from which
6 of 8 recipients of their products tested HIV pos
(2 RBC and 4 FP with 2 RBC testing negative)

A probable case of West Nile virus transfusion transmission

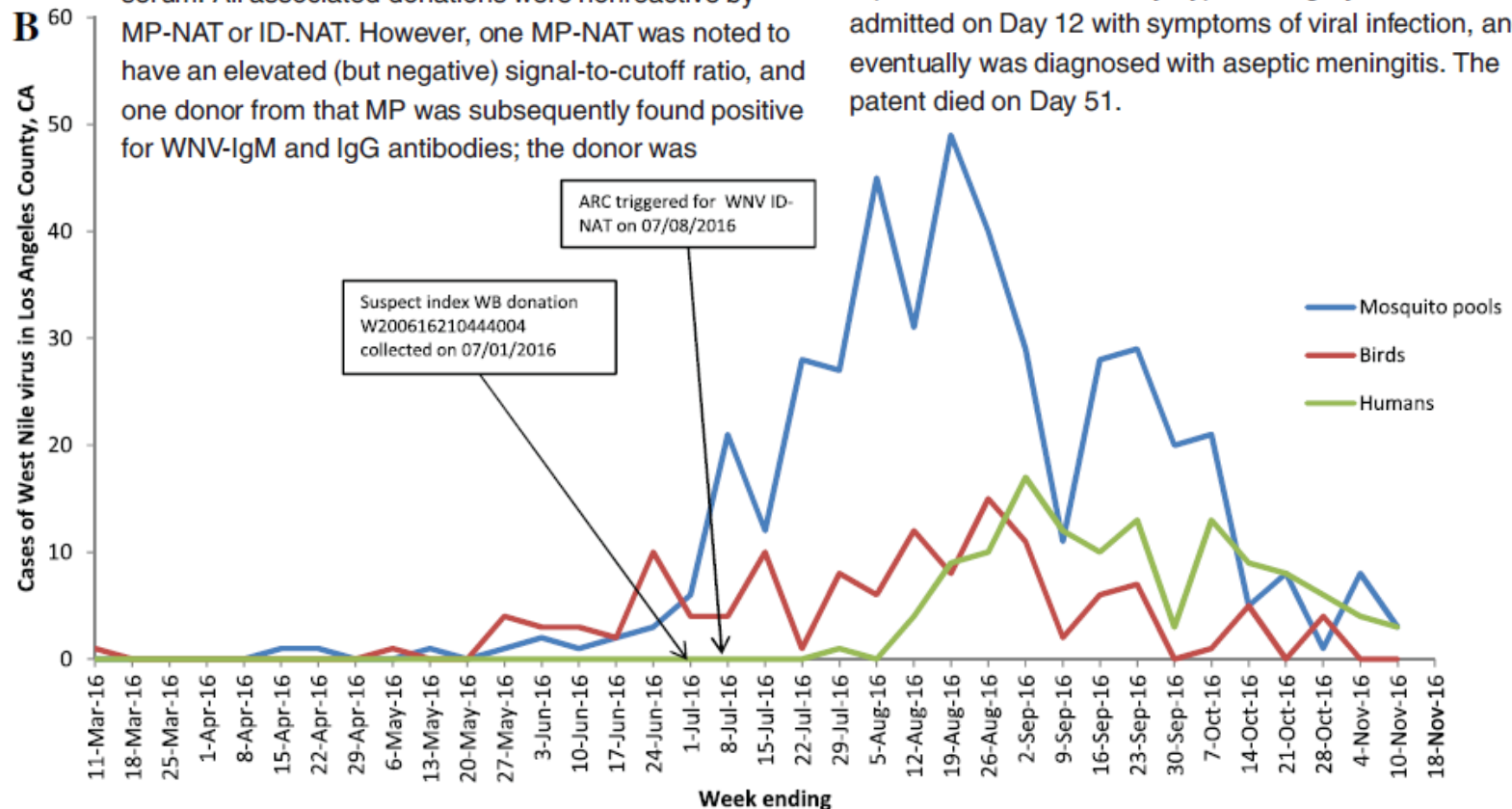
14th TT-WNV

TRANSFUSION 2017;57;850–856

Jamel A. Groves,¹ Hedyeh Shafi,² Jim H. Nomura,³ Ross M. Herron,⁴ Devin Baez,⁵
Roger Y. Dodd,¹ and Susan L. Stramer¹

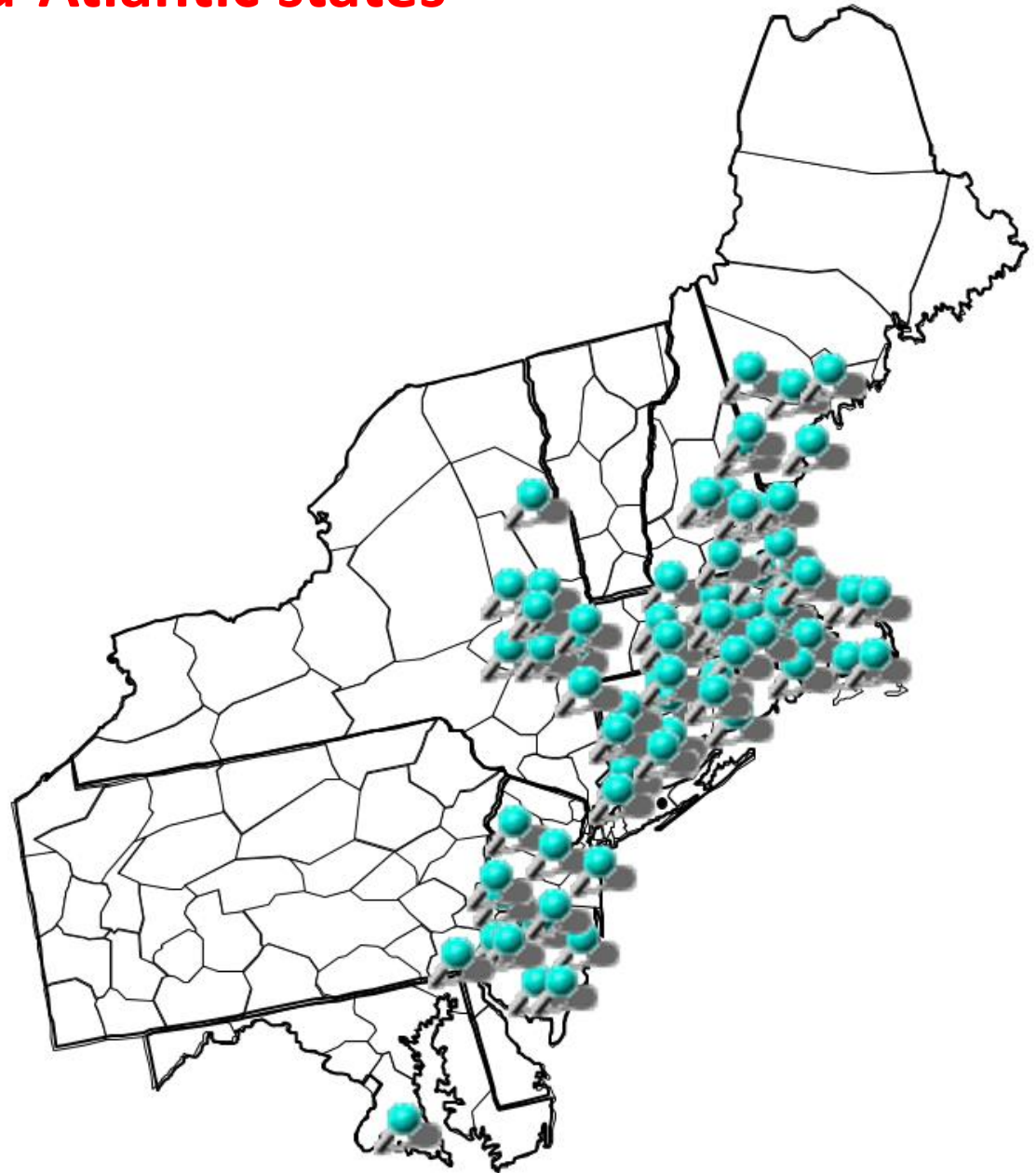
RESULTS: The patient was positive for WNV-immunoglobulin M (IgM) antibodies in his cerebrospinal fluid on Day 14 and was positive for WNV-IgM (on Days 14 and 16) and WNV-IgG antibodies (on Day 16) in his serum. All associated donations were nonreactive by MP-NAT or ID-NAT. However, one MP-NAT was noted to have an elevated (but negative) signal-to-cutoff ratio, and one donor from that MP was subsequently found positive for WNV-IgM and IgG antibodies; the donor was

STUDY DESIGN AND METHODS: A 78-year-old male patient who was treated for cardiac disease received 14 blood components from 30 donors in August 2016. He was discharged 7 days after aortic valve replacement and coronary bypass surgery, but was re-admitted on Day 12 with symptoms of viral infection, and eventually was diagnosed with aseptic meningitis. The patient died on Day 51.



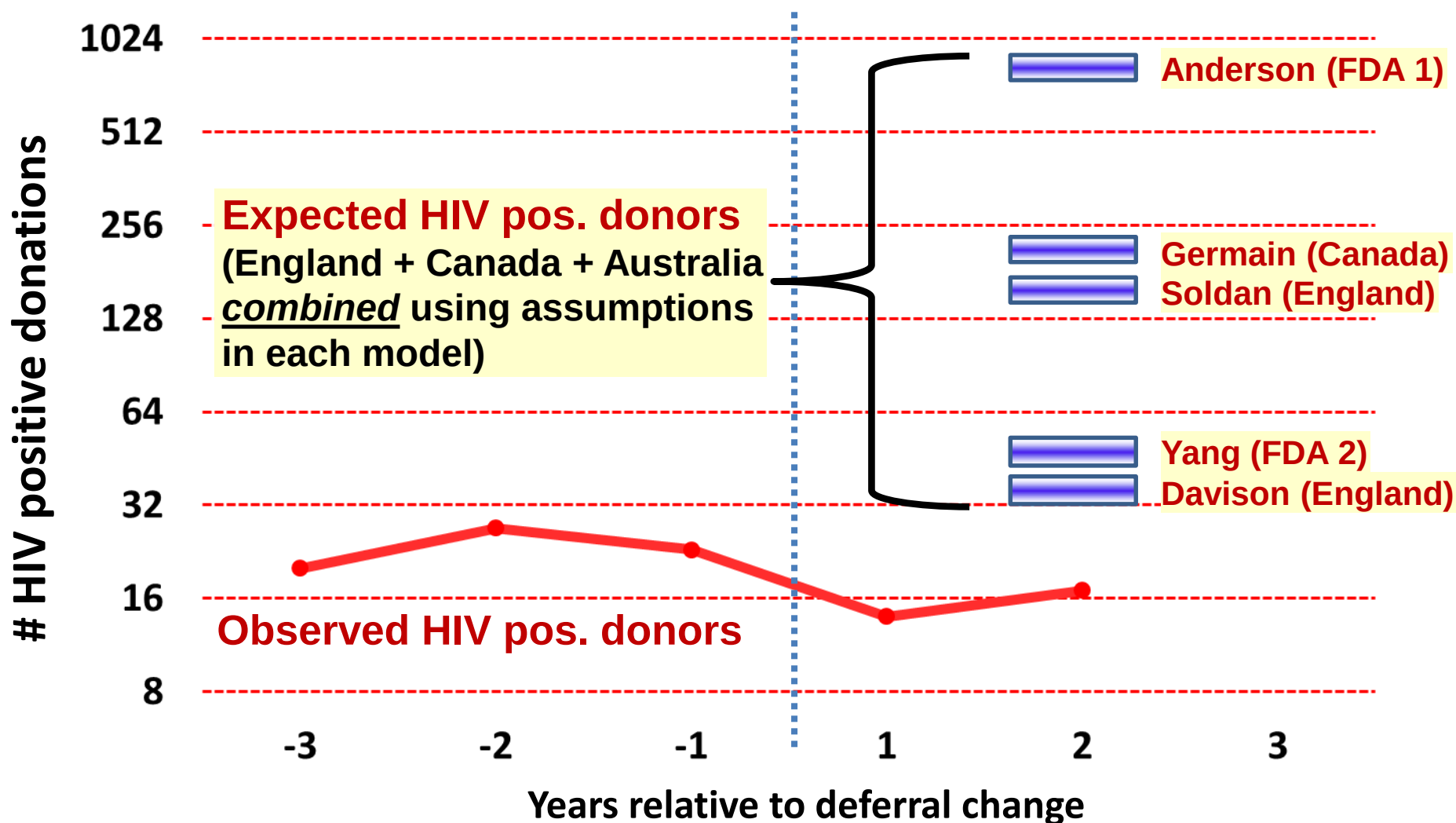
72 of 80 Babesia-implicated donors reside in New England or Mid-Atlantic states

State	# Positive donors
Connecticut	19
Massachusetts	18
Maine	6
Maryland	1
New Hampshire	5
New Jersey	8
New York	10
Pennsylvania	5



Models vs. observed

HIV + donations before/after MSM deferral changes



Modified with permission from Germain M. *Transfusion*. 2016.

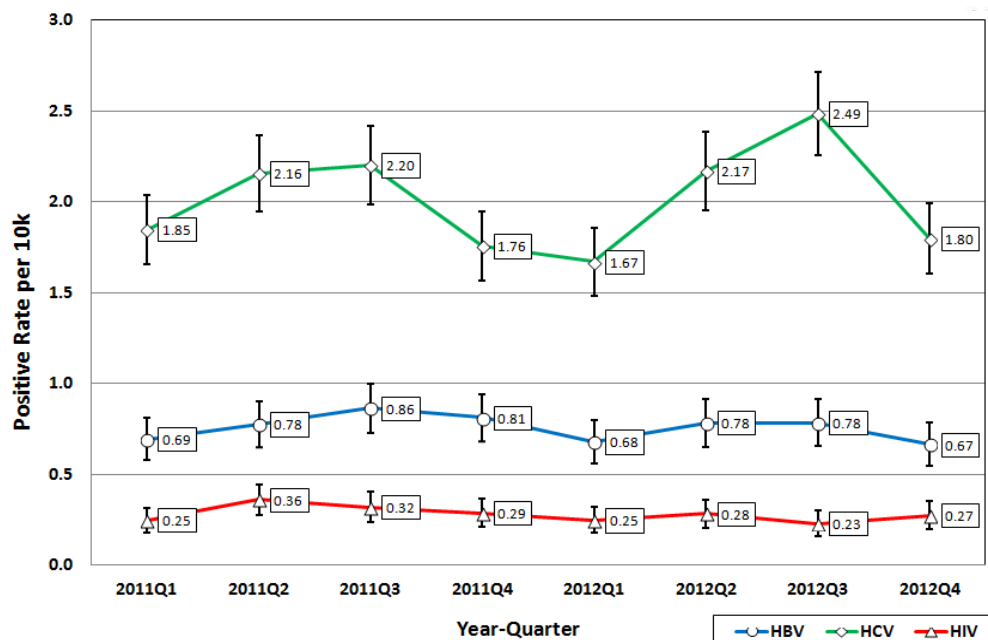
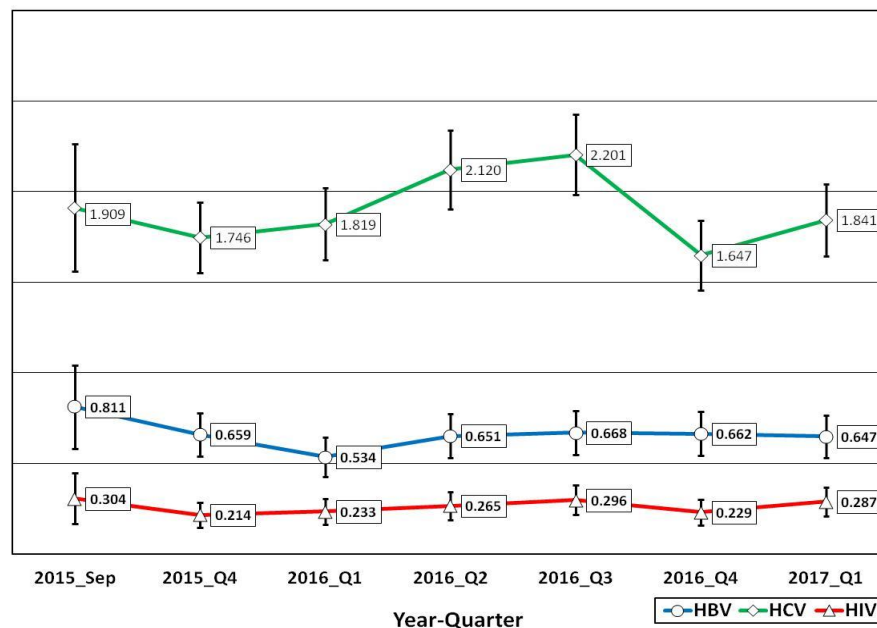
Presented by L. Katz; AABB 2017

Quarterly Consensus Positive Rates

Rate per 10k with 95% CI for HCV, HBV and HIV

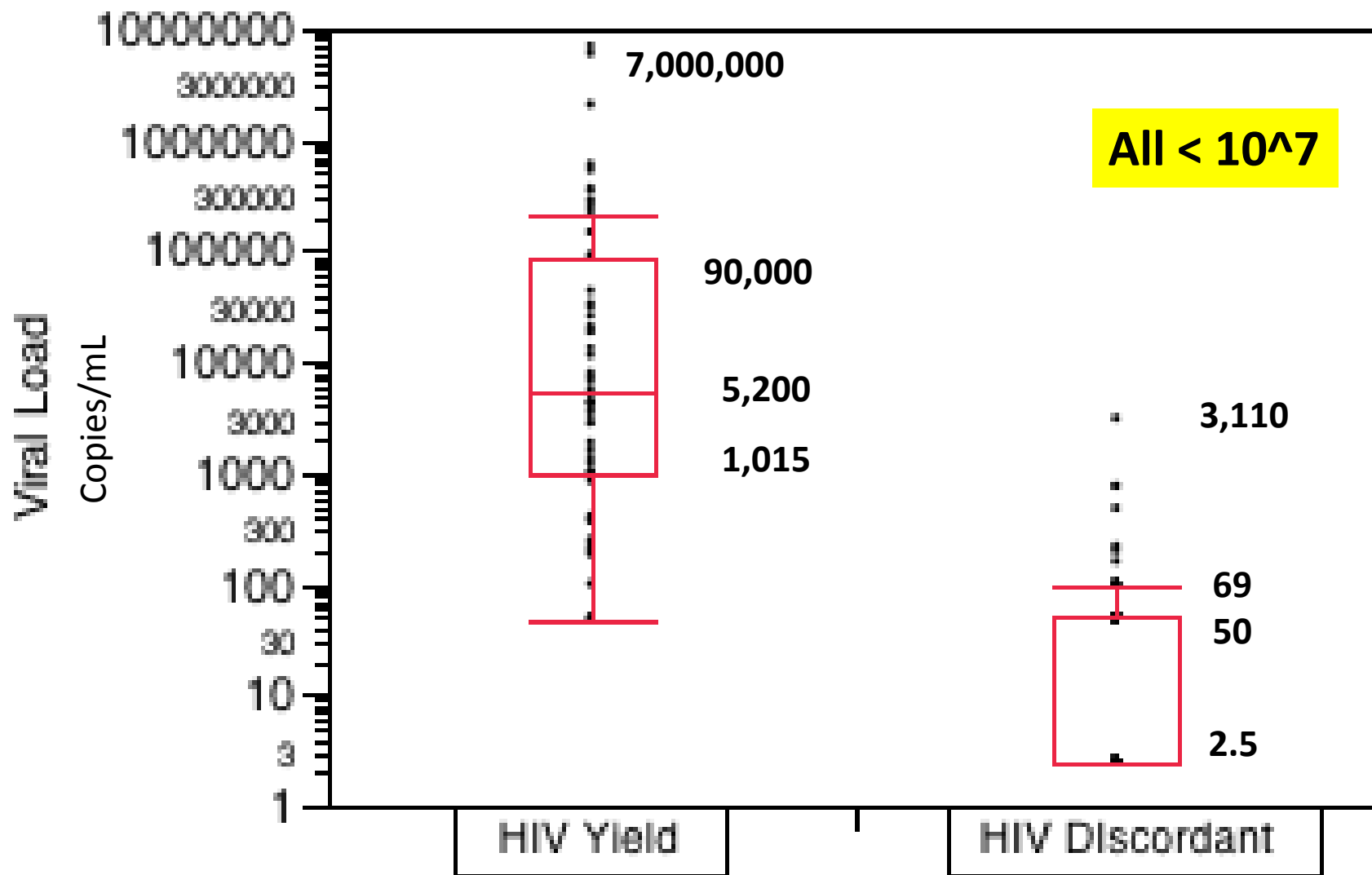
RF: 2011-2012
3 Centers

TTIMS: 2015 Sep – 2017 Q1
All Centers



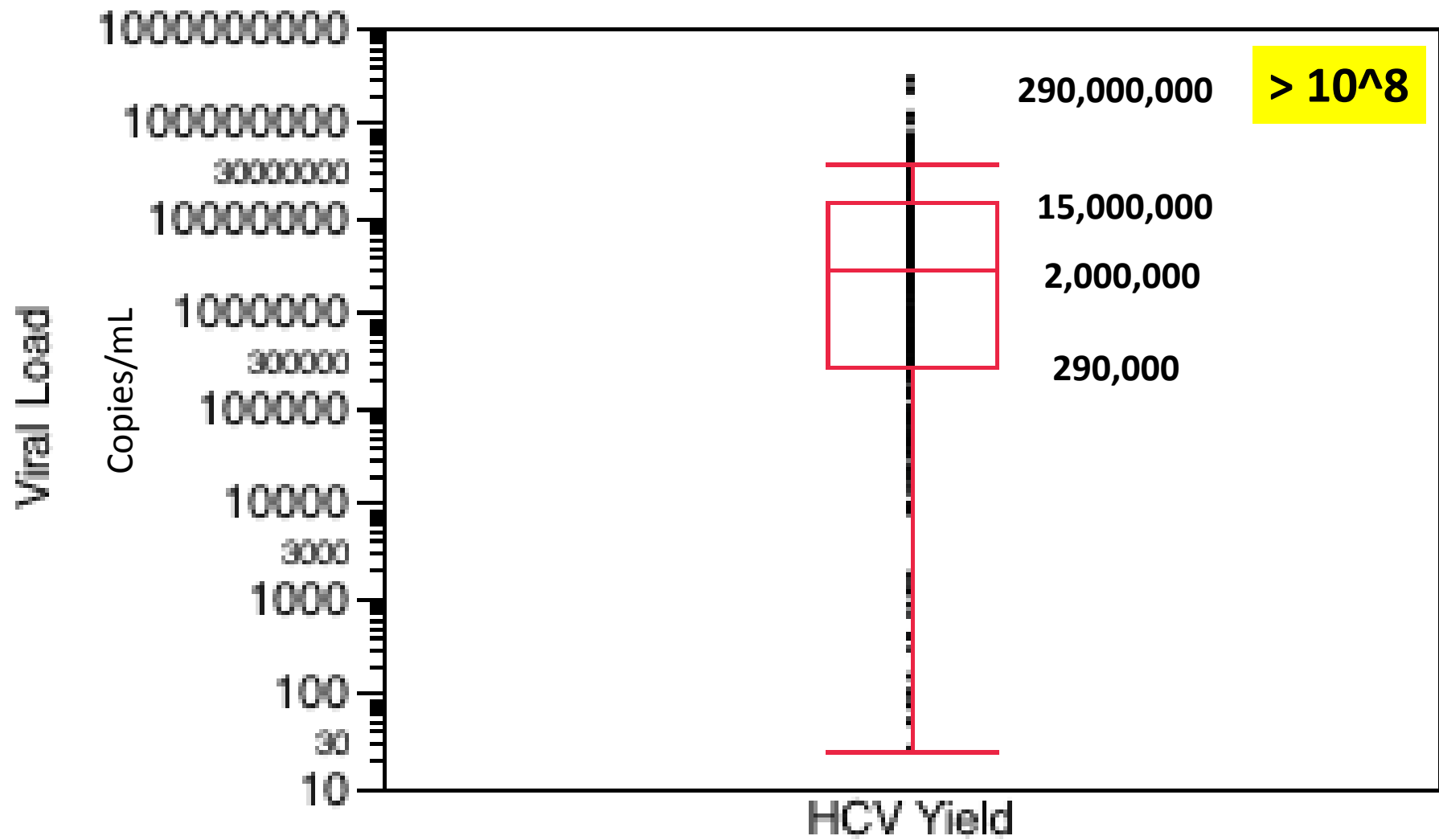
Viral Load Distributions of two classes of HIV Confirmed Positives

N = 341 (1999-2013)

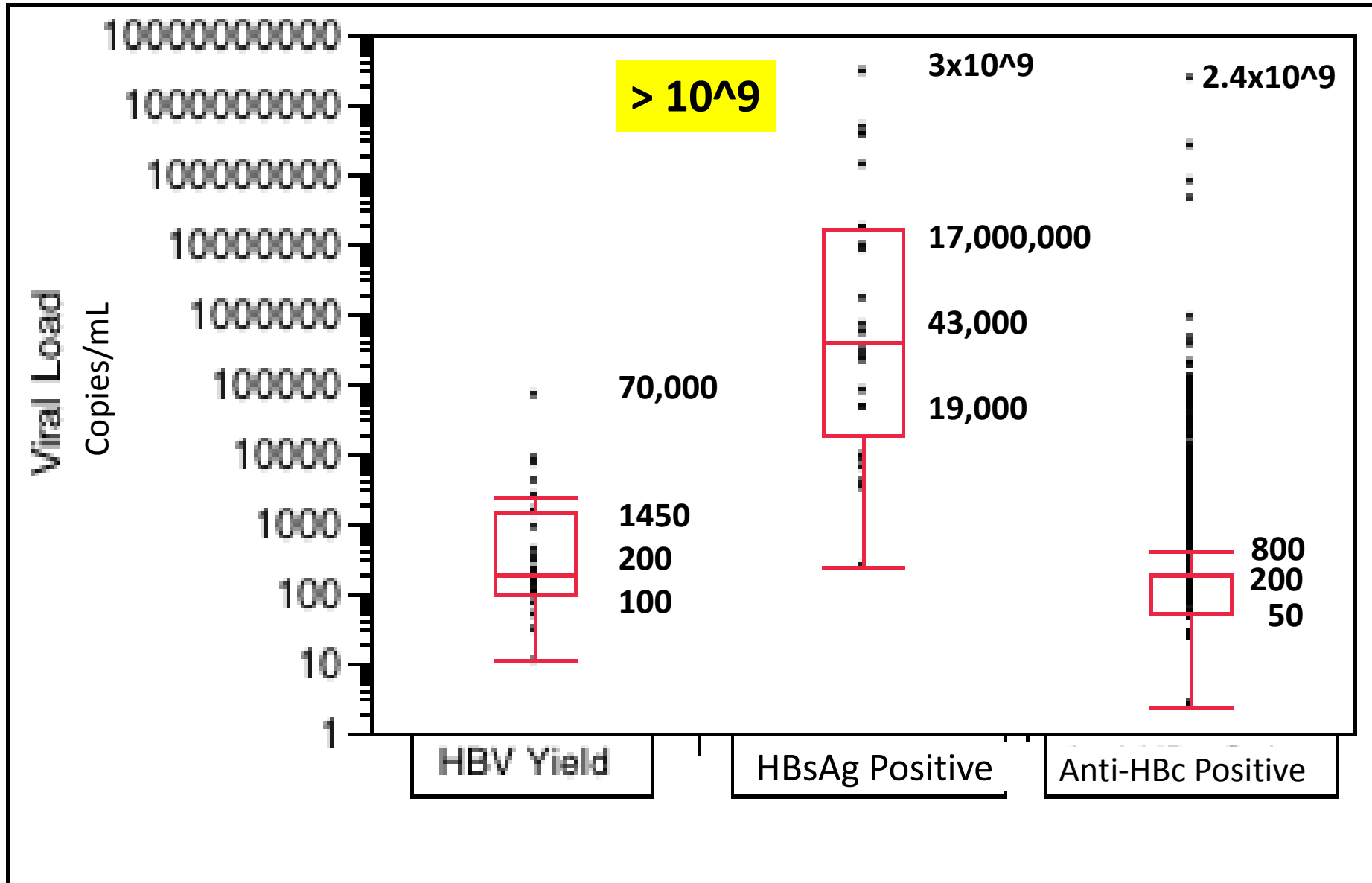


Viral Load Distributions of HCV Confirmed Positives

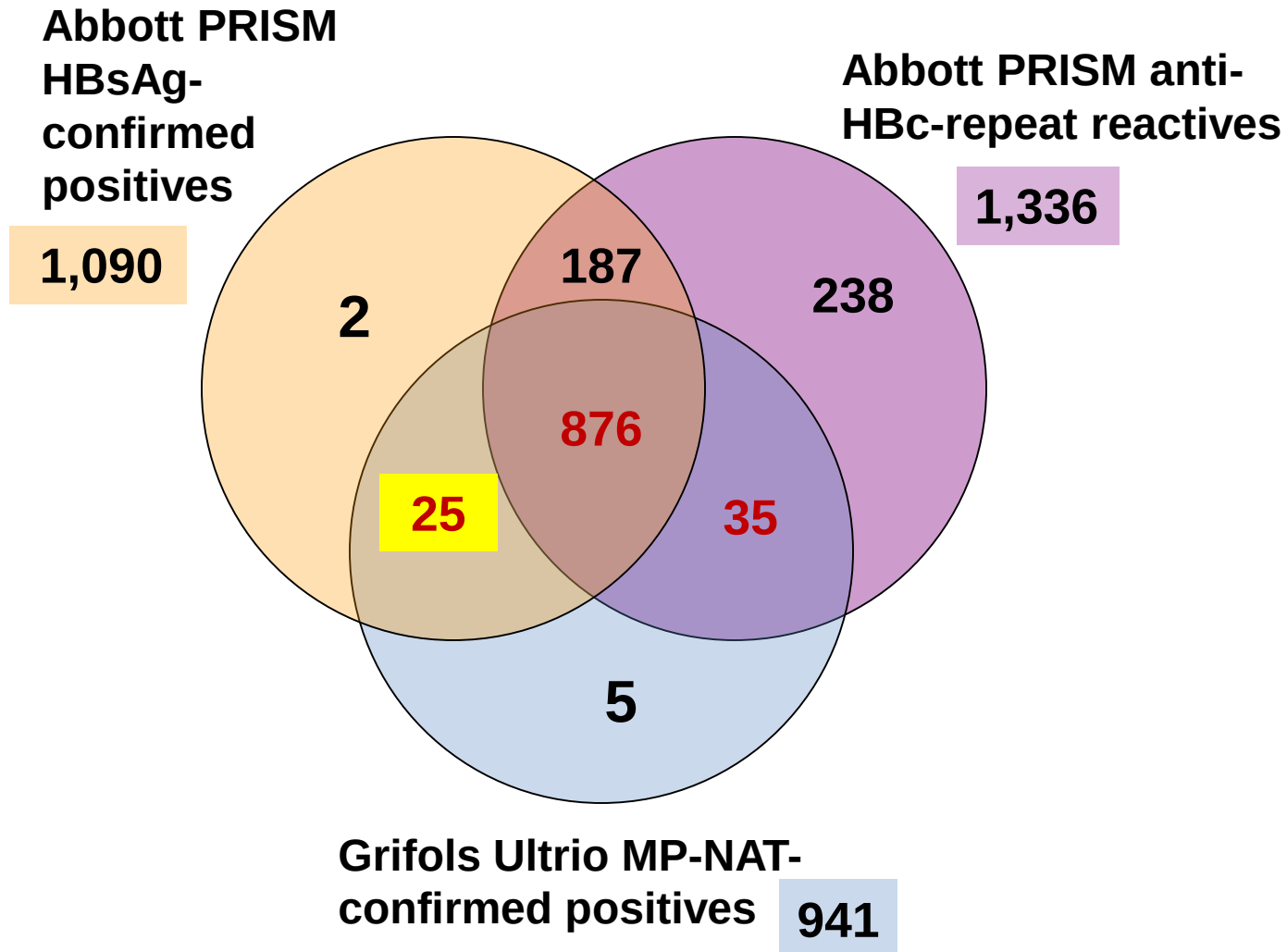
N = 289 (1999-2013)



Viral Load Distributions of three classes of HBV Confirmed Positives N = 2,526 (2009-2013)

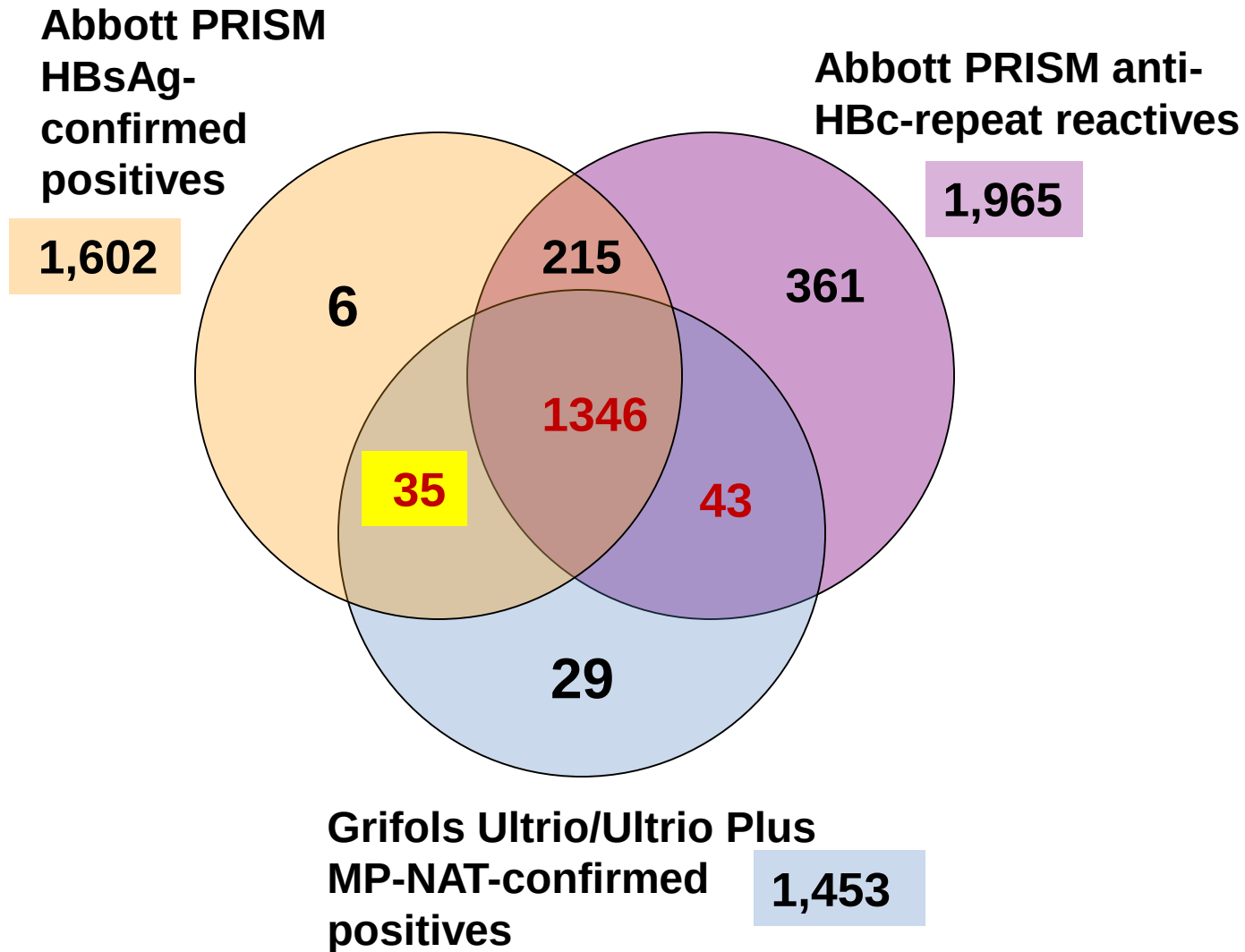


**HBV reactivity of 1,368 infected ARC donations,
12.8 million donations
July 1 2009 to June 30 2011***



*defined as HBV MP- or ID-NAT reactive

**HBV reactivity of 2,035 infected ARC donations,
22.4 million donations
July 1 2011 to June 30 2015***



*defined as HBV MP- or ID-NAT reactive

**HBV reactivity of 2,035 infected ARC donations,
22.4 million donations
July 1 2011 to June 30 2015***

**Abbott PRISM
HBsAg-
confirmed
positives**

1,602

**Abbott PRISM anti-
HBc-repeat reactivities**

1,965

HBV Yield Summary, 2009-15

8 HBsAg only/35 million donations = 1/4.4 million

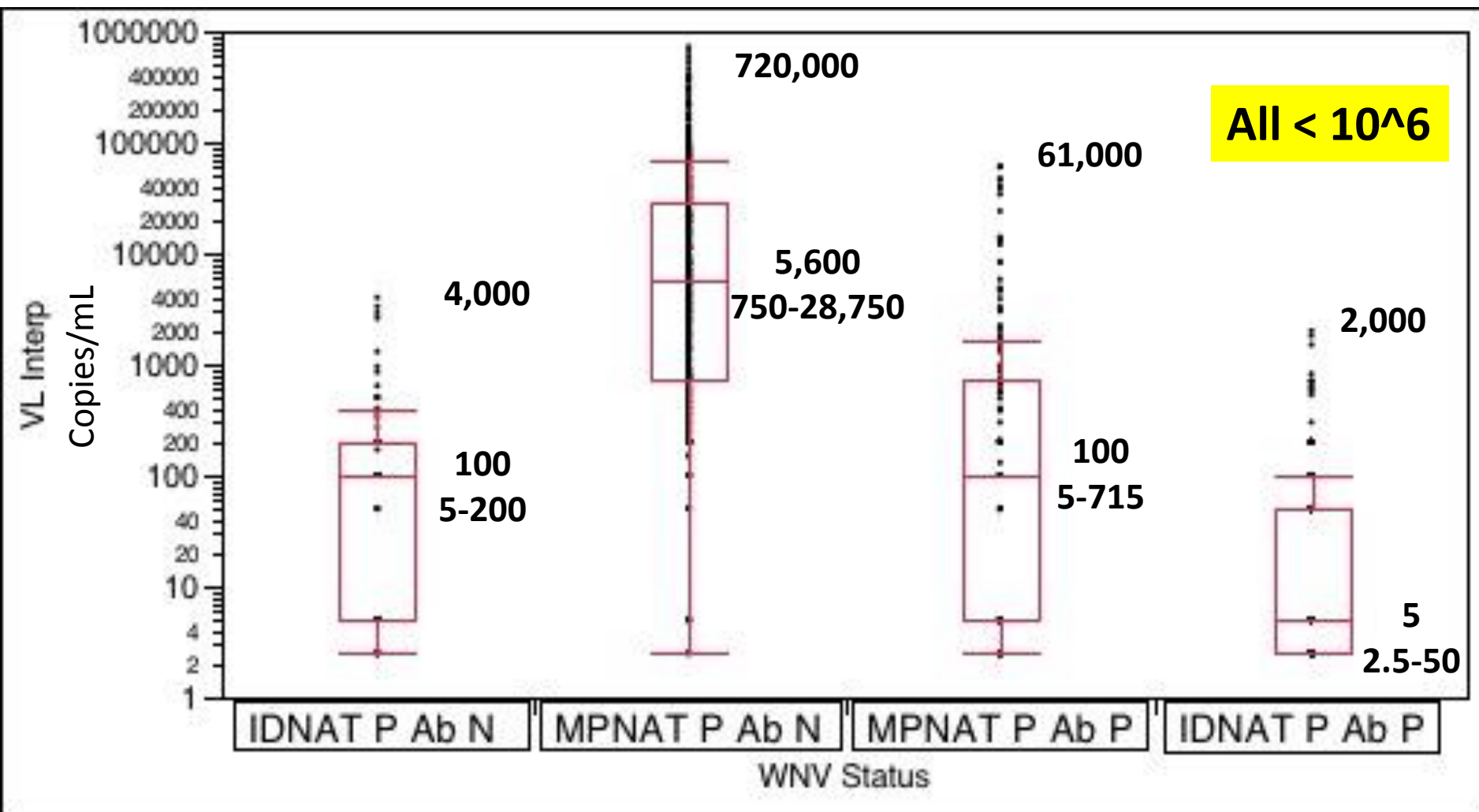
**Grifols Ultrio/Ultrio Plus
MP-NAT-confirmed
positives**

1,453

*defined as HBV MP- or ID-NAT reactive

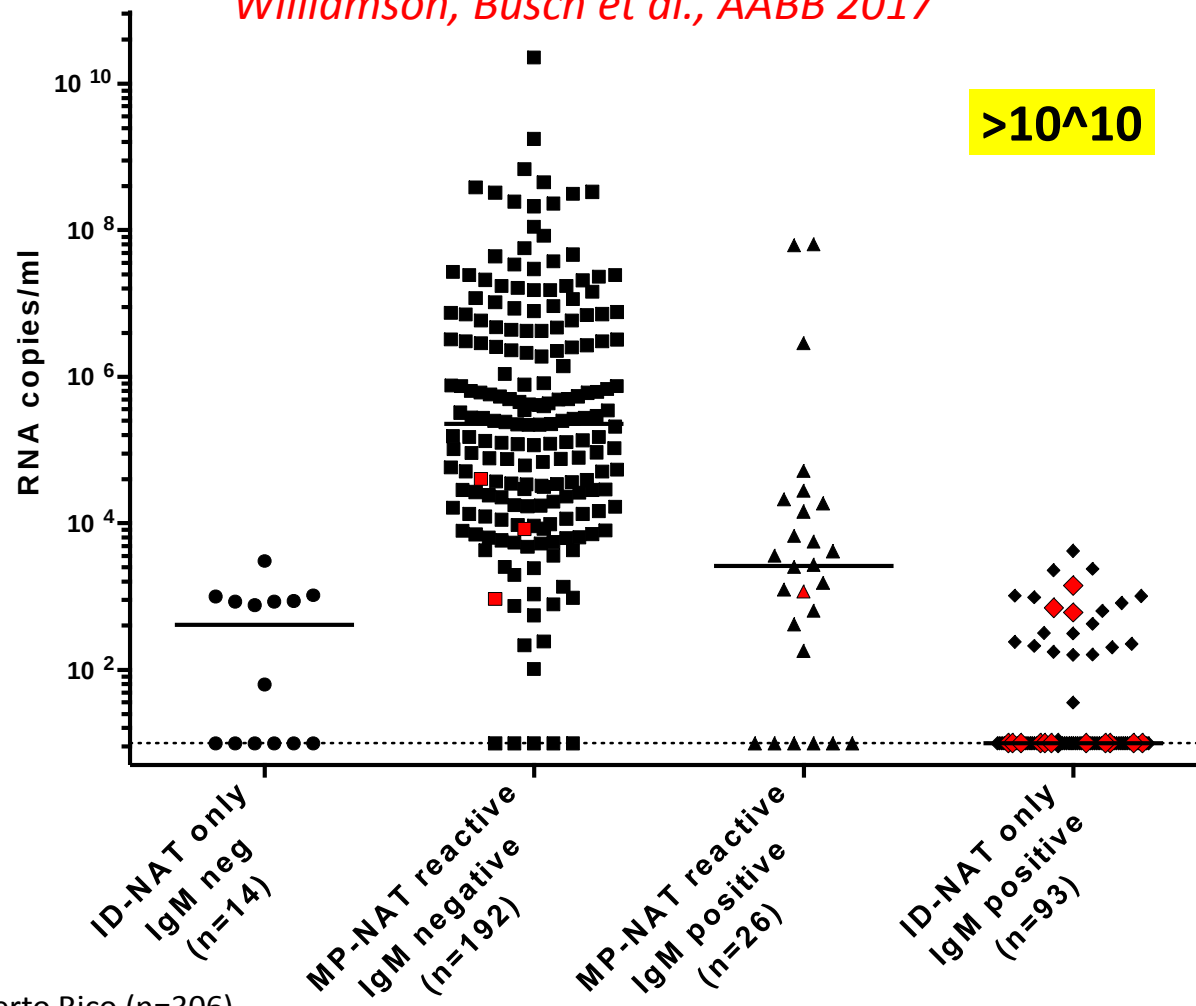
Viral Load Distributions according to the development of WNV markers in Confirmed Positives

N = 1477 (2003-2012)



Staging of ZIKV NAT yield cases with valid IgM results

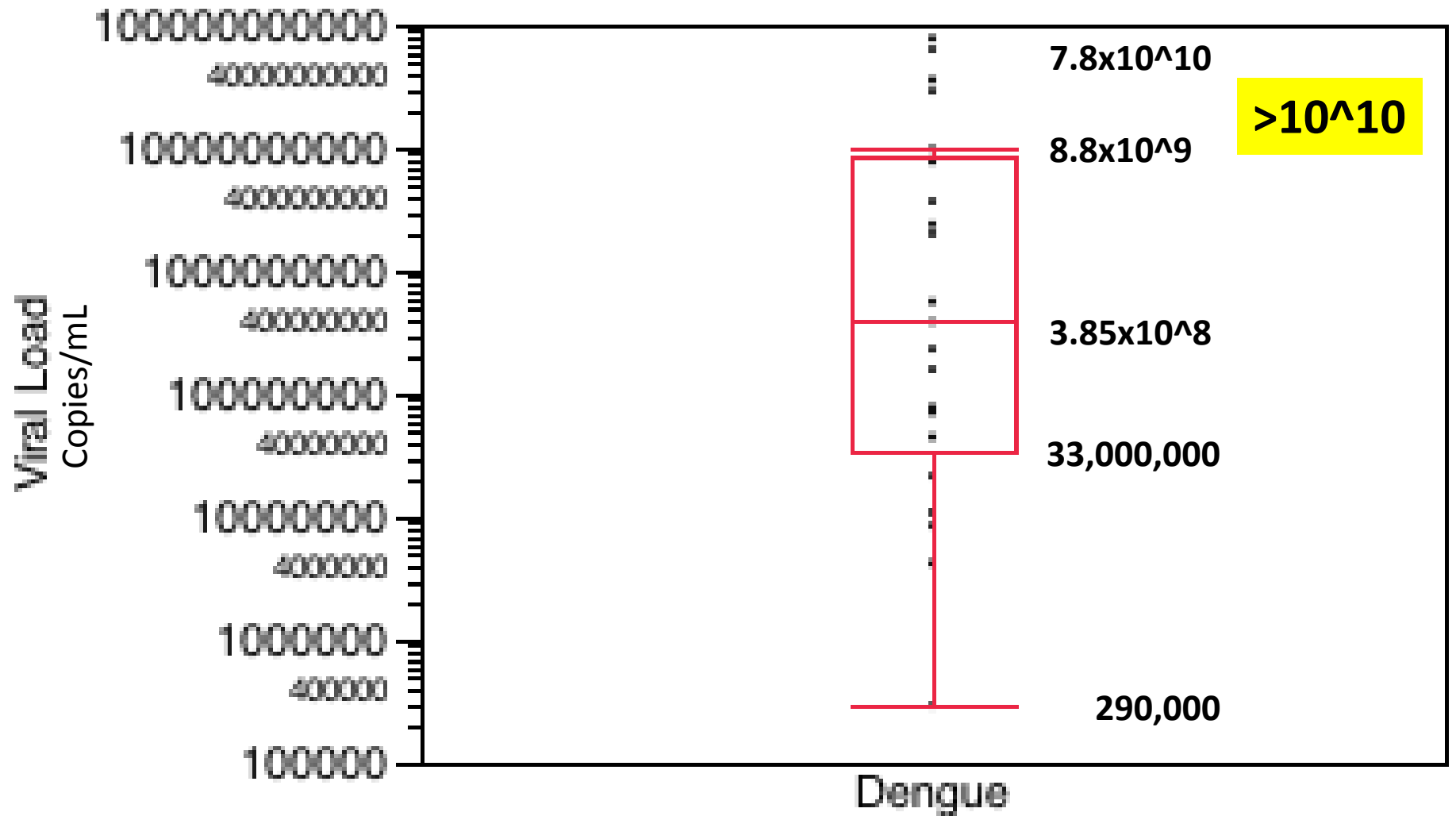
Williamson, Busch et al., AABB 2017



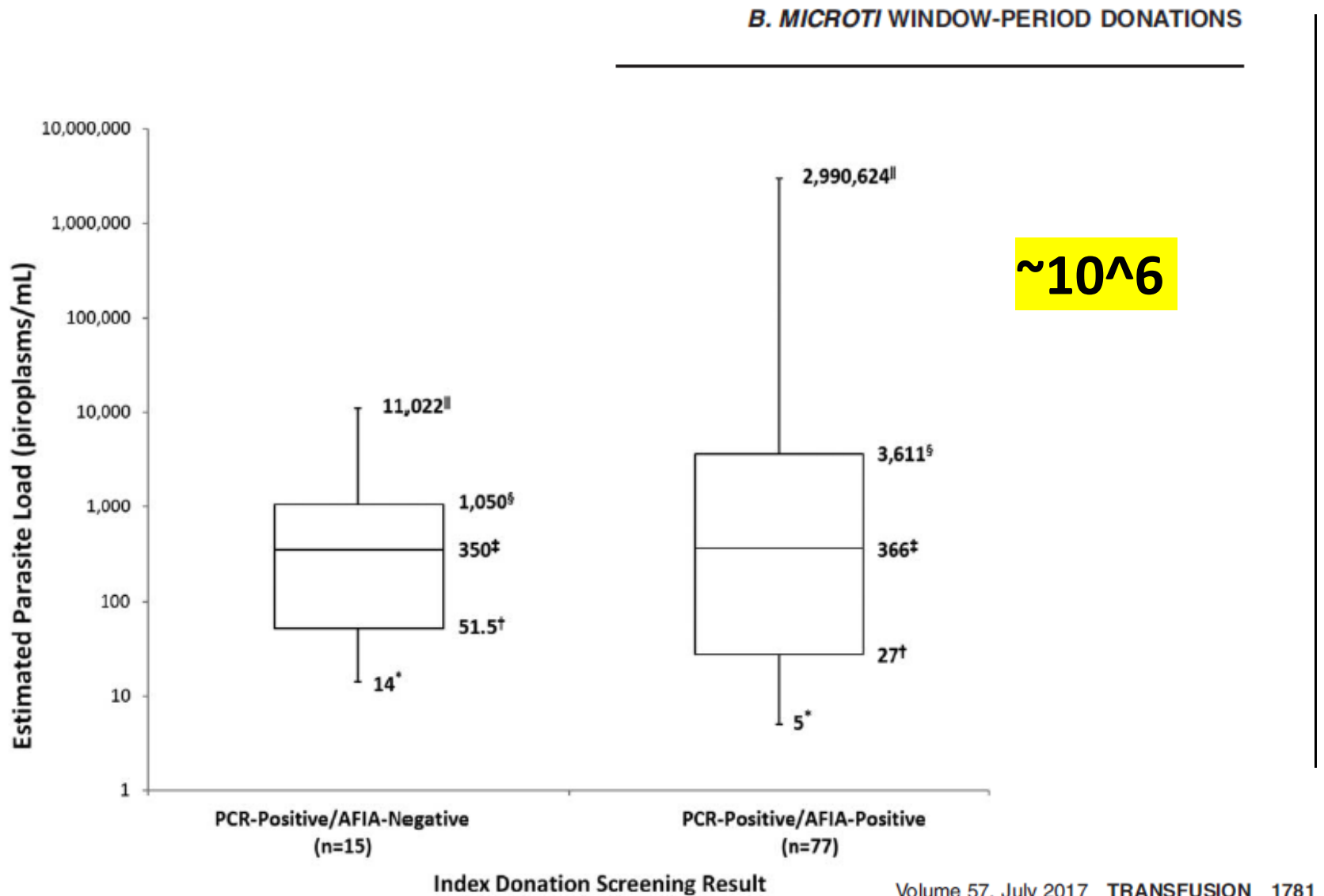
Black Symbols = Puerto Rico (n=306)

Red Symbols = Continental US (n=19)

Dengue Confirmed Positive Donor Viral Load Distributions, N = 21 (2010-2013)



Parasite DNA Distributions in Babesia Confirmed Positives, N = 92 (June 4 2012-Aug 31 2016)



A patient-oriented risk–benefit analysis of pathogen-inactivated blood components: application to apheresis platelets in the United States

Steven Kleinman, William Reed, and Adonis Stassinopoulos

TABLE 5. PI data in PCs with the INTERCEPT system

Enveloped viruses ⁴⁷	Titer reduction	Nonenveloped viruses	Titer reduction
HIV-1, cell-associated	>6.1	Bluetongue virus (model ds RNA virus)	6.1 to 6.4
HIV-1, cell-free	>6.2	Human adenovirus 5 (model ds DNA virus)	>5.9
HIV-1 (clinical isolate)	>3.4	Calicivirus (model, ss RNA virus)	1.7 to 2.4
HIV-2 (clinical isolate)	>2.5	SARS-CoV ⁴⁸	>6.2
HIV-1, latent provirus	To limit of detection	Parvo B19 ⁴⁹	2.0 to >6.0
HCV	>4.5	Parasites	Titer reduction
BVDV (model for HCV)	>6.0		
HBV	>5.5		
DHBV (model for HBV)	>6.2		
HTLV-I	4.7		
HTLV-II	5.1	<i>Plasmodium falciparum</i> ⁵⁰	≥6.0
CMV, cell-associated	>5.9	<i>Trypanosoma cruzi</i> ⁹	≥5.4
WNV	>6.0	<i>Babesia microti</i> ⁵⁰	>5.3
Chikungunya virus ⁵¹	>6.4	<i>Leishmania</i> species (promastigote and amastigote forms) ¹⁰	>5.0
Influenza A H5N1 (avian influenza) ⁵²	>5.9		

BVDV = bovine viral diarrhea virus; DHBV = duck hepatitis B virus.

doi: 10.1111/j.1537-2995.2012.03928.x

TRANSFUSION 2013;53:1603-18

TABLE 3. Bacterial inactivation data in PCs with the INTERCEPT system

Gram-negative bacteria	Titer reduction	Gram-positive bacteria	Titer reduction	Anaerobic Gram-positive bacteria	Titer reduction
<i>Escherichia coli</i>	>6.4	<i>Staphylococcus epidermidis</i>	>6.6	<i>Bifidobacterium adolescentis</i>	>6.5
<i>Serratia marcescens</i>	>6.7	<i>Staphylococcus aureus</i>	6.6	<i>P. acnes</i>	>6.7
<i>Pseudomonas aeruginosa</i>	4.5	<i>Listeria monocytogenes</i>	>6.3	<i>Clostridium perfringens</i> (vegetative)	>7.0
<i>Klebsiella pneumonia</i>	>5.6	<i>Corynebacterium minutissimum</i>	>6.3	<i>Lactobacillus</i> sp.	>6.9
<i>Salmonella choleraesuis</i>	>6.2	<i>Streptococcus pyogenes</i>	>6.8	Spirochetes	Titer reduction
<i>Enterobacter cloacae</i>	5.9	<i>B. cereus</i> (vegetative)	>6.0		
<i>Yersinia enterocolitica</i>	>5.9	<i>B. cereus</i> (including spores)	3.6		
				<i>Treponema pallidum</i>	≥6.8 to ≤7.0
				<i>Borrelia burgdorferi</i>	>6.8

TABLE 3. Bacterial inactivation data in PCs with the INTERCEPT system

Lets assume 5 – 6 log reduction of known agents; exceptions may be bacterial endospores (not linked to clinical disease) and nonenveloped viruses – B19, HAV, HEV (NAT likely needed to ↓ viral loads)

Caveat:

- Reported PI values for many are “> than” and the true limit is not known
- Titer of copies/mL is not an accurate representation of infectivity assays (at least 2 logs ↑ than infectivity assays)
- *In vitro* infectivity assays do not always correlate with *in vivo* infectivity

ZIKV Inactivation using INTERCEPT

Inactivation of ZIKV	Infectivity (Log ₁₀ TCID ₅₀ /mL)	Corresponding viral load (Log ₁₀ copies/mL)	Corresponding viral load (copies/mL)
Plasma ¹	>6.57	10.25	1.8 x 10 ¹⁰
Platelets (PAS) ²	>4.42	7.46	2.9 x 10 ⁷
RBC ³	>5.99	7.75	5.6 x 10 ⁷
Mean Asymptomatic donors ¹	NA	4.85±1.0	7.1 x 10 ⁴

¹Aubry et al., Transfusion 2016

²Santa Maria et al., Transfusion 2017

³Laughunn et al., Transfusion 2017

- Inactivation of infectivity levels corresponding to viral loads higher than the maximum viral load reported using the same calibrated assay in asymptomatic blood donors in French Polynesia (6.91 log₁₀ copies/mL)

Arboviral Inactivation using INTERCEPT

- Robust inactivation of DENV, CHIKV and ZIKV in all three blood components
- Recent data demonstrate inactivation of the vaccine strain of yellow fever and Mayaro virus

Arbovirus	Log ₁₀ Reduction		
	Plasma	Platelets	RBC
WNV	>6.8	>6.0	NA
DENV	>5.6	>4.3	>6.6
CHIKV	>7.6	>6.4	>7.1
ZIKV	>6.6	>4.4	>5.8
YFV (strain 17D)	NA	>5.9	NA
MAYV	NA	>6.9	>6.2
RRV	NA	>5.1	>5.5

- The system can be implemented in endemic areas in a proactive manner before an outbreak occurs or at the early stage of an outbreak
- Lack of availability of high sensitivity screening assays worldwide

WNV Window Period and Effect of PI

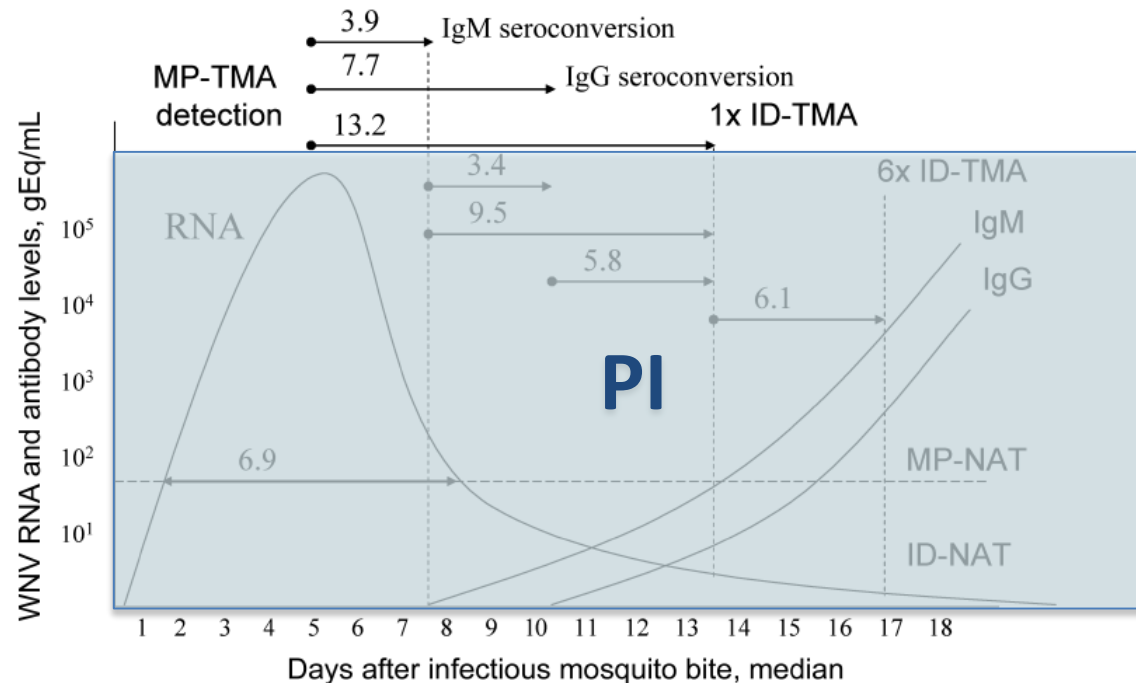


Figure 1. Dynamics of West Nile virus (WNV) RNA and WNV-specific antibody positivity and negativity. The top 3 intervals represent window periods that start with the index donation (i.e., the donation that tested positive for WNV in minipools of 16 donor specimens [MP] by transcription-mediated amplification [MP-TMA]). Although positive results of MP-TMA can occur anytime during the 6.9-day window period when results of MP nucleic acid amplification testing (NAT) are positive, for illustrative purposes the first 3 window periods are depicted as beginning at the midpoint of this window period. Values are not additive (i.e., the time from RNA detection to IgM detection [3.9 days] plus the time from IgM antibody to IgG antibody detection [3.4 days] does not equal the time from RNA detection to IgG antibody detection [7.7 days]), as noted in table 2. ID, individual donation; 1 × ID, single replicate; 6 × ID, 6 replicates.

PI: Mitigating the Risk of Bacterial Sepsis

- Data from 3 National Hemovigilance Programs
- Before and after adoption of INTERCEPT

	Conventional Platelets		Amotosalen/UVA Platelets	
Year	Units Transfused (n)	Transfusion Transmitted Sepsis (Fatalities)	Units Transfused (n)	Transfusion Transmitted Sepsis (Fatalities)
 FRANCE 2006- 2015	2,575,224	49 (9)	214,293	0 (0)
 SWITZERLAND* 2005-2015	156,773	13 (3)	167,200	0 (0)
 BELGIUM* 2009- 2015	252,809	9 (0)	227,797	0 (0)
Total	2,898,806	71 (12)	609,290	0 (0)

1:41,000

Benjamin R. *et al*, Transfusion, 2017; published online doi:10.1111/trf.14284 – Presented AABB Tuesday 10/10 at 2:30p

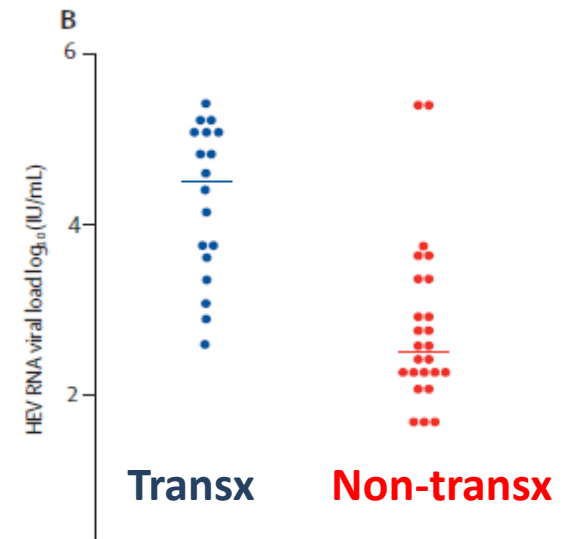
Hepatitis E virus in blood components: a prevalence and transmission study in southeast England

Lancet 2014; 384: 1766-73

Patricia E Hewitt, Samreen Ijaz, Su R Brailsford, Rachel Brett, Steven Dicks, Becky Haywood, Iain T R Kennedy, Alan Kitchen, Poorvi Patel, John Poh, Katherine Russell, Kate I Tettmar, Joanne Tossell, Ines Ushiro-Lumb, Richard S Tedder

- Oct 2012-13 => 225,000 donations HEV RNA screened (MP 24)
- **79 (1:2848)** HEV gt 3 pos => 129 blood components => 62 transfused => 43 recips followed => **18 (42%)** HEV RNA pos
- Infection more likely if higher viral loads
- Immunosuppression delayed or prevented seroconversion

Although viral loads generally low ($<10^6$ IU/mL), inactivation resistant, thus PI ineffective



Interpretation Our findings suggest that HEV genotype 3 infections are widespread in the English population and in blood donors. Transfusion-transmitted infections rarely caused acute morbidity, but in some immunosuppressed patients became persistent. Although at present blood donations are not screened, an agreed policy is needed for the identification of patients with persistent HEV infection, irrespective of origin, so that they can be offered antiviral therapy.

Proposal

- Most agents inactivated at 5-6 log reduction level based on infectivity models (INTERCEPT); however, there are exceptions: B19, HAV, HEV
- Regardless of pathogen burdens, should easily be managed by NAT+PI, where NAT eliminates high pathogen loads and remainder is inactivated
 - Why should we retain serology?
 - Likely want to retain MP-NAT: HIV, HBV, HCV, WNV, ZIKV
- Can we move to a MP-NAT-only paradigm with PI?
 - MP-NAT for screening minus serology
 - Reentry by ID-NAT/serology including
 - Deferrals for testing/health histories

ID Testing in the US – Post Universal PI

Routine testing for 10 ID agents using 13 screening tests on 6 screening platforms and 19 supplemental platforms/tests

Infect Disease Agent	Serology-Based Screen + Suppl	Nucleic Acid-Based Screen + Suppl
HIV-1/2	1 (PRISM)+3 (IFA, EIA, rapid test)	1 (MP) + 2 (serology; alt NAT)
HCV	1 (PRISM) + 1 (EIA)	1 (MP) + 2 (as above)
HBV	2 (PRISM)+ 2 (neut [Ag], PCR [Ab])	1 (MP) + 2 (as above)
HTLV-I/II	1 (PRISM) + 2 (WB + EIA)	0
<i>T. pallidum</i>	1 (PK7300)+ 2 (EIA => RPR)	0
<i>T. cruzi</i> *	1 (PRISM) + 2 (ESA + EIA)	0
WNV	0	1 (MP) + 2 (as above)
ZIKV	0	1 (MP) + 2 (as above)
Babesia	1 (AFIA)	1 (MP) + 2 (as above)
CMV*	1 (PK7300)	0
HEV		1 (MP) + 2 (as above)
Total	9 + 12	5 + 14

*Not performed on all donations

Routine Use of Pathogen Inactivation for all components could change the way we ensure blood safety *tomorrow*

- Proactive vs Reactive - protect from EIDs before identification
- Close Window Periods and eliminate occult infections
- Reduce/eliminate bacterial transmissions
- Simplify testing, donor deferral/reentry policies
- Decrease # donor deferrals
- Protect from intracellular pathogens that avoid immune detection
- Stop transmission of nucleic acids with unrecognized, or underappreciated functions
- Reduce/eliminate alloimmunization
- Single inventory?

