The US Transfusion Transmissible Infections Monitoring System (TTIMS)

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Monitoring of TTIs in the US Blood Supply

- There are many independent blood centers and blood systems in the US
- Therefore, no one blood collector can provide a complete picture of TTI prevalence and incidence rates, and projected risks nationally
- Overall donor infection rates are low, so large datasets needed to monitor possible trends
- Until recently there was no mechanism for routine, central collection of blood donor, donation and TTI data representing more than half of US collections
- Such monitoring is essential in the face of policy change

Transfusion Transmissible Infection Monitoring System

REDS-II Transfusion Transmitted Viral Infection Marker Prevalence and Risk Factor (RF) Study

- Funded by NHLBI under the Recipient Epidemiology and Donor Evaluation Study-II (REDS-II)
- Pilot study objectives:
  - Establish mechanisms to collect TTI data in blood donors from multiple blood systems covering different geographical regions
  - Determine “surveillance” definitions
  - Calculate prevalence/NAT yield for HIV, HBV, HCV, HTLV
  - Determine risk factors for HIV, HBV, HCV HTLV positives and controls
  - Determine motivations and other contributors to donation behavior
- Participants:

American Red Cross (ARC); Blood Systems (BSI); New York Blood Center (NYBC) OneBlood (OB) for risk factor studies

1. Custer et al. *Transfusion* 2015 May;55(5):1098-107. doi: 10.1111/trf.12951.
2. Vahidnia et al. *Transfusion* 2016 Aug;56(8):2013-20. doi: 10.1111/trf.13678
3. Vahidnia et al. *Qual. Life Res.* 2017 Feb;26(2):349-357. doi: 10.1007/s11136-016-1392-5.
4. Dodd et al. *Transfusion* 2016 Nov;56(11):2781-2789. doi: 10.1111/trf.13759.

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REDS-II RF Study: Participants

Sites/Participation 2011-2012				
Year	ARC	BSI	NYBC	All Centers
2011	6,182,133	956,624	439,705	7,578,462
2012	5,892,588	925,114	414,730	7,232,432
Total by Center	12,074,721	1,881,738	854,435	14,810,894
% by Center	81.5	12.7	5.8	

OneBlood participated in the Risk Factor interview portion of the study

REDS-II RF Study: Viral Marker Data

- Defined a common data structure for each system
  - ID test results
  - Demographics
- Implemented a “surveillance” positive definition
  - Reviewed test algorithms – differences exist among centers
  - Defined a common algorithm used by each system
- Established data structure
- Developed data transmission methods
- Implemented Quality Control measures
  - Reviewed all data, corrected problems/issues
  - Collected and assembled numerator and denominator data
- Analyzed and reported data for 2011-2012

REDS-II RF Study: Surveillance Definition Categories

Marker	Confirmed NAT-Yield	Concordant NAT/Serology*
HIV	**RNA (dHIV pos) + RNA conf'd (indep sample) and/or Ab Seroconversion (SC)****	**Ab RR + RNA (dHIV)**
HCV	**RNA (dHCV pos) + RNA conf'd (indep sample) and/or Ab SC**	**Ab RR + RNA (dHCV)**
HBV	**DNA (dHBV pos) + DNA conf'd (indep sample) and/or Ag/Ab SC**	**Ag RR+ DNA (dHBV) Ag RR + Ab RR + DNA (dHBV) Ab RR + DNA (dHBV)**
HTLV	**N/A**	**Ab RR/conf'd (NAT N/A)**

*Seroconversion (F/U) for ARC donors only

**Eliminates supplemental testing not uniformly applied

Policy Changes: MSM Deferral

- Implemented in 1985
  - 1977 was thought to be the start of the HIV epidemic
  - Anti-HIV testing lacked sensitivity
  - Little known about immunopathology
  - Permanent deferral for MSM any time since 1977
- Developing concerns
  - MSM express sense of discrimination
  - Social support for MSM manifested by donation boycotts, etc.
  - Political pressure
  - Anti-HIV tests improve/NAT implemented; however, WP remains
- Progress
  - Computer controls prevent erroneous release of quarantined units
  - Blood organizations call for change following worldwide response
  - Data and modeling imply change to a 1-year deferral is acceptable
  - REDS-II Risk Factor study established a baseline
  - May 2015 DRAFT HIV Guidance => FINAL Guidance Dec 2015

Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products

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Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
December 2015

Per Guidance, "A Transfusion Transmissible Infections Monitoring System (TTIMS) is being implemented in the United States in order to facilitate monitoring of the safety of the U.S. blood supply for a variety of different pathogens.

FDA will use TTIMS to further investigate and refine blood safety screening measures over the coming years.

Through this monitoring system a variety of donor risk factors can also be evaluated, based in part upon further investigation of units donated that are detected upon screening to contain infectious agents.

As part of its ongoing efforts to ensure the safety of the blood supply, FDA intends to routinely review information from TTIMS along with emerging scientific evidence to reevaluate its donor deferral policies."

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"In September 2015 the FDA and NHLBI launched the Transfusion-Transmissible Infections Monitoring System (TTIMS) program designed to establish an integrated, comprehensive blood donor and donation monitoring system for TTIs in the United States . . . FDA will use TTIMS to further investigate and refine blood safety screening measures over the coming years.

TTIMS is both a monitoring program and an opportunity to deploy research tools to understand HIV, HBV, HCV, and emerging infections in US blood donors and donated blood. TTIMS has two closely synchronized components, a **Donation Database Coordinating Center (DDCC)** led by the ARC and a **Laboratory and Risk Coordinating Center (LRCC)** led by Blood Systems Research Institute (BSRI)"

Transfusion-transmissible infection monitoring system: a tool to monitor changes in blood safety. Custer et al. *Transfusion* 2016 Jun;56(6 Pt 2):1499-502. doi: 10.1111/trf.13632.

Transfusion Transmissible Infection Monitoring System

TTIMS: Transfusion-Transmissible Infections Monitoring System

- Funded by the FDA, NHLBI and HHS via contracts starting in September 2015 with 4 x 1-year renewals
- Consists of two coordinating centers:
  - Donation Database Coordinating Center (DDCC)
    - American Red Cross (Stramer – PI)
  - Laboratory and Risk Factor Database Coordinating Center (LRCC)
    - Blood Systems Research Institute (Custer – PI)

Transfusion Transmissible Infection Monitoring System

TTIMS: Structure and Participation

- Governance:
  - Executive Committee
    - Steve Anderson, PhD, MPP, FDA, Chair
    - Susan L. Stramer, PhD, DDCC
    - Brian Custer, PhD, MPH, LRCC
    - Simone A. Glynn, MD, MSc, MPH, NHLBI
    - Alan E. Williams, PhD, FDA
  - Steering Committee includes OASH and CDC as well as representatives from the organizations listed below

- Participating Blood Centers and Test Providers:
    - American Red Cross (ARC)
    - Blood Systems Inc. (BSI)
    - New York Blood Center (NYBC)
    - OneBlood (OB)
    - Creative Testing Solutions (CTS)

Objectives of TTIMS: DDCC

- The primary objective:
  - Monitor HBV, HCV and HIV in US blood donors by developing and maintaining a complete database including data from participating blood centers representing >50% of the US blood supply
  - Build integration between DDCC/LRCC
    - Daily data exports, QC, data sharing, identification of key units for LRCC
  - Perform relevant data analyses; report results
    - Donor Prevalence
      - Sex, age groups, self-reported race/ethnicity, donation status, DHHS reporting regions
    - Donation Prevalence
    - Incidence Density
      - NAT yield
      - Seroconverting repeat donors (window period x interdonation interval)

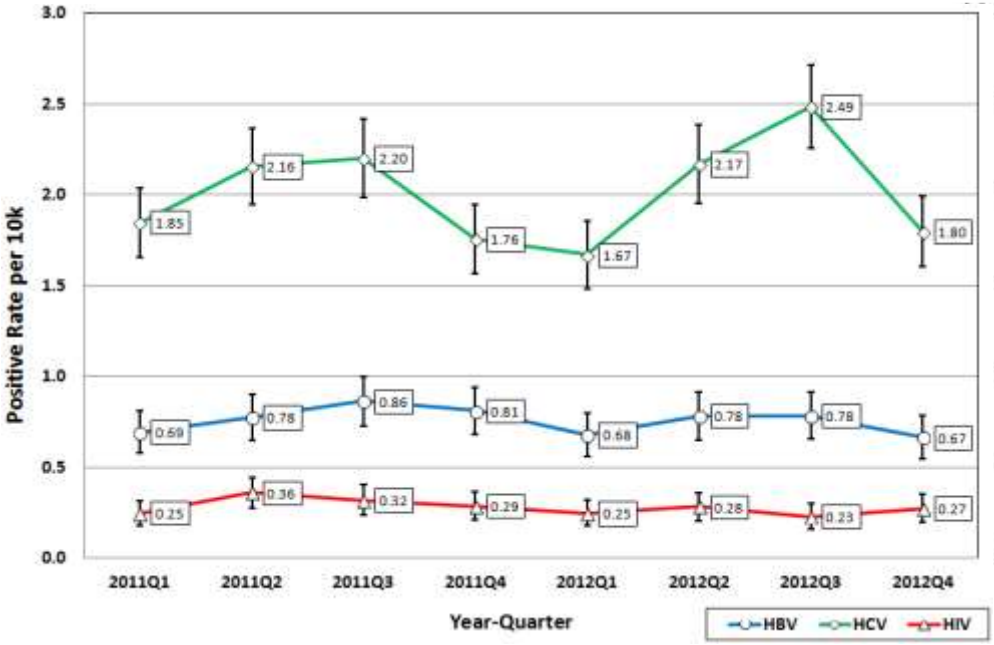
DDCC: Consensus Positive Definitions

- Same as REDS-II Viral Marker and Risk Factor Study
  - Confirmed NAT-Yield and concordant NAT/serology reactives; eliminates further supplemental testing that is not uniformly applied
- Removed HTLV
- Added HIV controllers (NAT neg)
  - Confirmed by subsequent testing of an independent sample as HIV-1 antibody positive and HIV NAT reactive in replicate testing

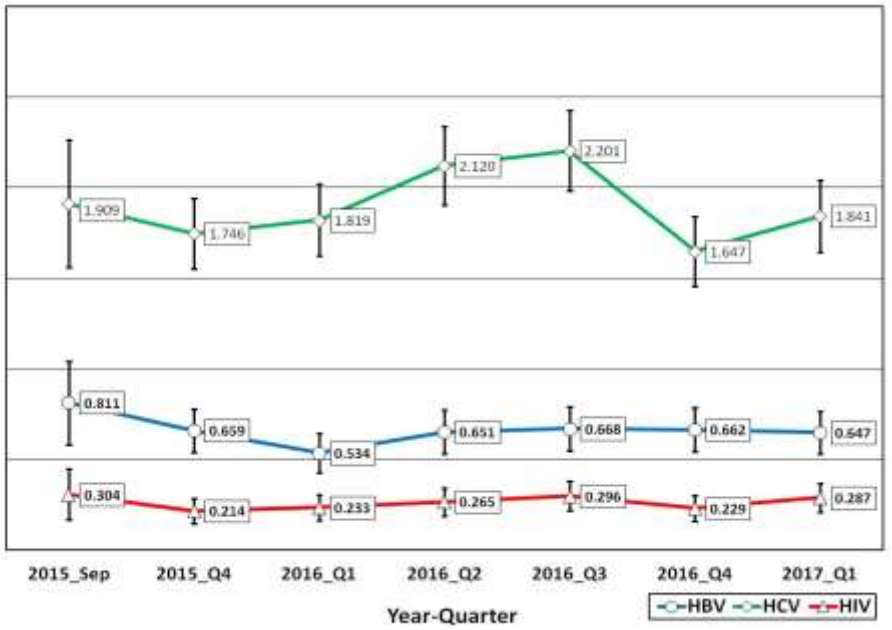
Quarterly Consensus Positive Rates

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

RF: 2011-2012
3 Centers



TTIMS: 2015 Sep – 2017 Q1
All Centers



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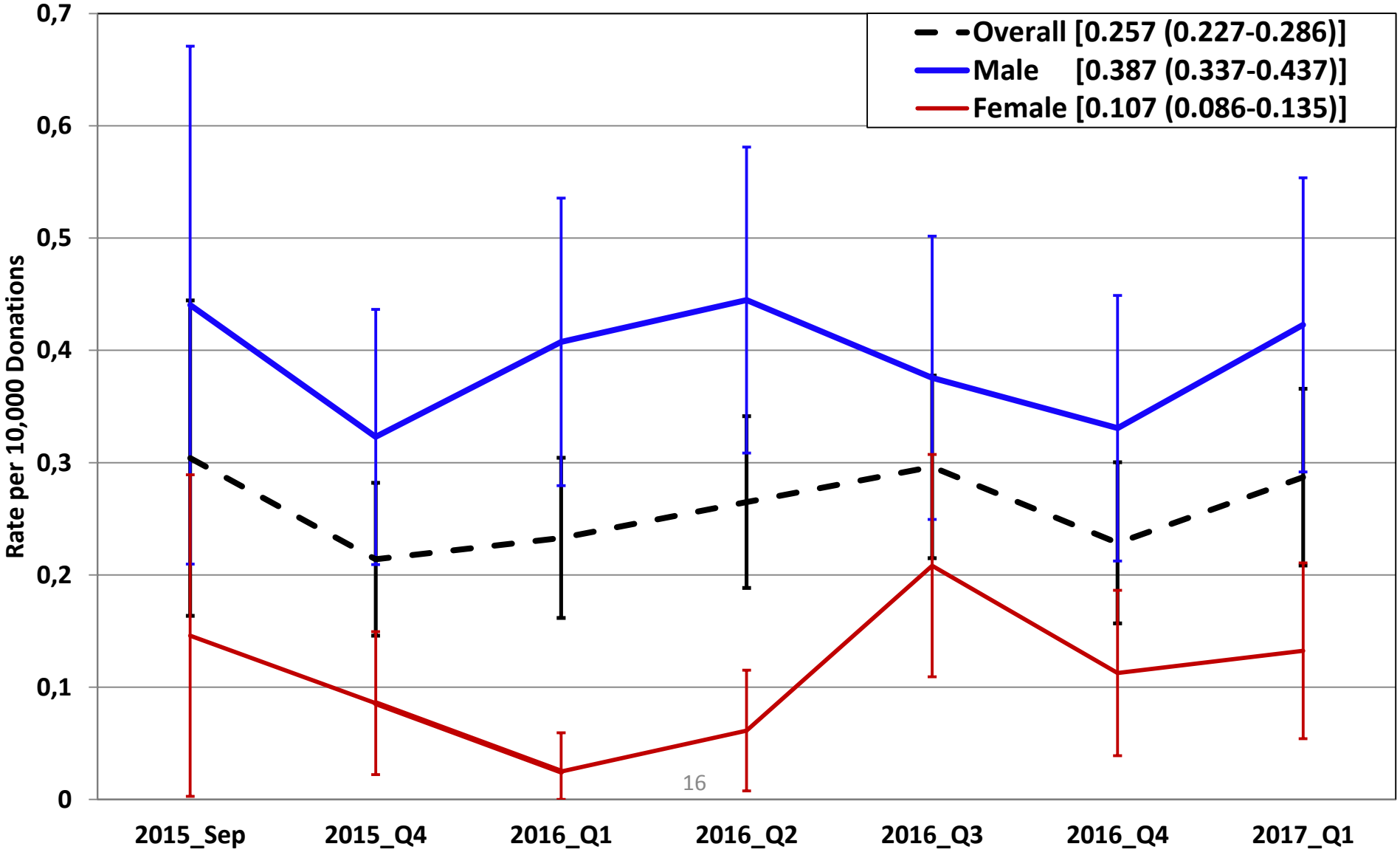
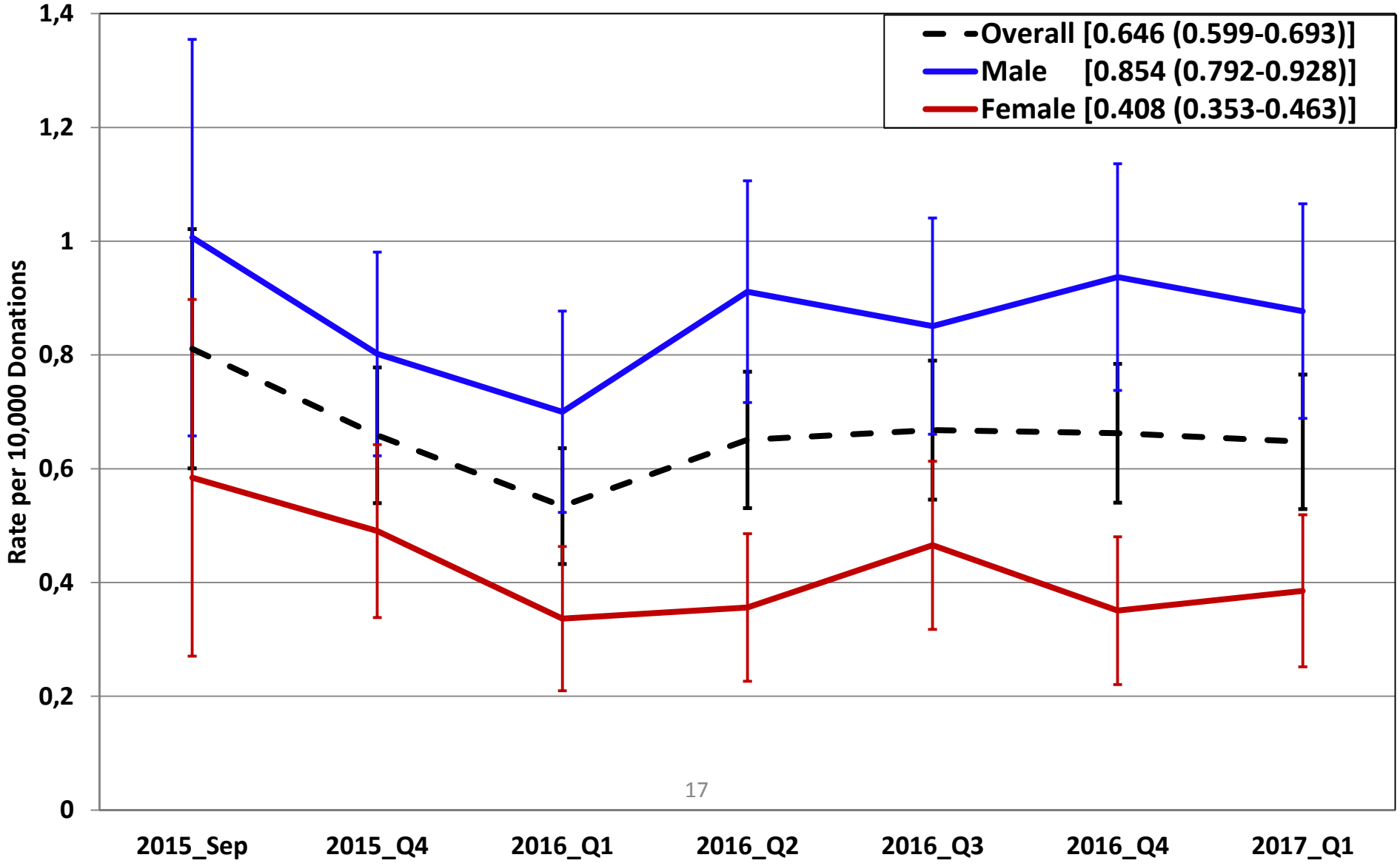
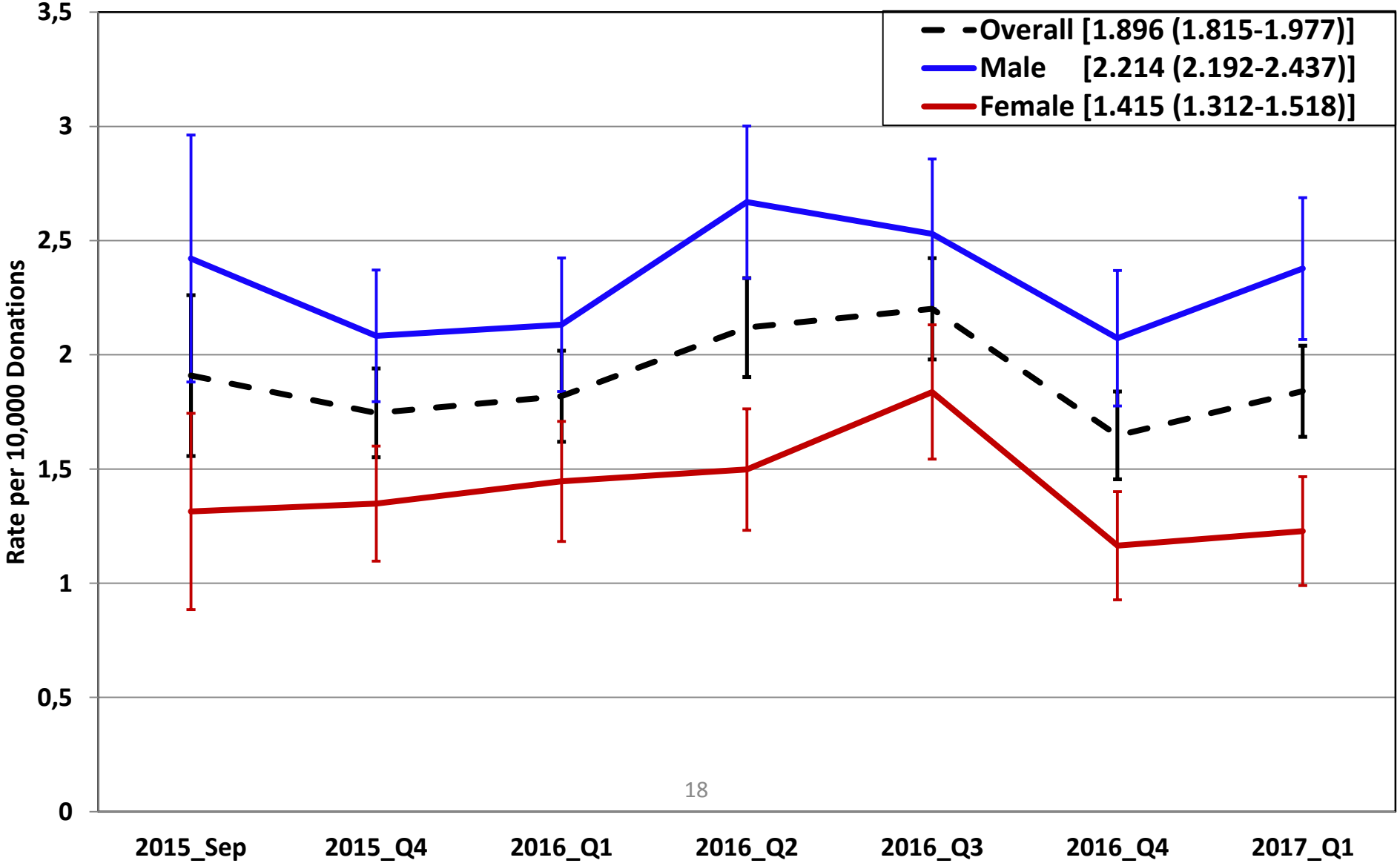
Quarterly Consensus Positive HIV Rates by Gender and Overall per 10k w/95% CI



Quarterly Consensus Positive HBV Rates by Gender and Overall per 10k w/95% CI

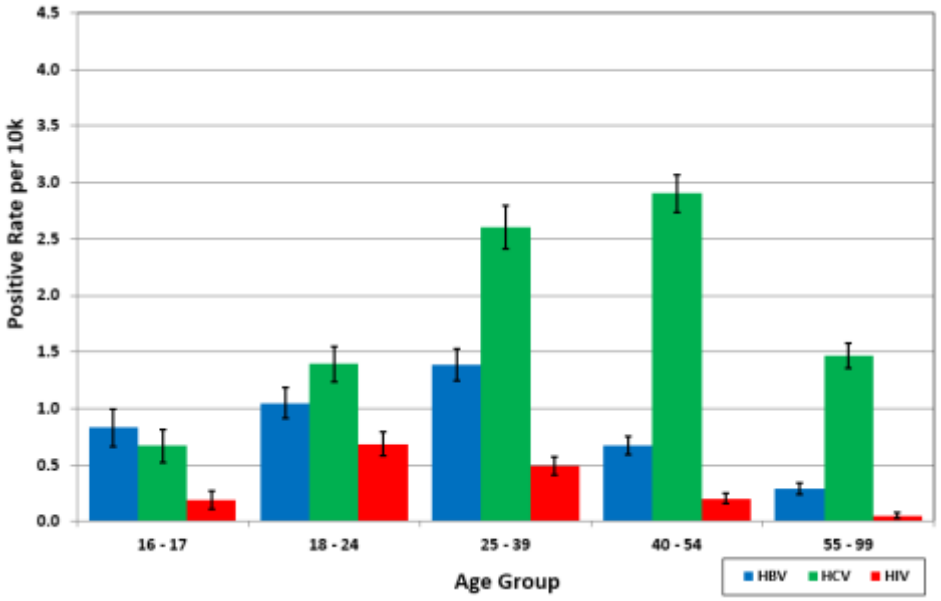


Quarterly Consensus Positive HCV Rates by Gender and Overall per 10k w/95% CI

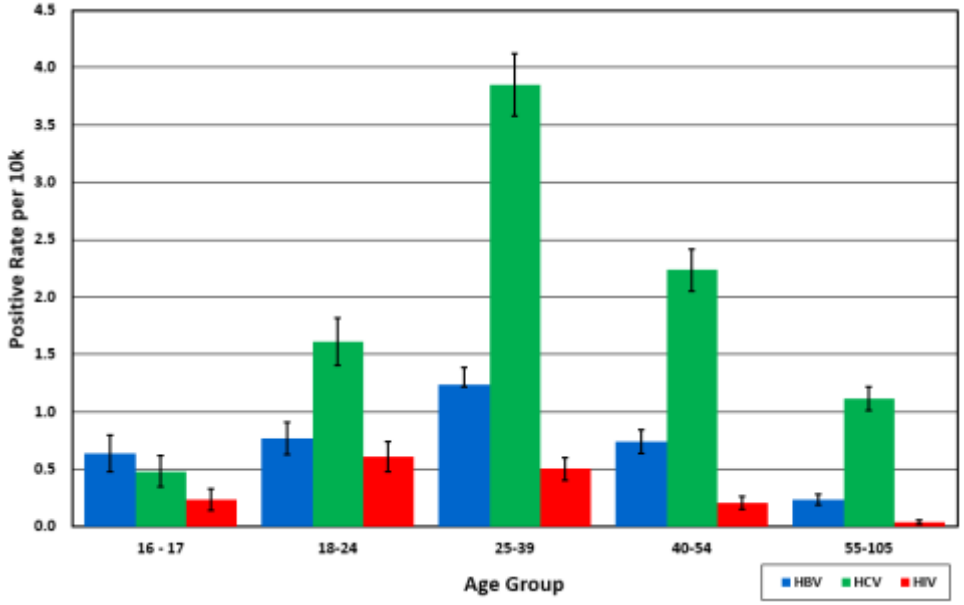


Consensus Positive Rates by Age
per 10k with 95% CI for HCV, HBV and HIV

RF: 2011-2012
3 Centers



TTIMS: 2015 Sep – 2017 Q1
All Centers



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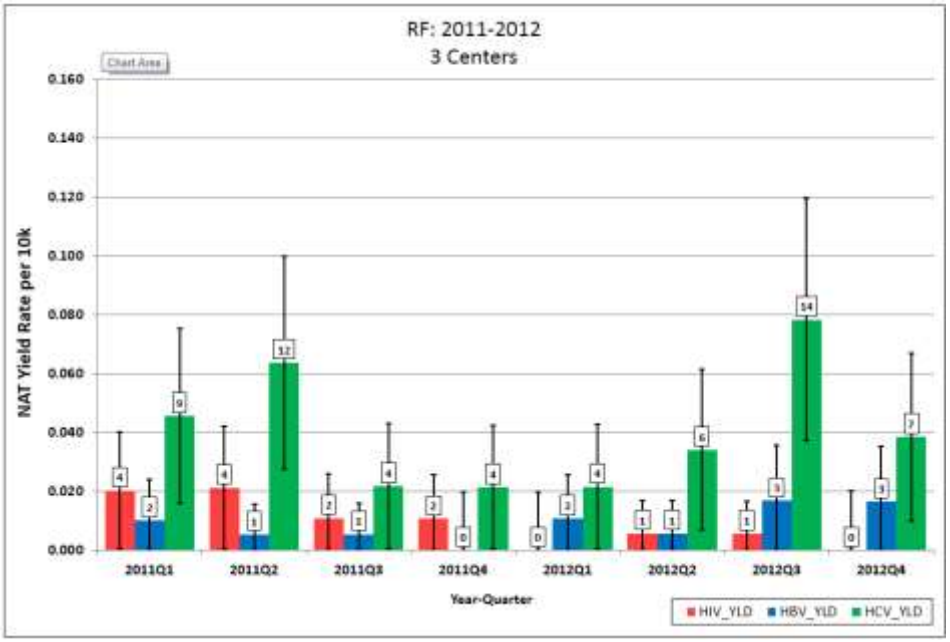
Evaluation of Changes in Prevalence

- Infection prevalence rates are known to vary throughout the year in US blood donors, and so in order to assess evidence for meaningful change, it is necessary to compare annual prevalence rates rather than shorter periods of time
- Also must assess other systemic changes like the proportion of first time and repeat donation by ABO/Rh to assess if other factors and secular trends are influencing prevalence rates
- Changes in overall rates will need to be examined in the context of the demographic structure of the donor population and also in relation to the results of the risk factor studies

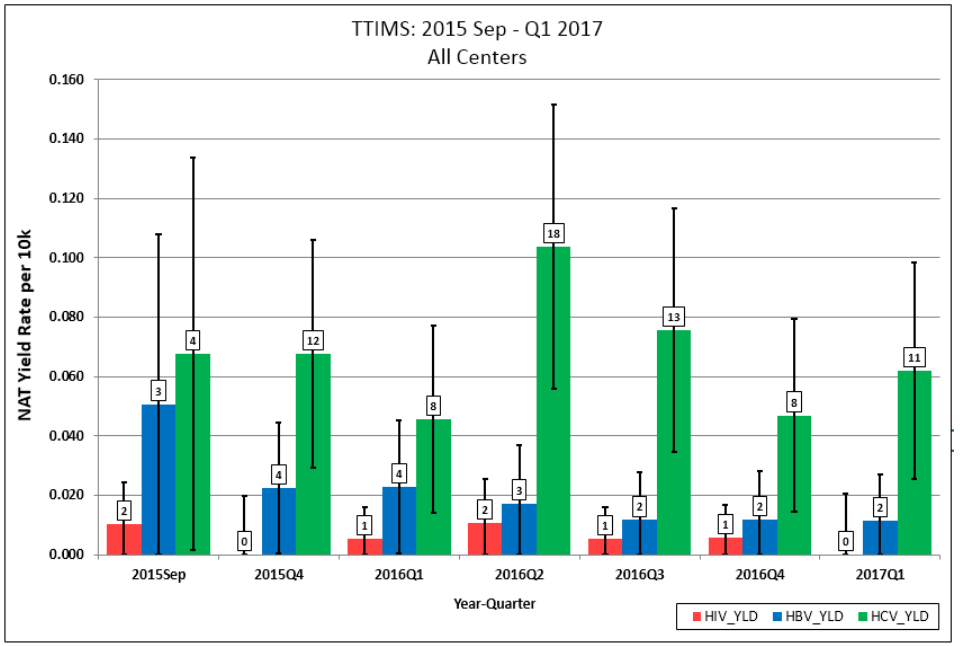
Quarterly NAT-Yield Rates

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

RF: 2011-2012
3 Centers



TTIMS: 2015 Sep – 2017 Q1
All Centers



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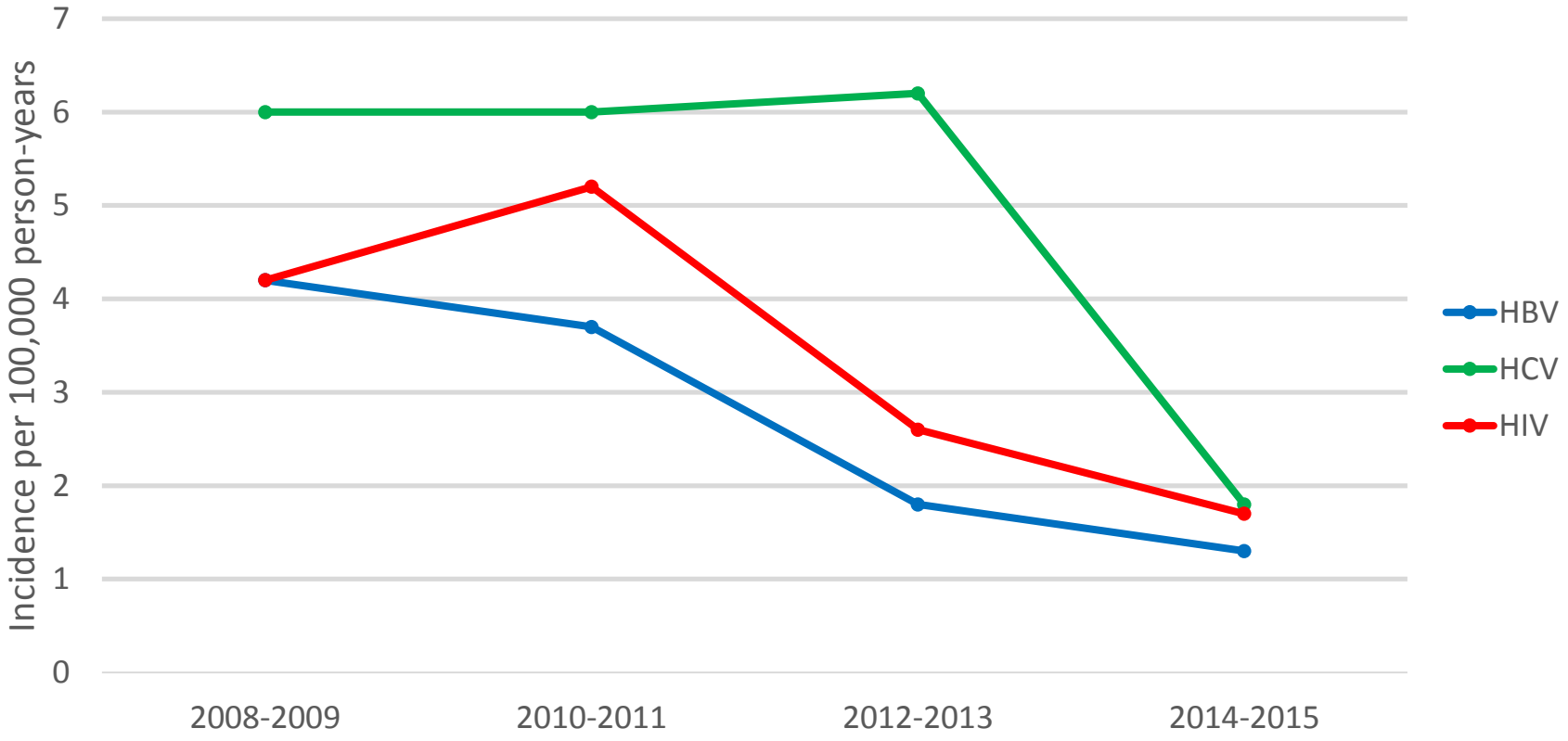
Incidence (per 100,000 person-years)
Four 2-year periods for American Red Cross Donors



Crowder, et al. AABB 2017

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Incidence and Residual Risk
Four 2-year periods for American Red Cross Donors

		Incidence Rate (/100,000 PY)	*	Infectious Window Period (days)	=	Residual Risk
2008-2009	**HIV**	**4.17**		**9.1**		**1:962,135**
	HCV	**6.03**		**7.4**		**1:817,990**
	HBV	**4.17**		**18.5**		**1:473,037**
2014-2015	**HIV**	**1.65**		**9.1**		**1:2,435,350**
	HCV	**1.84**		**7.4**		**1:2,679,572**
	HBV	**1.26**		**18.5**		**1:1,564,945**

Incident donors significantly more likely to be:
Male
Caucasian
Age 18-24 (HIV), 18-39 (HCV), ≥40 years (HBV)

Crowder, et al. AABB 2017

Objectives of the TTIMS: LRCC

- Support collection and analysis of risk factor data in donors with confirmed infections (cases) and donors who test false positive (controls).
  - Risk factors by sex, age groups, self-reported race/ethnicity, donation status, DHHS reporting regions
  - Compare risk factor data to those obtained in the REDS-II Viral Marker Prevalence and Donor Risk Factor Study.
- Serve as the biospecimen (plasma) repository for the TTIMS project.
- Perform recency testing on HIV plasma samples from donors with HIV concordant positive donations
  - Assess recently acquired infection by sex, age groups, self-reported race/ethnicity, donation status, DHHS reporting regions
  - In collaboration with the DDCC assess new approaches for calculating incidence with recency data
- Conduct viral genetic sequence analyses on plasma samples for HIV (NAT yield and seropositive), HCV (NAT yield) and HBV (NAT yield) positive blood donors to determine genotypes and drug resistance (where applicable) of donor infections.
- Integrate separate data to gain deeper insight into donor behavior

REDS-II RF Study: Risk Factor Interview Enrollment

- Case-control study, Interviews from July 2011 to April 2013
- Achieved enrollment:

Infection	Cases		Controls	
	Enrolled	% Eligible	Enrolled	% Eligible
HIV	196	43%	1587	39%
HCV	316	37%		
HBV	292	40%		
HTLV	198	48%		

Custer et al. *Transfusion* 2015

Factors Associated with HIV Infection in Blood Donors	Adjusted Odds Ratio,* 95% Confidence Interval & p-value		
Sex with someone who is HIV+	138.2	28.3 – 675.2	<0.001
MSM	64.9	28.8 – 146.1	<0.001
IDU	3.3	0.4 – 25.1	0.25
3+ nights in detention/jail	2.8	1.5 – 5.4	<0.01
Tattoo or body piercing	2.6	1.5 – 4.4	<0.01
Multiple sexual partners in last year	2.2	1.3 – 3.7	<0.01

*Adjusted for first-time/repeat status, race/ethnicity, age, gender, income

Factors Associated with HTLV Infection in Blood Donors	Adjusted Odds Ratio,** 95% Confidence Interval & p-value		
Sex with IDU	21.5	9.6 – 48.0	<0.001
Exchanging money or drugs for sex	6.4	1.3 – 30.7	0.02
Multiple sexual partners in last year			
Males	1.3	0.5 – 3.1	0.62
Females	4.3	2.3 – 7.8	<0.001
STD Ever	2.7	1.5 – 4.7	<0.01

** Adjusted for first-time/repeat status, race/ethnicity, age, gender, born in US, Asian, African or S. American heritage

Factors Associated with HBV Infection in Blood Donors	Adjusted Odds Ratio*, 95% Confidence Interval & p-value		
Sex with IDU	11.4	4.7 – 27.6	<0.001
IDU	8.1	3.5 – 18.7	<0.001
Household member with Hepatitis	7.6	3.0 – 19.7	<0.001
3+ nights in detention/jail	2.3	1.3 – 4.2	<0.01

***Adjusted for first-time/repeat status, race/ethnicity, age, gender, income, born in US, Asian, African or S. American heritage**

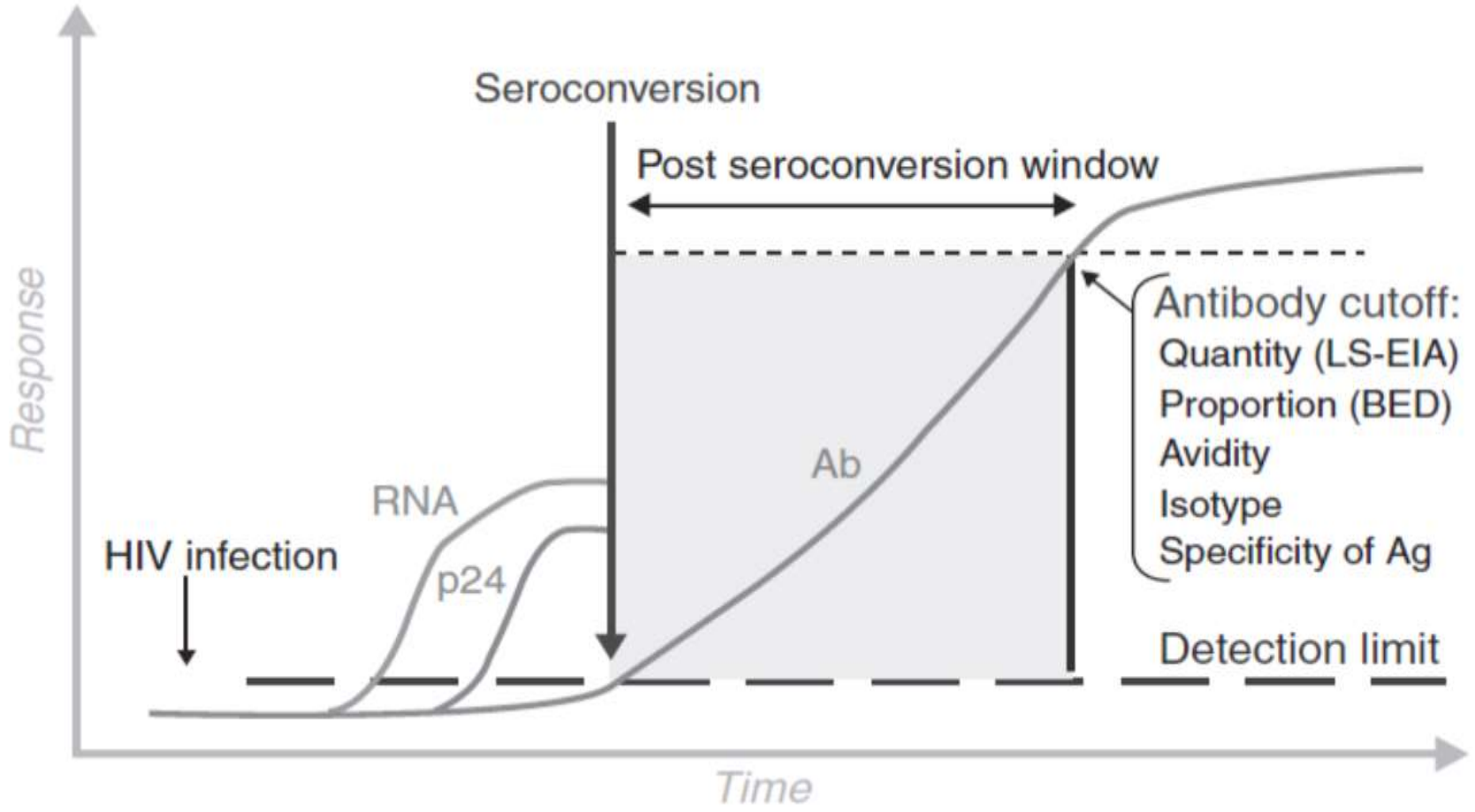
Factors Associated with HCV Infection in Blood Donors	Adjusted Odds Ratio**, 95% Confidence Interval & p-value		
IDU	42.1	13.0 – 136.3	<0.001
Household member with Hepatitis	15.4	5.9 – 40.3	<0.001
Sex with IDU	9.7	4.4 – 21.2	<0.001
3+ nights in detention/jail	7.5	4.3 – 12.9	<0.001
Transfusion Ever	5.1	2.7 – 9.6	<0.001
Tattoo or body piercing	3.5	2.0 – 5.9	<0.001

****Adjusted for first-time/repeat status, race/ethnicity, age, gender, education, born in US**

Risk Factor Interviews

- Domains of Interview:
  - Demographics including SES, Motivations for donation, Sexual history and behaviors, Other risk behaviors, Sexual partner risks, Medical exposures
- Complex approvals process in the US
  - IRBs and Office of Management Budget approvals now obtained and interviews will commence this fall
- All interviews conducted by trained donor counselors using a common questionnaire and protocol
- Web-based data collection – immediate availability in research database within the SMS
- Qualifying cases (meeting study definitions)
- Anti-HIV or HBsAg false positives (controls)

A Typical Incidence Assay Dynamic



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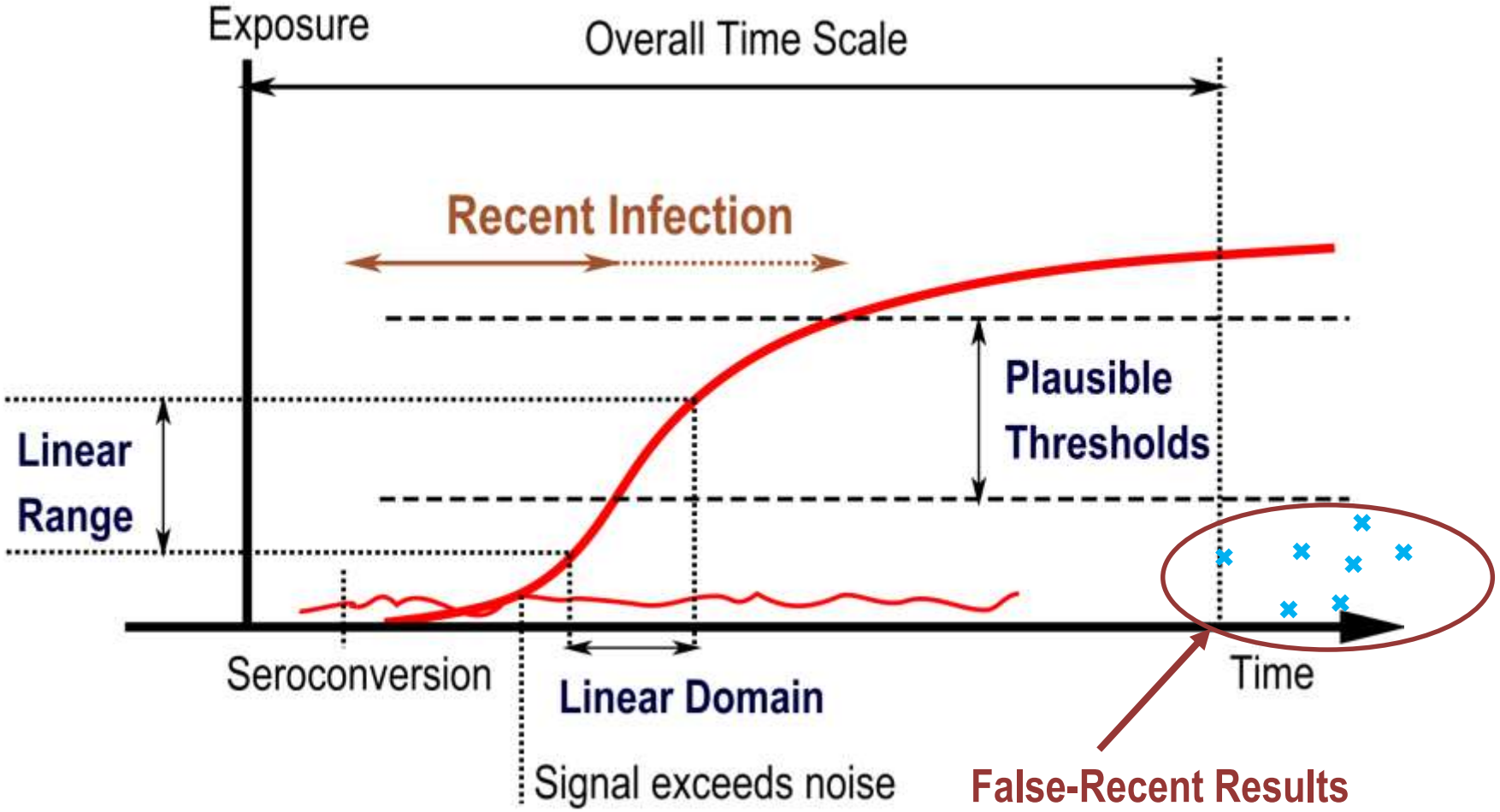
A Typical Incidence Assay Dynamic



- **Trade-off between Mean Duration of Recent Infection (MDRI) and False Recency Rate (FRR)**
- **Context-dependent performance**
- **Specimen repository versus population**

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Current Activities

Classify HIV concordant positive infections (NAT + seropositive) as recently acquired or longstanding

- Sedia Limiting Antigen (LAg) Avidity test*
  - MDRI of ~130 Days (95% CI 118 – 142 days)
  - FRR of 1.9% (95% CI 1.2%-2.8%)

  *reported performance – in established HIV concordant positive donations the FRR is expected to be lower
  - Product insert cut-off ODn is 1.5
  - Samples with initial result ODn ≤ 2.0 are tested again
- Available stored samples for testing

Period	Total
Retrospective Testing Q1 2010 – Q3 2015*	608
TTIMS Period Q4 2015 – Q1 2017	149

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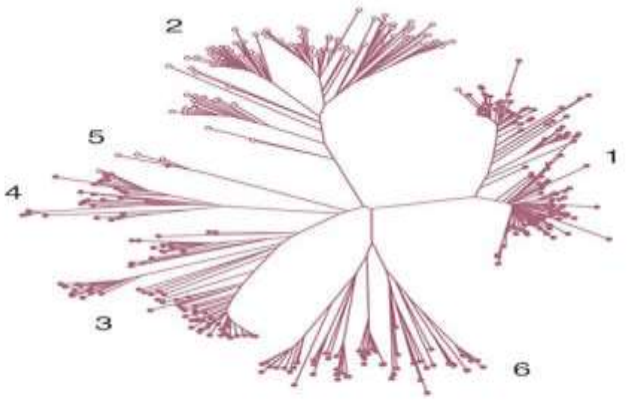
Molecular Surveillance



- HIV, HBV, HCV
  1. For HIV, a fragment of 1275 base pairs (bp) of polymerase including the protease and reverse transcriptase genes
  2. For HCV, a fragment of 363 bp in the core gene
  3. For HBV, a fragment of 2015 bp, including the envelope and polymerase genes

- Followed by NexGen sequencing

- Reporting of HIV genotypes and drug resistance
- Reporting of HBV and HCV genotypes (and drug resistance)

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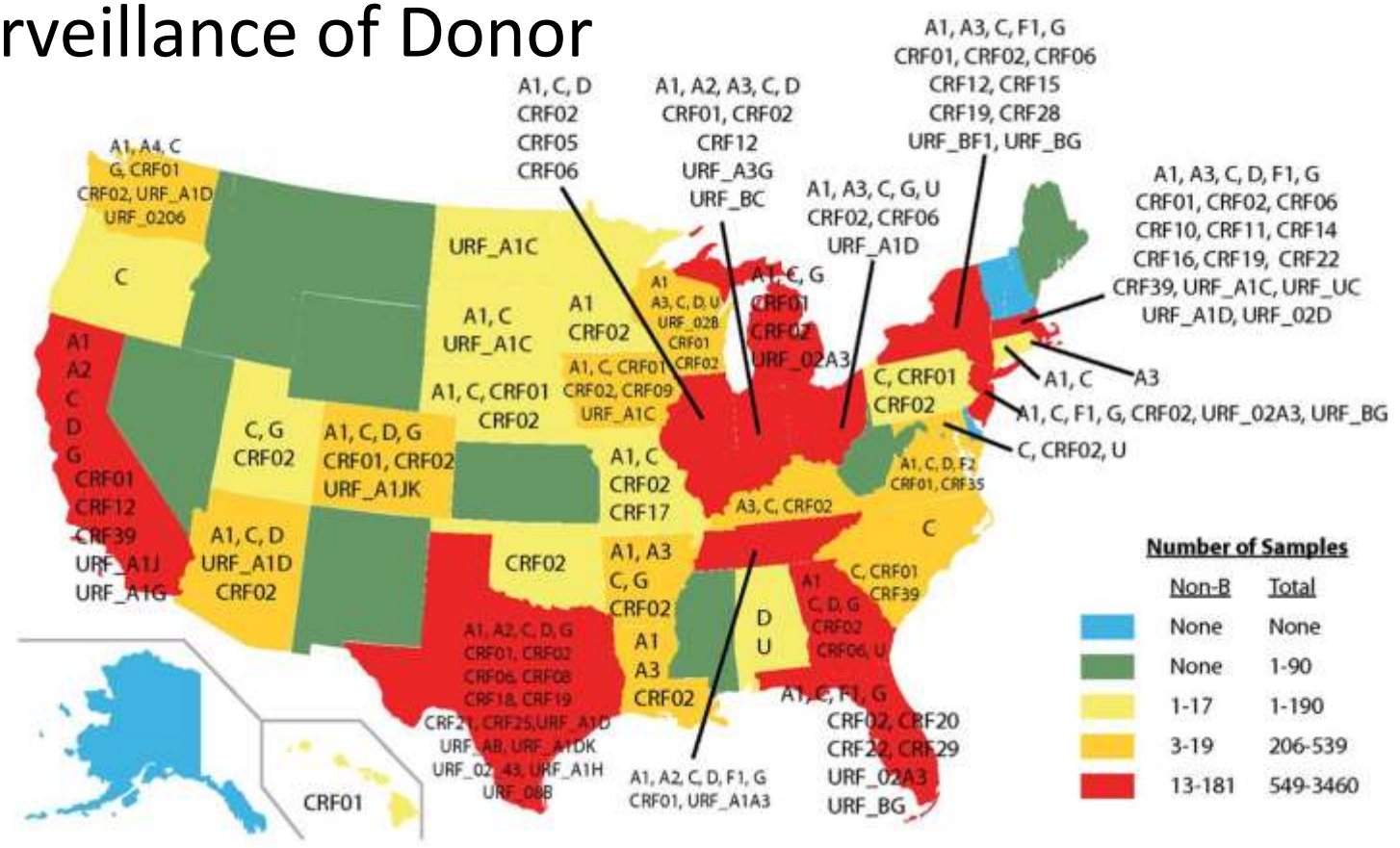
Molecular Surveillance of Donor Infections



Pyne et al. *J Clin Microbiol* 2013;51: 2662-9.

Study Period	Population	Number studied	Number (%) Non-B HIV-1 Subtype	Subtypes Detected
1984-1985	TSS donors & hemophiliacs	143	0	0
1993-1996	Donors in CDC study	383	2 (0.8%)	1 C, 1 CRF A/G
1997-1998	Donors in CDC study	163	3 (1.8%)	3 Cs, 1 HIV-2
1999-2000	Donors in CDC study	130	4 (3.1%)	2 C, 1CRF01, 1A
1999-2007	Donors to ARC	208	6 (2.9%)	1 A, 1 D, 2 CRF A/G, and 1 URF_BF
2006-2009	Donors in REDS-II study	381	7 (2.5%)	4 C, 2CRF02, 1 A

Considerations

- Mechanisms have been developed to collect/analyze data from multiple blood systems → first national sampling for monitoring of blood donor "infections"
- Infection rates continue to be very low among US blood donors
- A relatively large change in infection rates would be needed for statistical significance
- Changes in infection rates will be greatly influenced by collection practices (impact of the current focus on "right type" of donors)
- TTIMS DDCC/LRCC:
  - Could be used to support future changes in policy
  - Will establish a baseline from which to assess changes in infection rates in response to MSM 77 → MSM 1 year

Summary

- TTIMS is a multi-center, multiple objective donor biovigilance initiative
- TTIMS has established the capacity to monitor infection prevalence and incidence in nearly 60% of donations collected in the US
- Risk factor and laboratory analyses will provide further insight into donor infections in the US
- Recent changes in donor deferral policies for HIV will be monitored using TTIMS
- TTIMS will be able to assess whether the experience reported in other countries following donor policy change is evident in the US

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CTS

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NYBC

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OneBlood

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