ISBT TTID WP London Presentations

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Quality control testing of pathogen inactivation-treated blood components by mtDNA real-time PCR

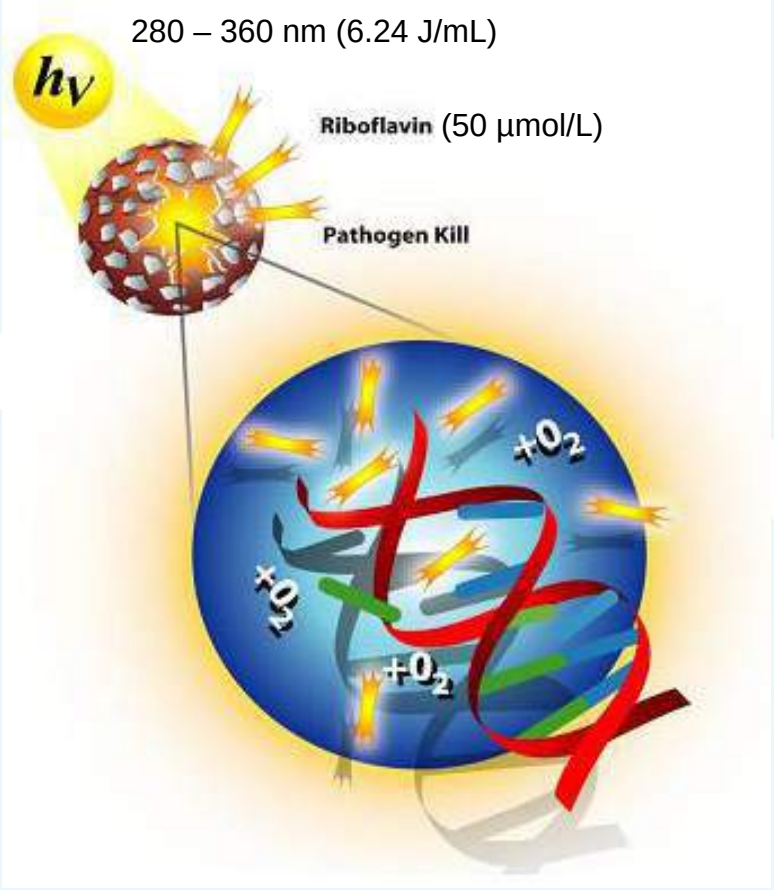
Sonia Bakkour, PhD

ISBT London TTID WP

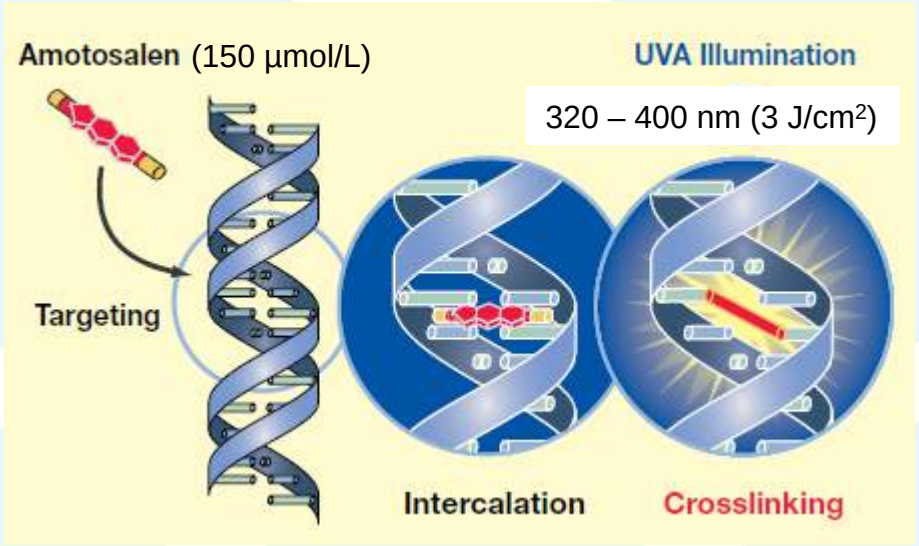
June 26, 2015

Blood Systems Research Institute

Mechanism of action of PI technologies



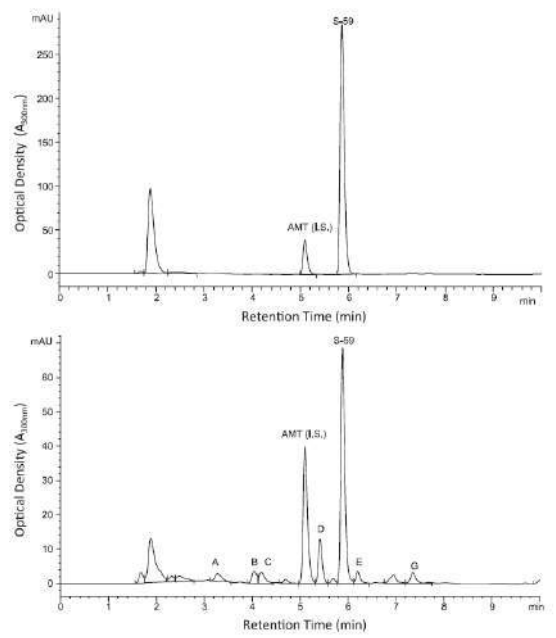
- Oxidative damage to guanine bases
- Strand breaks



- Intra-strand crosslinks
- Inter-strand crosslinks

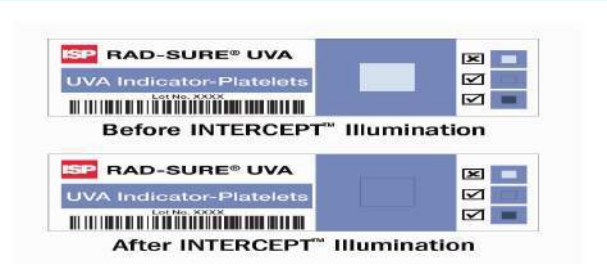
Confirmation of PI completion

HPLC



Liu W et al., Transfusion 2011

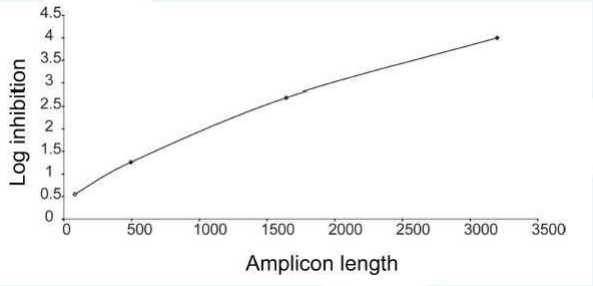
UV sensitive label



Isola H et al., Vox Sang 2010

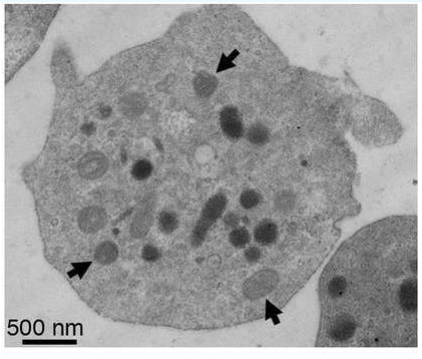
PCR inhibition

Virus	Preamp length (bp)	Preamp cycles
HBV	495	14
	1642	16
	3200	22



Allain JP et al., JID 2006

Mitochondrial DNA as a target for PCR inhibition by PI



Boudreau LH et al., Blood 2014

In platelet units:

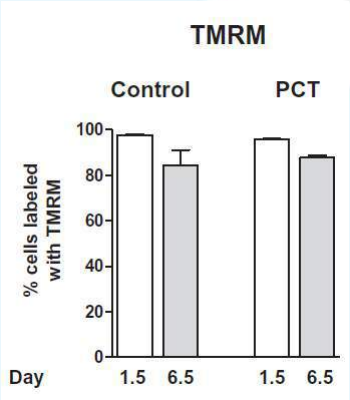
- 99.8% of mtDNA from platelets
- 0.2% of mtDNA from rWBC

TABLE 1. Immediate effects of Mirasol PRT treatment on PLT mitochondria*

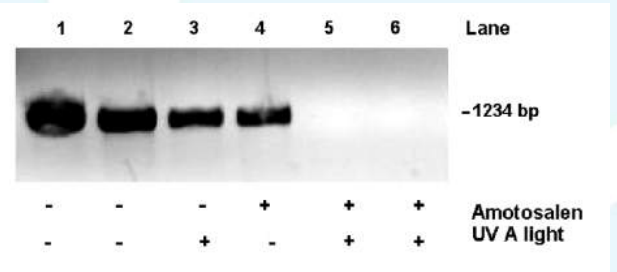
Variables	Control (n = 5)	Mirasol PRT (n = 7)
pH at 22°C	7.45 ± 0.02	7.51 ± 0.06
Mitochondria		
Polarization (%)	94.7 ± 1.8	95.9 ± 1.7
Depolarization (%)	1.5 ± 1.0	1.0 ± 1.2
MTT (OD490)	0.875 ± 0.027	0.885 ± 0.055
ATP (μmol/10^{11} PLTs)	5.08 ± 0.72	4.64 ± 0.93

* No significant difference between the control and treated PLTs was found for all tested variables.

Li J et al., Transfusion 2005



Hechler B et al., Transfusion 2013

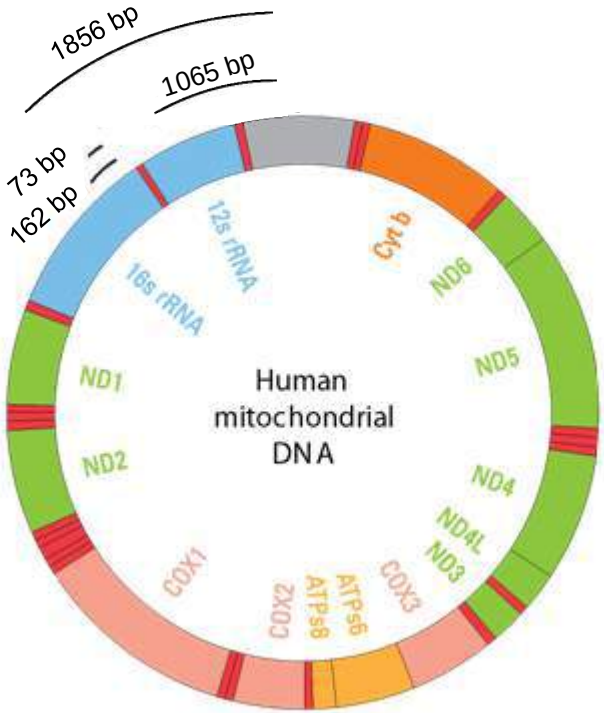


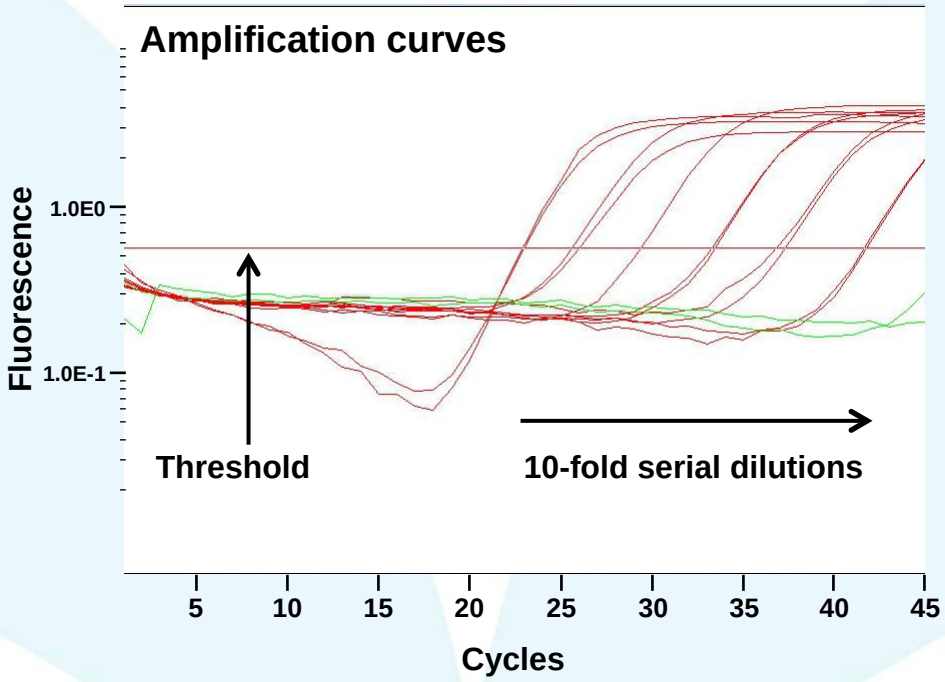
Bruchmüller I et al., Platelets 2005

Conventional gel-based PCR:

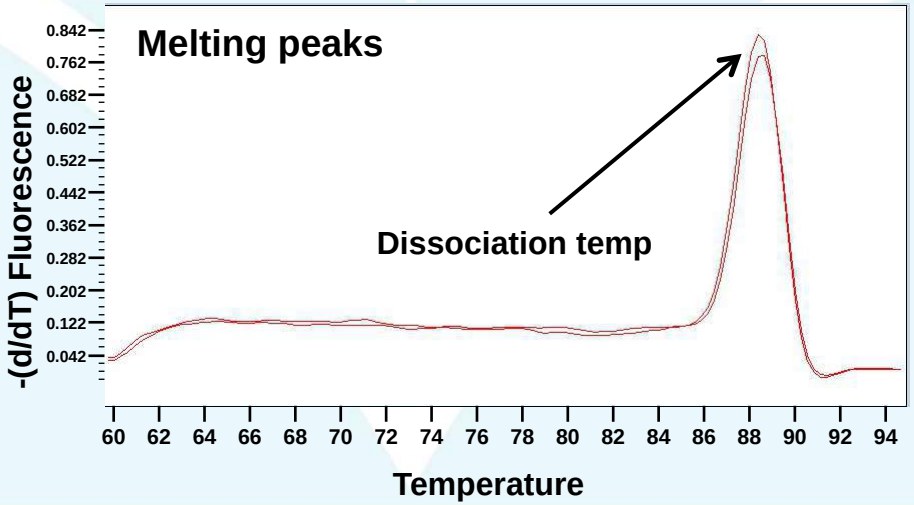
- Endpoint detection, signal plateau
- Low-throughput

mtDNA real-time PCR assays





Amplicon size	Dynamic range	E
73 bp	≥ 6 log	102%
162 bp	≥ 6 log	104%
1065 bp	5 log	81%
1856 bp	4 log	79%



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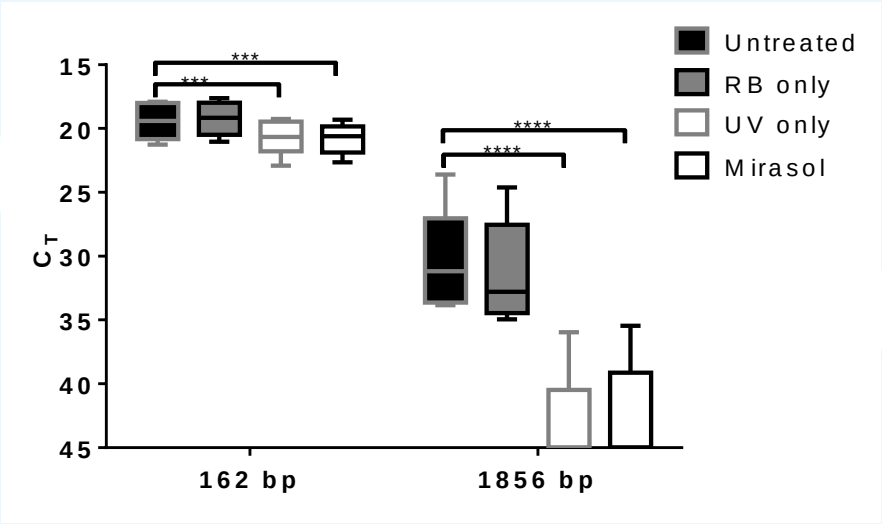
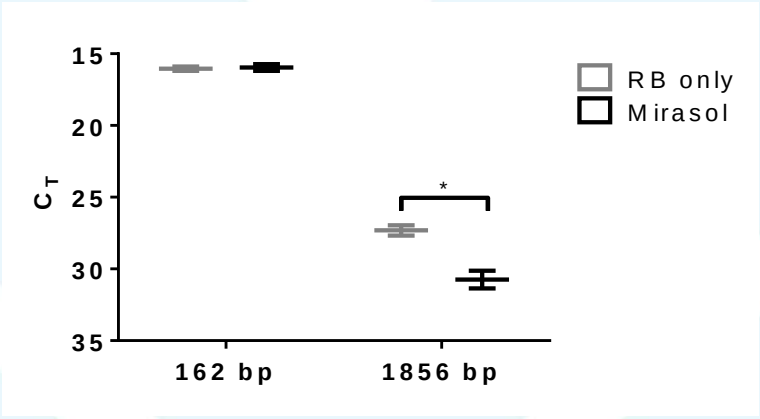
Proof-of-principle:
Effect of Mirasol PRT on purified mtDNA

Spiking in PBS:
~ 4 log reduction



Spiking in plasma:
~ 1 log reduction



Bakkour S et al., Vox Sang 2014

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Platelet processing procedure for mtDNA qPCR inhibition assay

Platelet unit (~ 10^9 PLT / mL)

↓

Freeze small volume aliquot (~ 1 mL)

↓

Batch mode Extract DNA from 200 µl (~ 2 x 10^8 PLT equivalent)

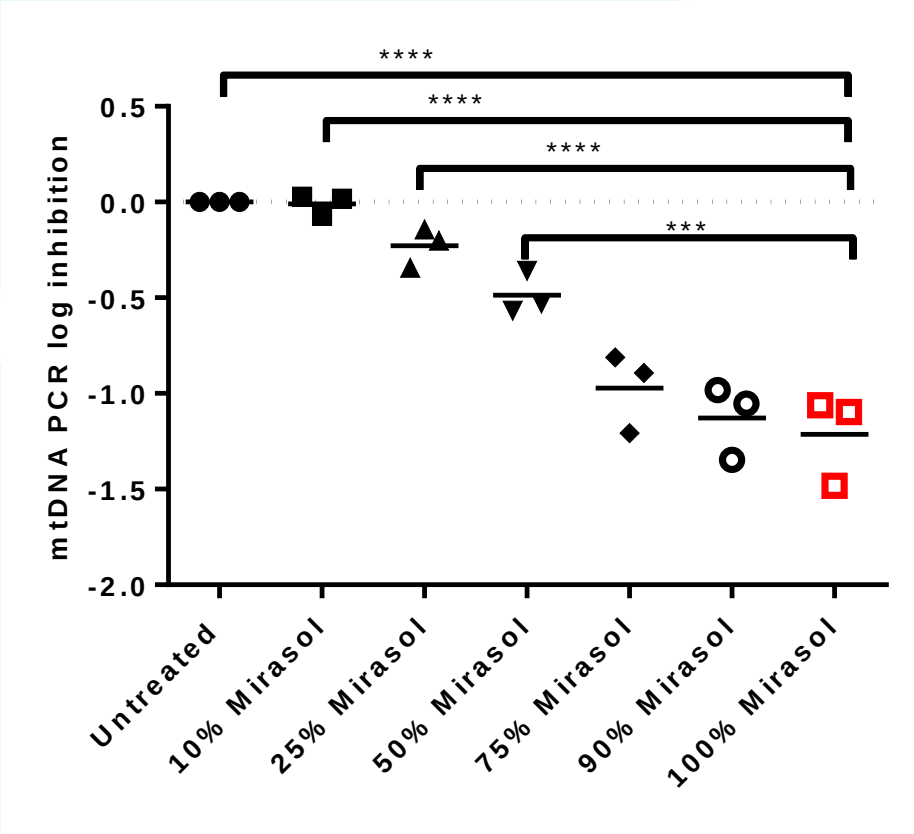
↓

Elute in 200 µl

↓

Amplify 15 µl per PCR well
(~ 15 x 10^6 PLT equivalent), in duplicate

Effect of Mirasol PRT on mtDNA in platelets: dose response



Inhibition calculated based on 1856 bp assay, normalized using 162 bp internal control assay.

Bakkour S et al., Vox Sang 2014

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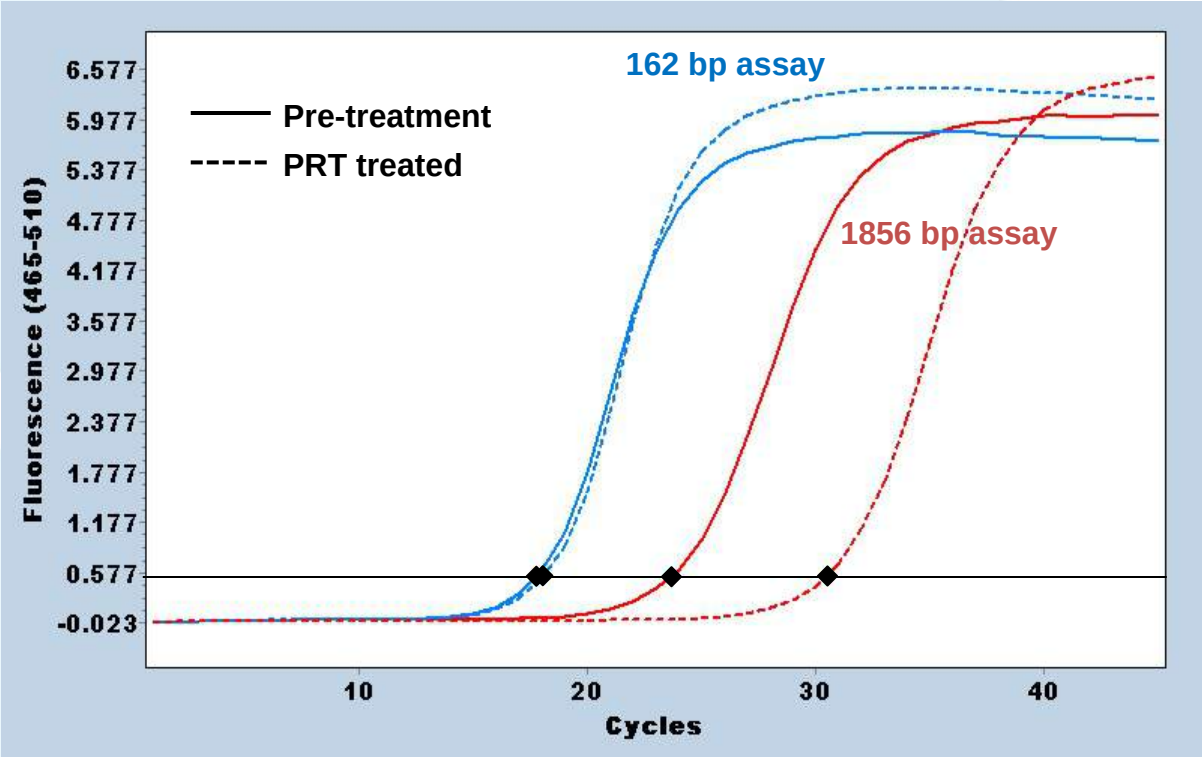
Quantification of mtDNA PCR inhibition by delta CT



Short amplicon assay serves to normalize variations in sample prep

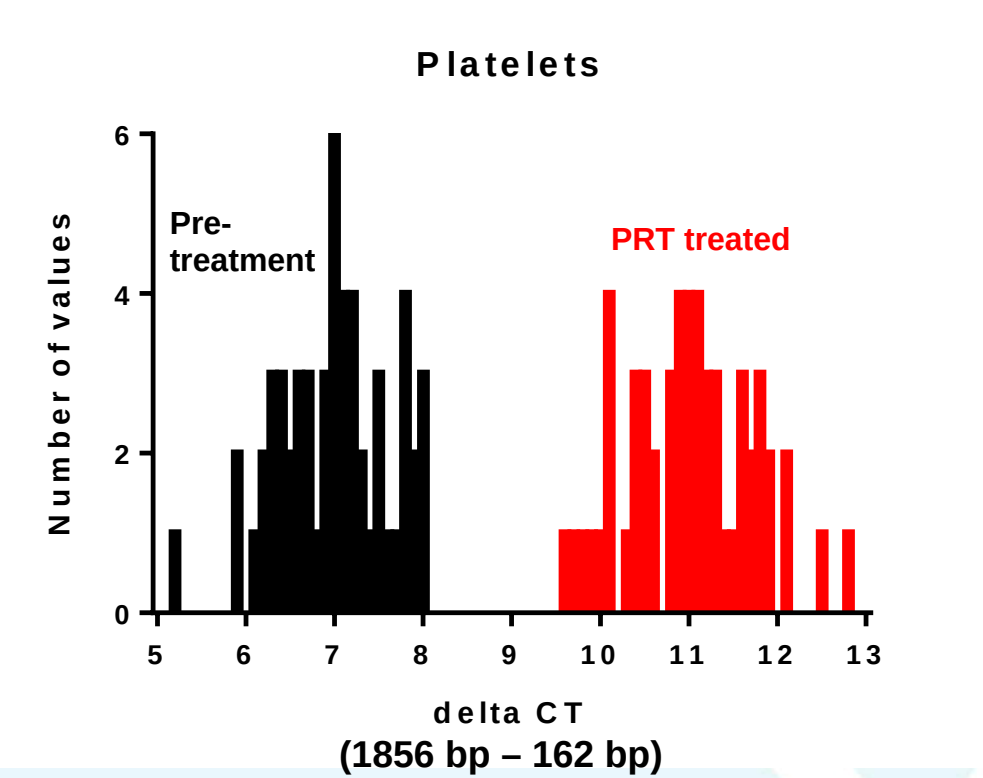
<u>Experimental setting:</u>
Both pre- and post-PRT samples available

Delta Ct (1856_{treat} – $1856_{control}$) = 7 cycles
Delta Ct (162_{treat} – $162_{control}$) = 0 cycles

<u>Routine QC setting:</u>
Post-PRT samples tested to verify inactivation

Delta Ct (1856 – 162):
13 cycles → inactivated product
7 cycles → failure to inactivate product

Blinded QC study of Mirasol PRT in PREPAReS using large vs small amplicon mtDNA PCR inhibition



100% discrimination of PRT treated products vs pre-treatment products (n = 55 each)

Bakkour S et al., Vox Sang 2014

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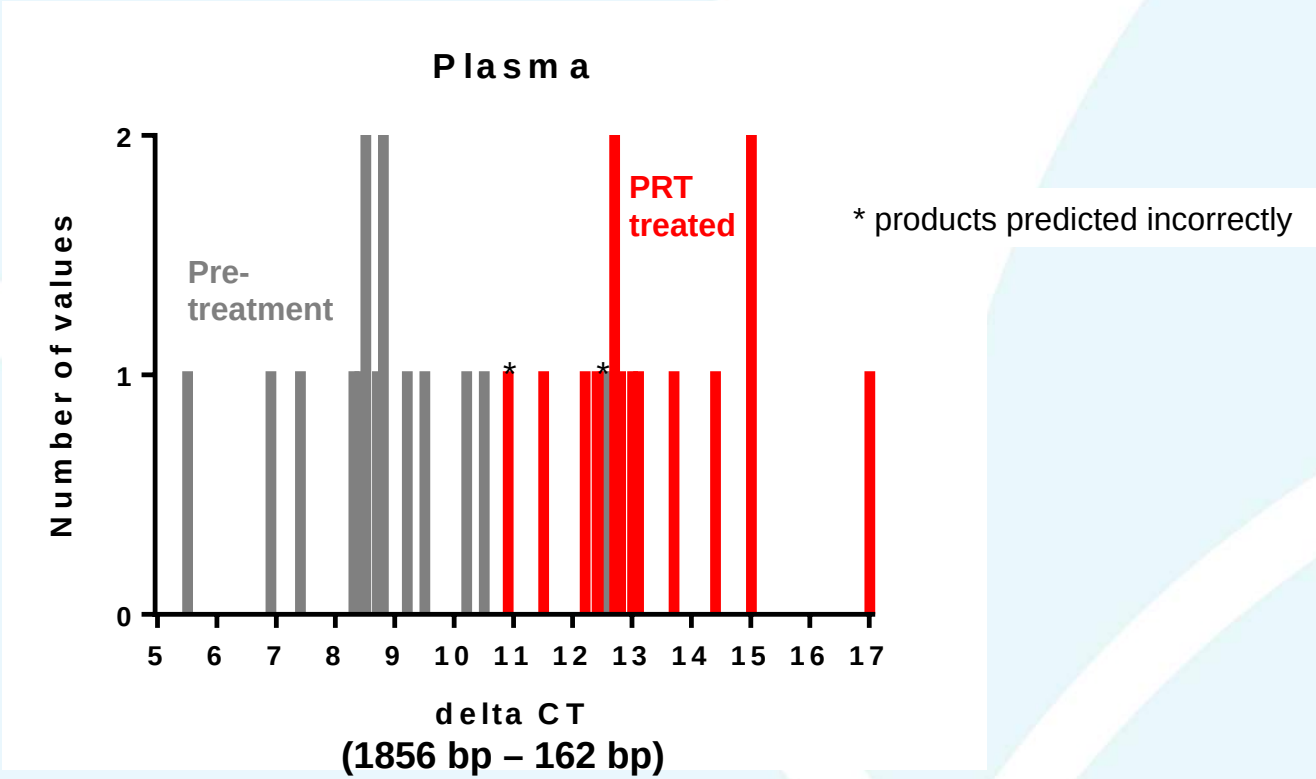
Effect of Mirasol PRT on mtDNA in plasma: blinded study



93% discrimination of PRT treated products vs pre-treatment products (n = 15 each)

Bakkour S et al., Vox Sang 2014

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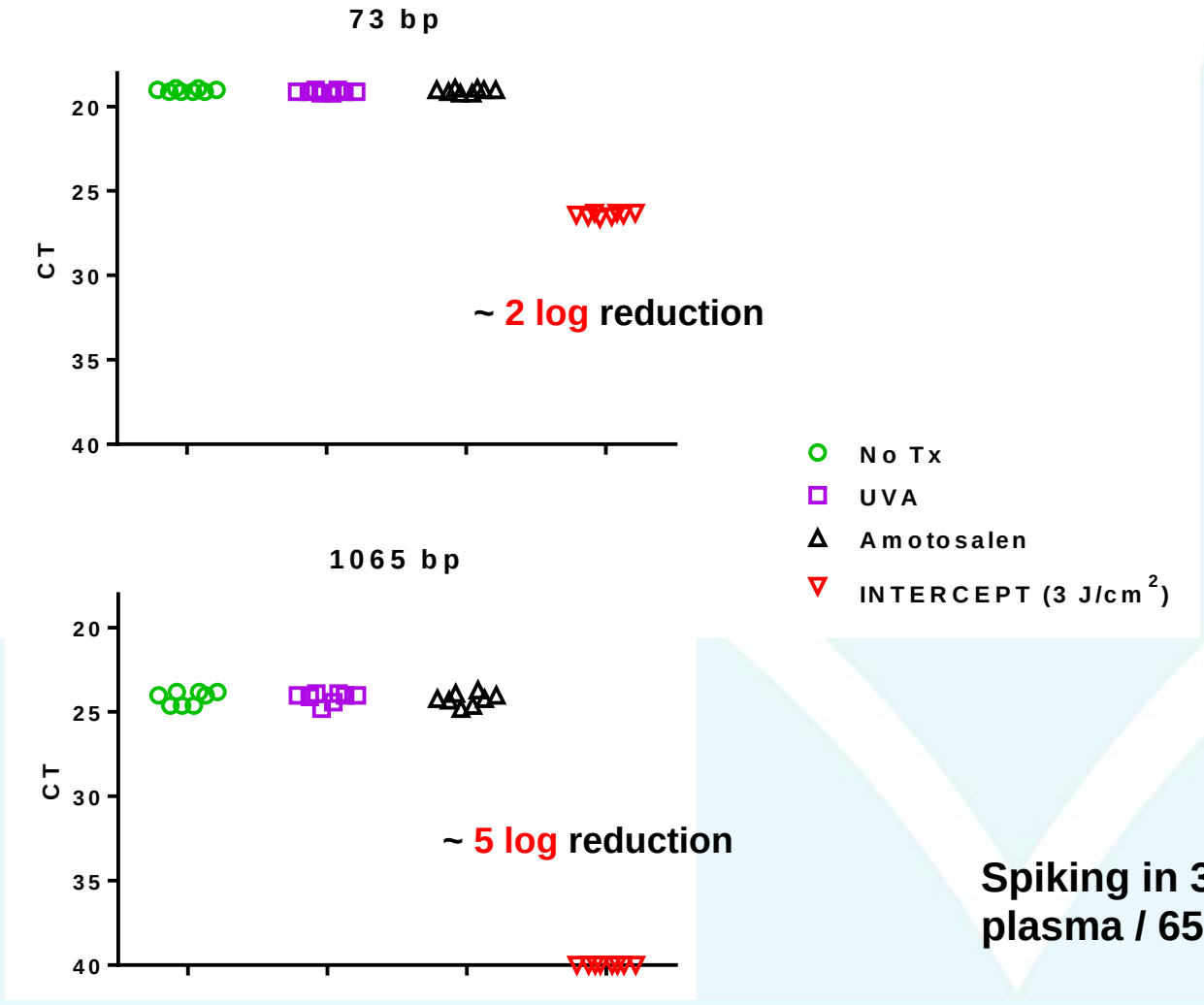
Proof-of-principle:
Effect of INTERCEPT PRT on purified mtDNA



Spiking in 35% plasma / 65% InterSol

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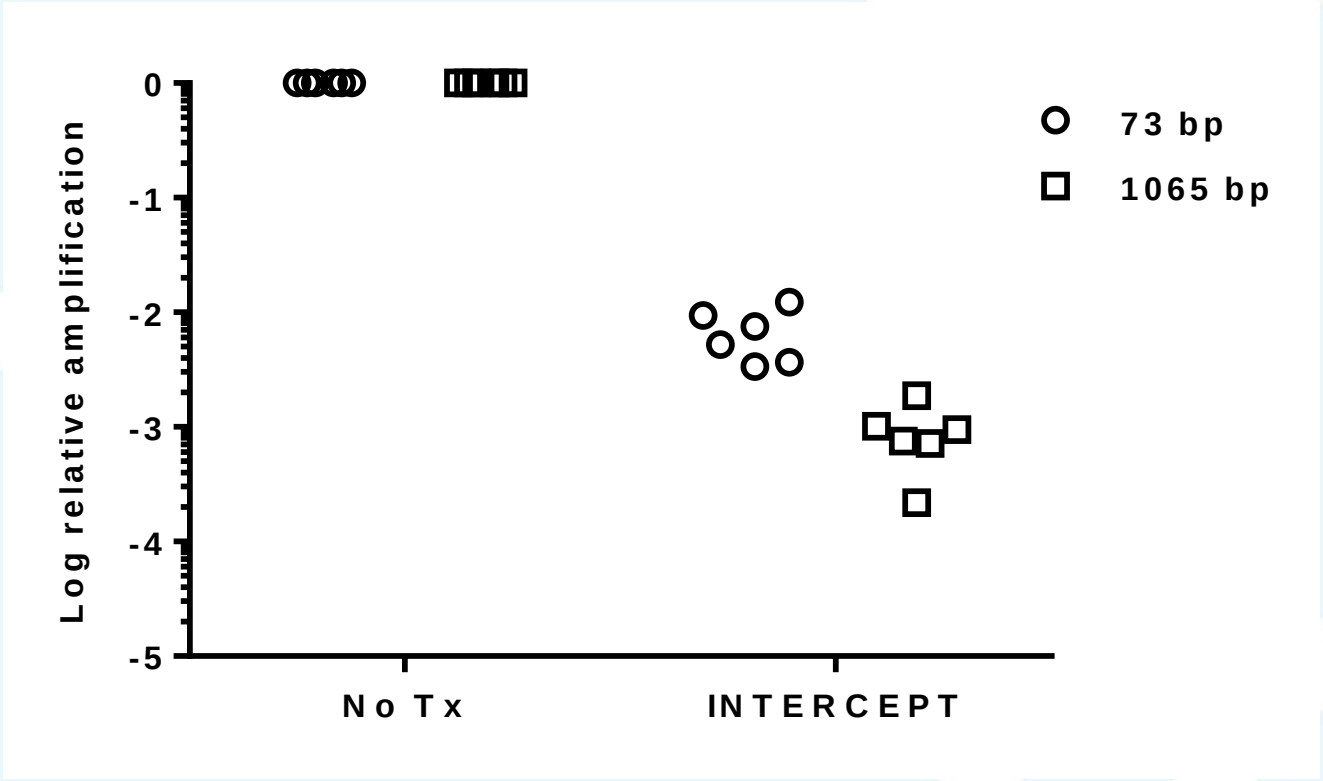
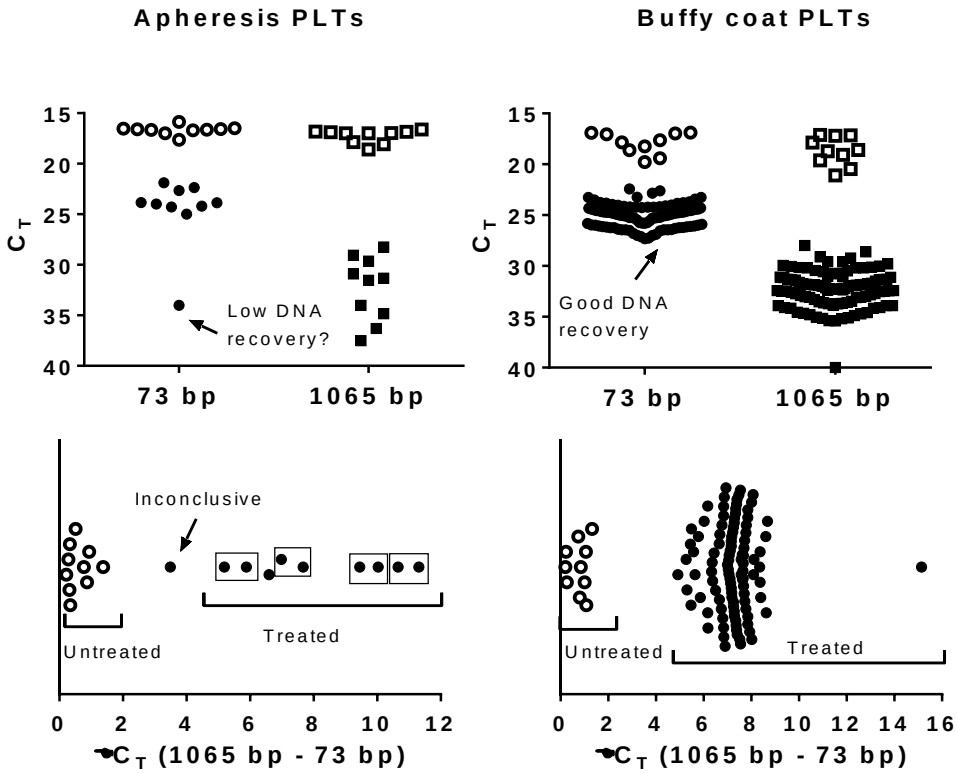
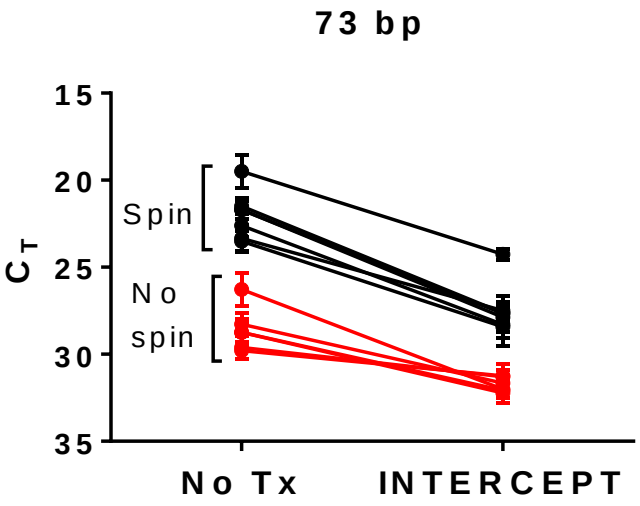
Effect of INTERCEPT PRT on mtDNA in platelets

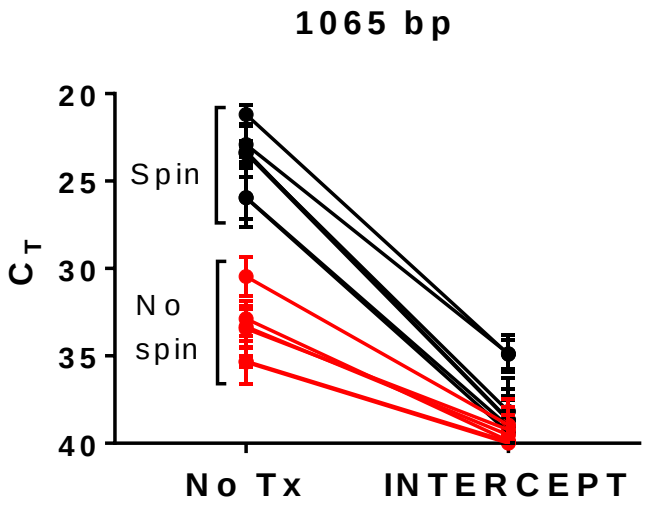


ΔC_T quantification of mtDNA PCR inhibition in blinded platelet samples



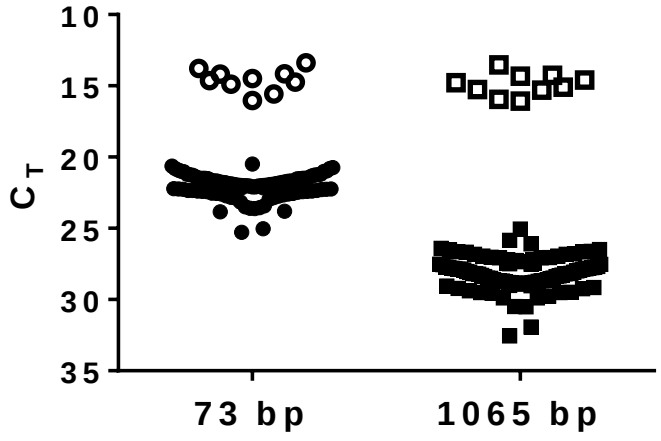
Effect of INTERCEPT PRT on mtDNA in plasma: signal enrichment through centrifugation

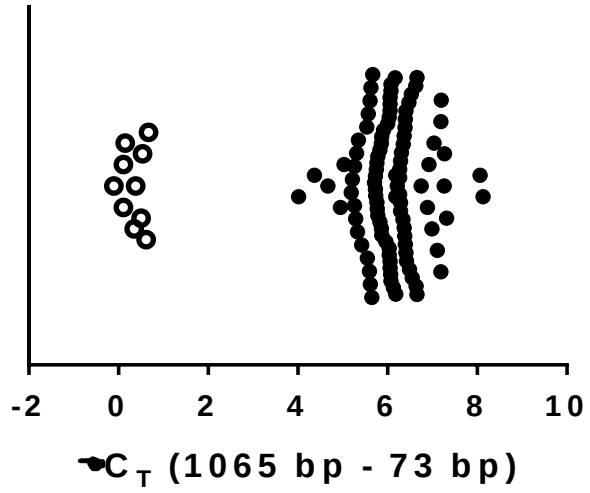




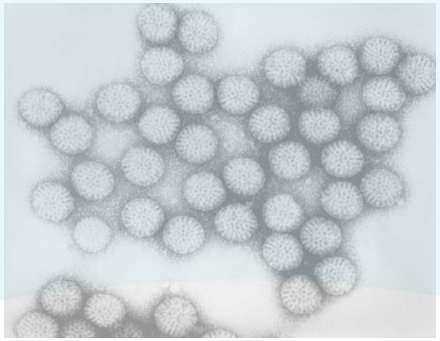
1.8 mL plasma spun at 21,000 x g for 15 min

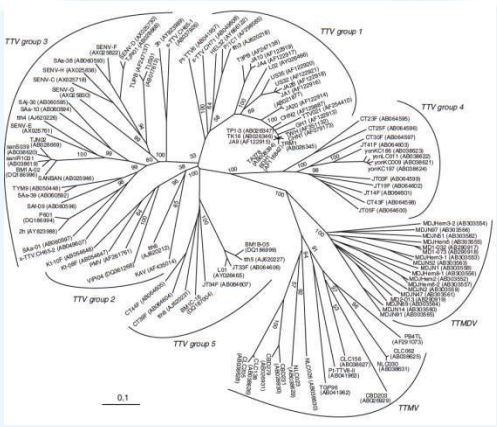
Effect of INTERCEPT PRT on mtDNA in centrifuged plasma: blinded study





Molecular assays of anelloviruses as evidence of PI efficacy





- Most frequently detected virus in human plasma/serum by deep sequencing
- Each species has multiple genotypes
- Detection rate and diversity greater in highly transfused patients
- Transfusion transmitted
- Evaluate ability of PI to prevent TT:
  - Test for replication of transfused genetic variants in recipients of +/- PI components
    - NGS
    - Allele-specific PCR

Summary

- Different mtDNA amplicon target lengths are used to detect PCR inhibition induced by different PI technologies.
- Evaluation of PI treated plasma requires further sample processing to increase mtDNA signal.
- Potential use of mtDNA PCR inhibition assay:
  - QC test for illuminated products
  - Tool for investigating breakthrough infections

➢ Who should perform the testing?
➢ Selection of samples for testing?
➢ Other PI technologies?

Thank you!

Blood Systems Research Institute

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TERUMOBCT
Unlocking the Potential of Blood

- Ray Goodrich

  Susanne Marschner

  Janna Mundt
- Pieter van der Meer (Sanquin)

Molecular characterization of hepatitis B virus strains infecting blood donors with high HBsAg and undetectable HBV DNA levels: implications for blood safety and screening policy

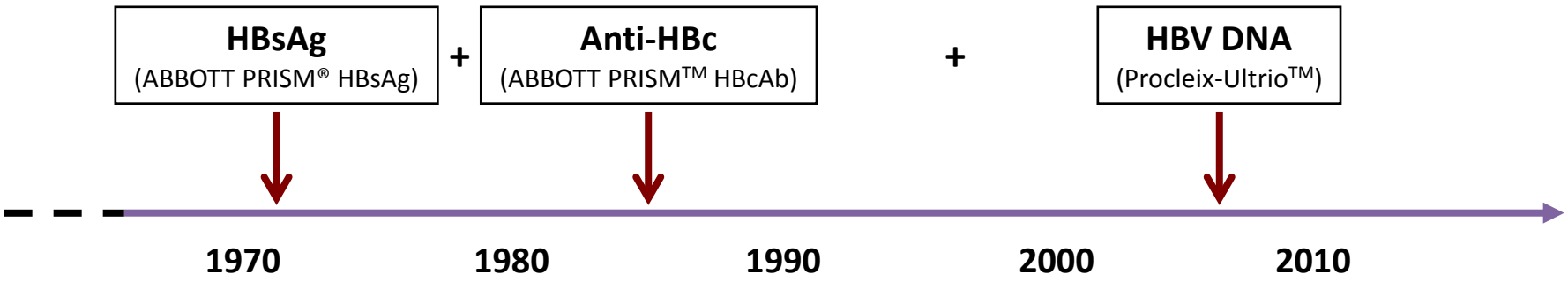
D Candotti

Institut National de la Transfusion Sanguine
Dept. Agents Transmissibles par le Sang
Paris, France

Relative efficacy of HBV screening assays

HBV infection features	Detected by		
	HBsAg	Anti-HBc	HBV NAT
Window period	*No*	*No*	**Yes**
Primary OBI	*No*	*No*	**Yes**
2nd window period	*No*	**Yes**	**Yes**
Chronic infection	**Yes**	**Yes**	**Yes**
Anti-HBc+ OBI	*No*	**Yes**	**Yes**
Anti-HBs only OBI	*No*	*No*	**Yes**
Anti-HBc only	*No*	**Yes**	*No*
HBsAg only	**Yes**	**?**	*No*

HBV screening in French blood donations



- High sensitivity and adequate specificity
- Pre-seroconversion window period & occult infections

→ **Estimated HBV residual risk: 1 in 4 millions donations**

But:

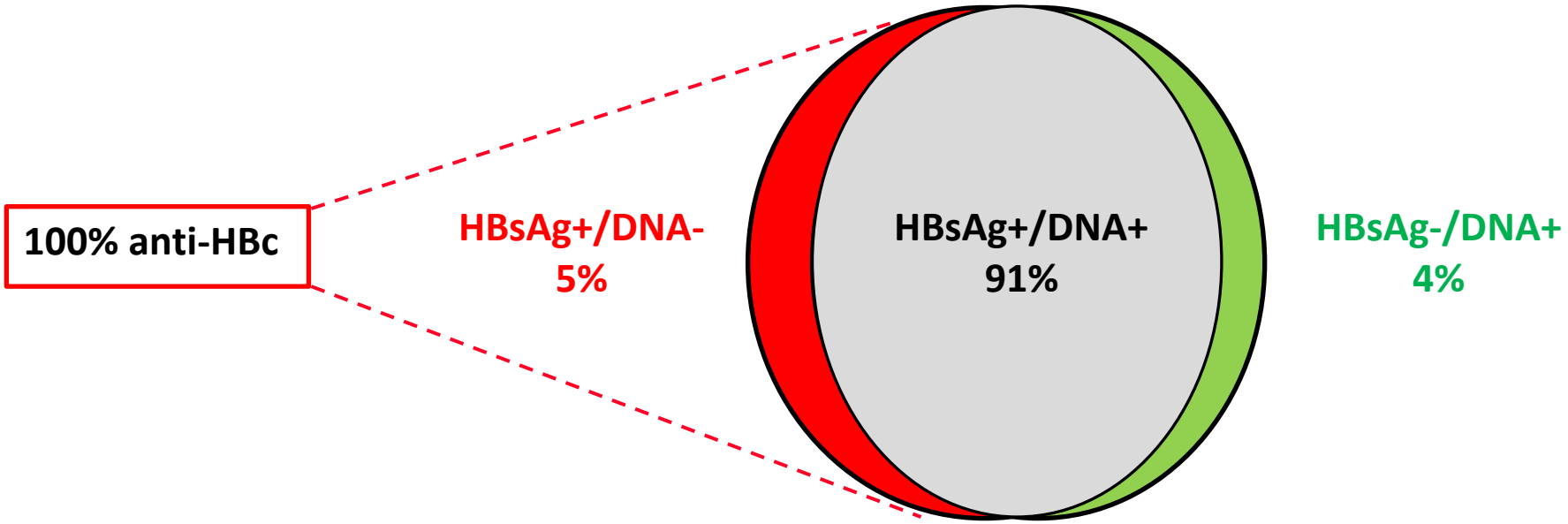
- High cost
- Redundancy of HBsAg and HBV DNA direct markers

Maintaining HBsAg testing?

- Cost reduction of blood testing
- Complementarity of anti-HBc and HBV DNA testing
  (Enjalbert et al. Transfusion 2014;54:2485-95)
- Anti-HBc testing issues on blood availability in high endemic settings
- **Potential impact on blood safety?**

Distribution of HBV markers in French blood donors

- Period: 2010-2013
- Excluding overseas territories
- 10 186 279 donations tested → **806 HBV reactive (≈ 1/10,000)**



HBsAg & HBV DNA discrepant levels in 740 samples confirmed HBsAg+

Sample screening	Number (%)	HBV DNA load (IU/mL) (COBAS TaqMan HBV; LOQ 6 IU/mL)		
		Undetected	< 6	≥ 6
NAT* neg.	41 (5%)	13 (32%)	20 (49%)	8 (19%)
NAT pos.	699 (95%)			
• HBsAg < 100 IU/mL	58 (8%)	1 (2%)	12 (21%)	45 (77%)
• HBsAg > 100 IU/mL	641 (87%)	13 (2%)	27 (4%)	601 (94%)

*NAT: Procleix-Ultrio (LOD 12 IU/mL)

Hypotheses

- **Ratio: 1 viral particle / 1,000-10,000 HBsAg**

  - Natural course of infection

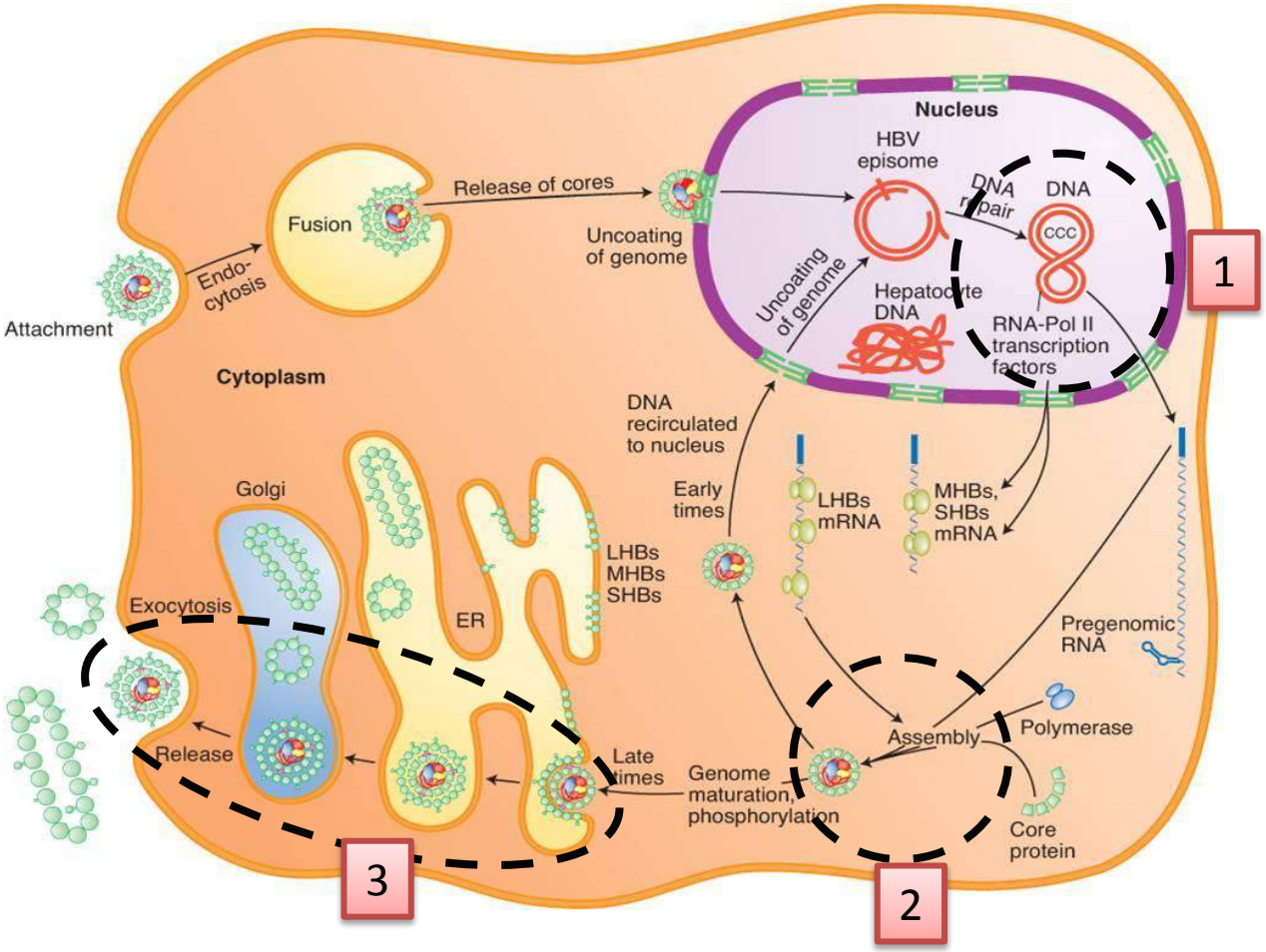
  - HBV genotypes

- **Hypotheses:**

  - NAT failure

  - Impaired viral replication

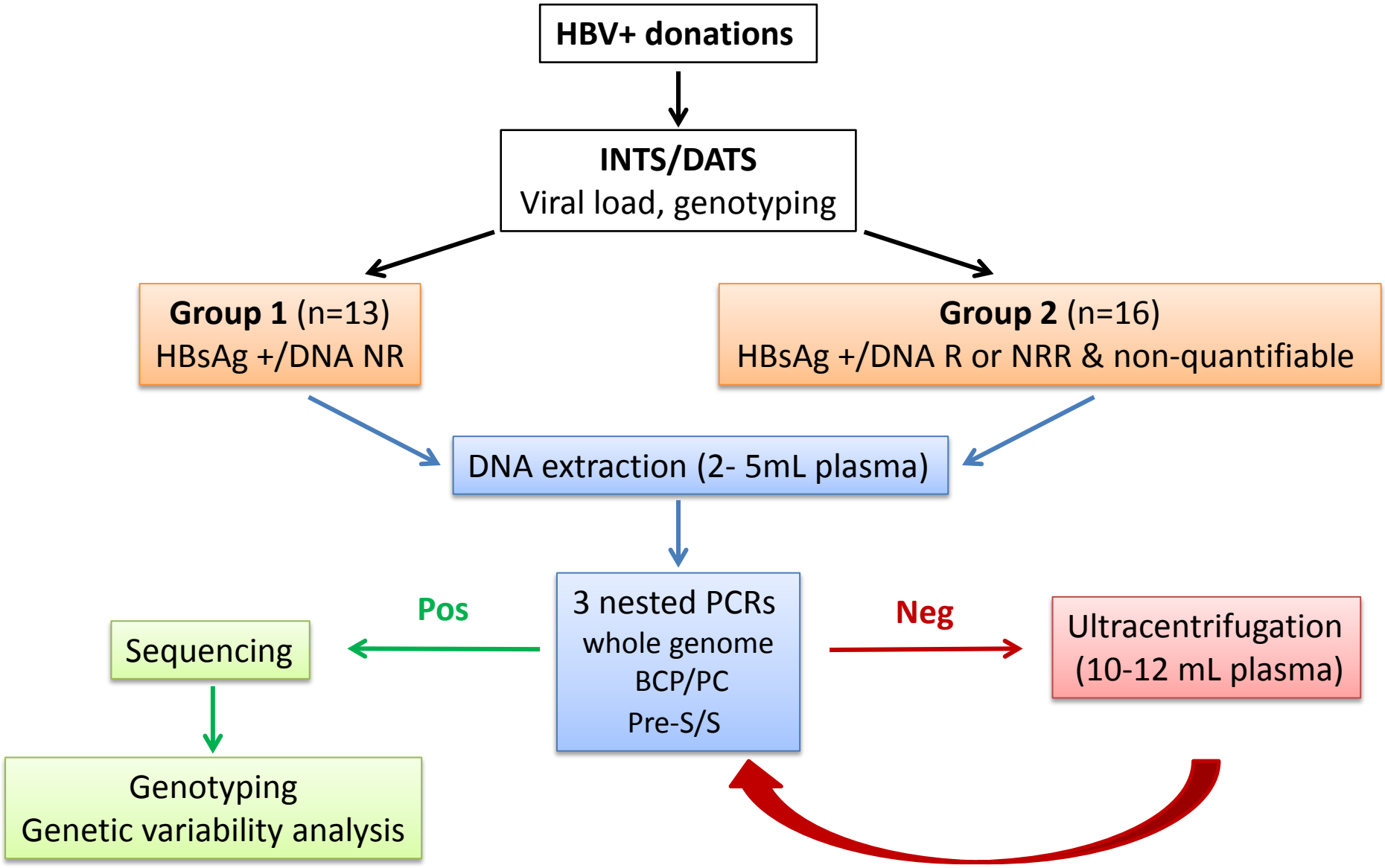
- **Infectivity?**



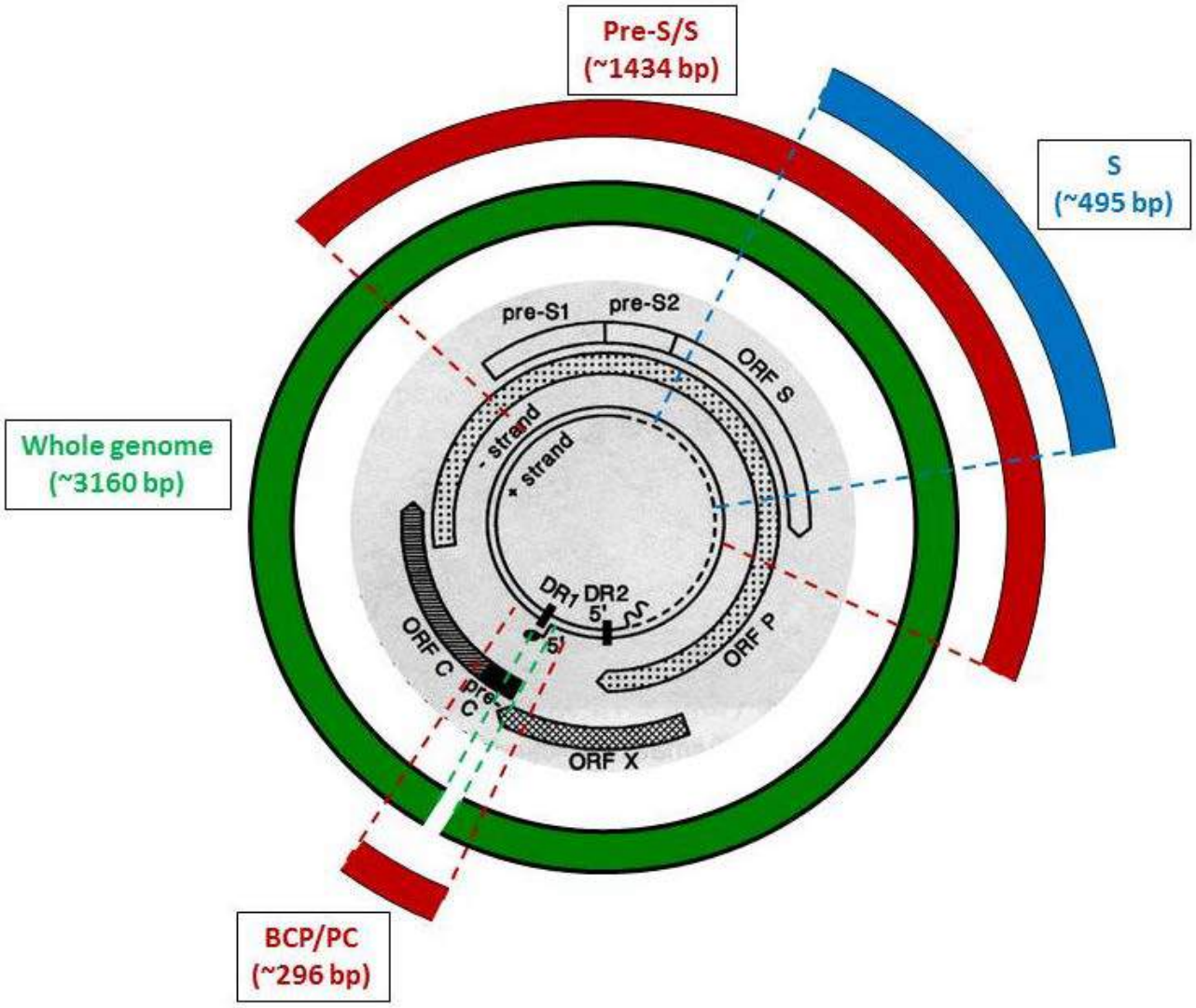
Objectives

- Prevalence of HBsAg+/ NAT non-reactive or non-repeatable reactive donations
- Detect and/or confirm HBV DNA presence
- Evaluate and compare performance of NAT assays to detect these samples
- Perform genetic characterization of the viral strains associated with this phenotype
- Evaluate viral replicative properties *in vitro* as a surrogate marker of infectivity

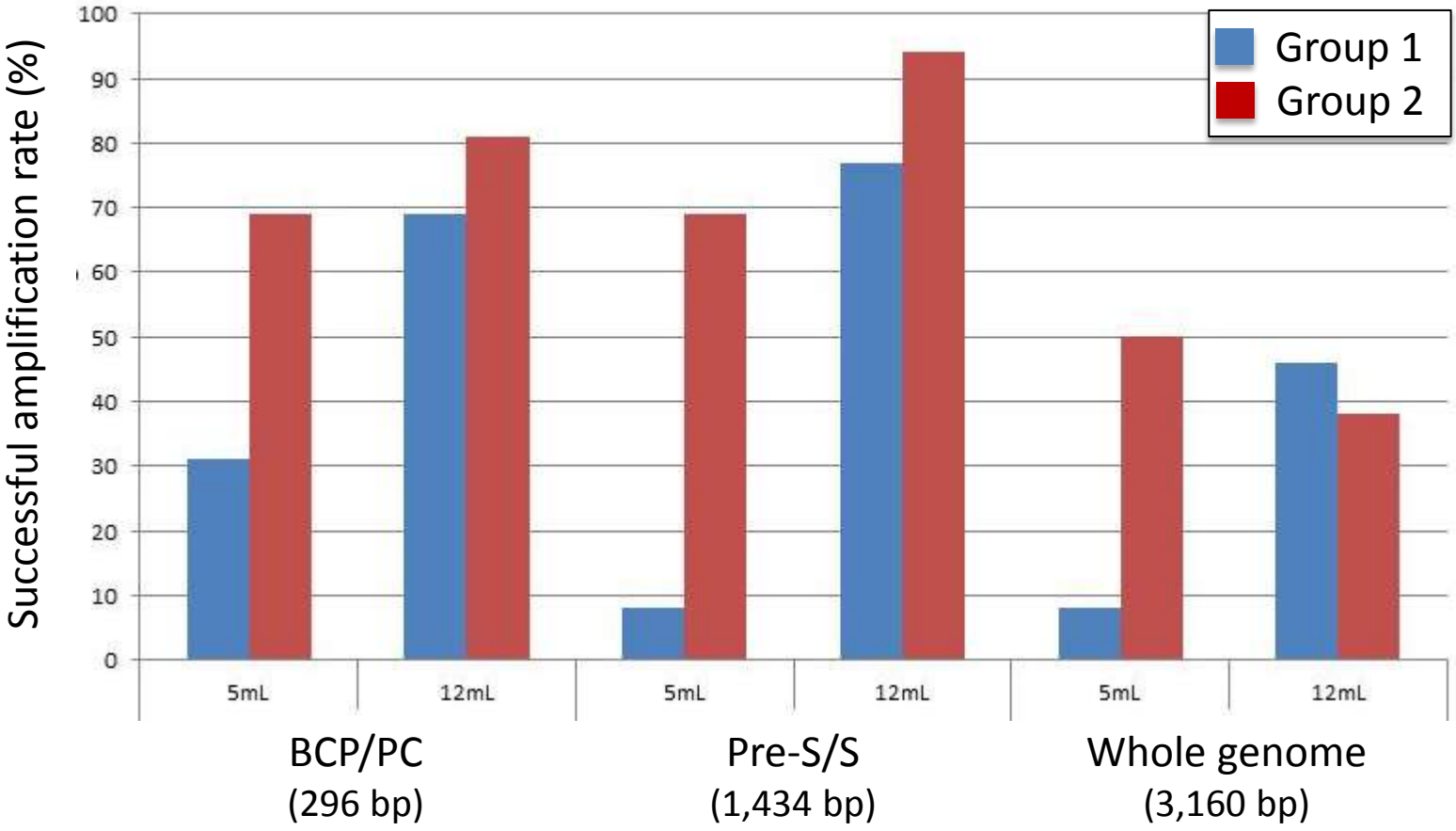
Study design



HBV DNA amplification



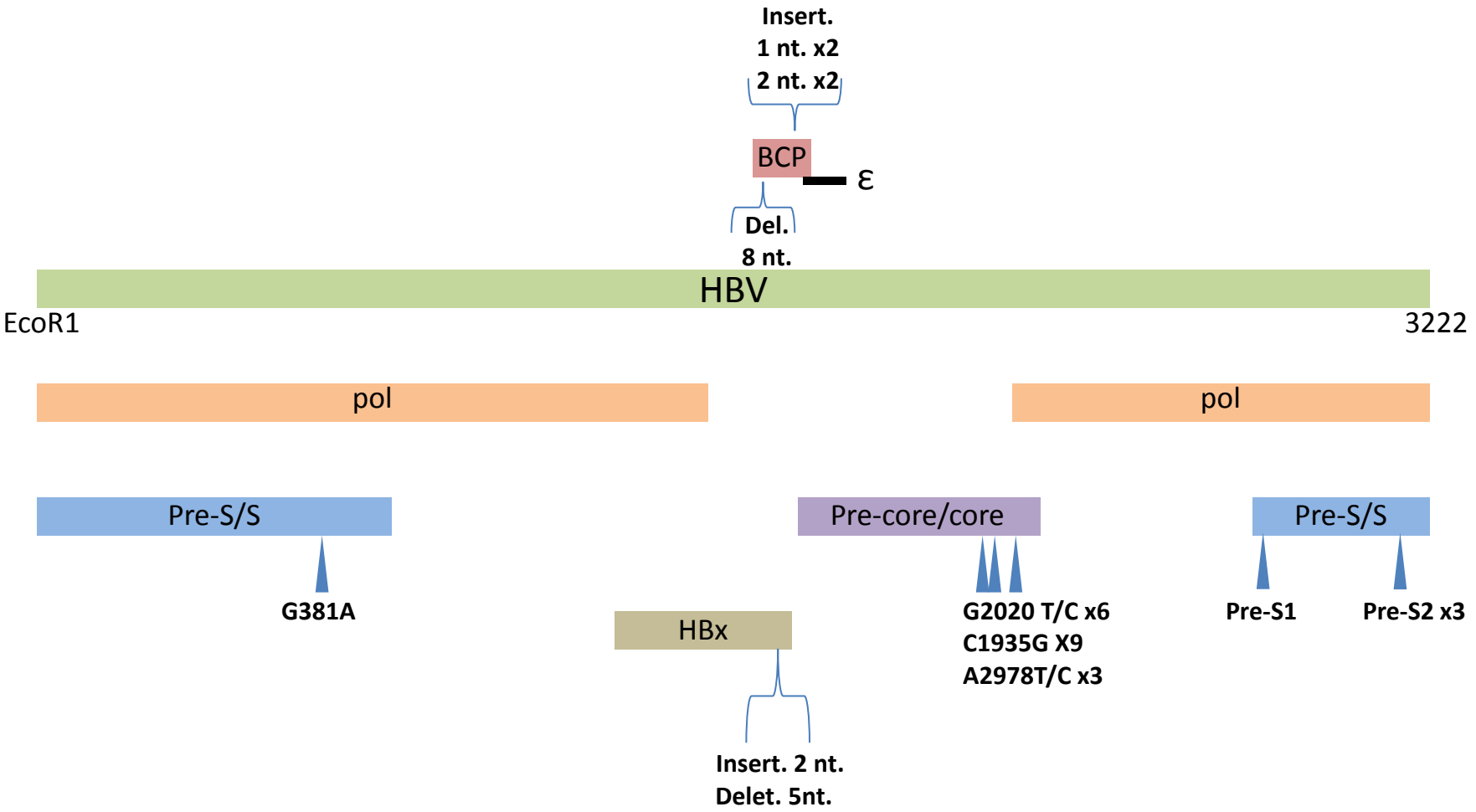
HBV DNA amplification performance



Preliminary results

	Group 1 (n = 13)	Group 2 (n = 16)	Total (n = 29)
Age (y) (mean; range)	34 (19 – 59)	35.5 (18 – 61)	34.8 (18 – 61)
HBsAg (ng/mL) (median; range)	1,355 (110 – 39,500)	2,113 (150 – 19,030)	1,881 (110 – 39,500)
HBV DNA confirmed	**12 (92%)**	**15 (94%)**	**27 (93%)**
HBV genotypes			
• A	-	9	9 (35%)
• B	1	-	1 (4%)
• C	2	1	3 (11%)
• D	7	2	9 (35%)
• E	1	3	4 (15%)

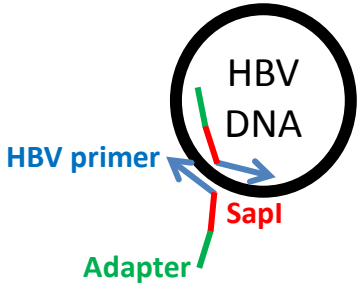
Sequences analysis



Construction of HBV replicons

Method 1

1st PCR amplification with HBV-specific primers



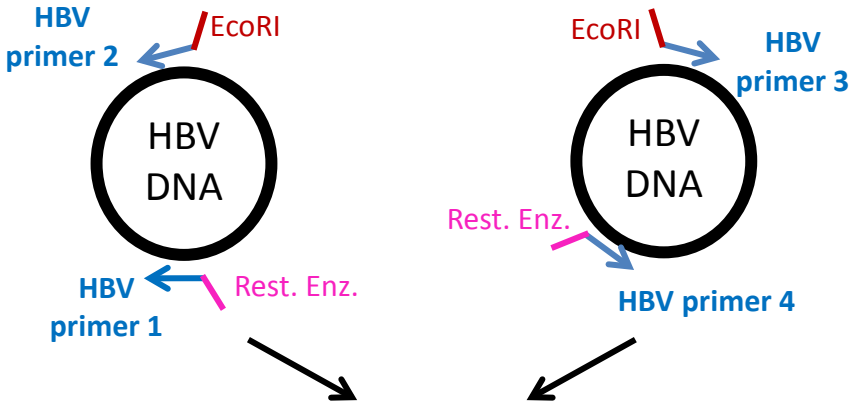
2nd PCR amplification using adapters

Huh7 transfection & re-circularization with SapI

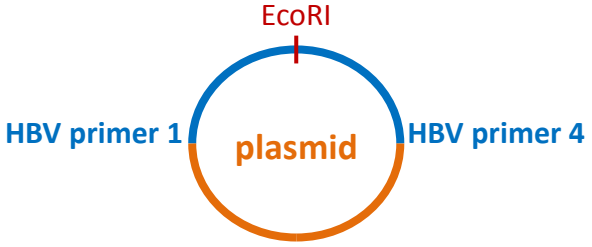
HBV genome expression & replication

Method 2

2 distinct PCR amplifications



Cloning of 1.2 HBV construct



Huh7 transfection

HBV genome expression & replication

Preliminary conclusions & perspectives

- **Conclusions:**
  - Extremely low level of HBV DNA confirm in >90% of ID-NAT non-reactive blood donations with concomitant high HBsAg levels
  - Phenotype not associated with donor age or HBV genotype
  - Impaired viral replication rather than NAT failure is suggested
  - Mutations potentially affecting viral replication identified

- **Perspectives:**
  - Increase the number of samples and controls of various genotypes
  - Collaborative study (Croatia, Poland, Switzerland, South Africa, Malaysia,…)
  - Develop an *in vitro* HBV replication system
    - functional characterization of HBV variants
    - evaluation of infectious risk
    - increase knowledge about distinct molecular control of viral replication & HBsAg production →potential clinical implications
  - Funding

Acknowledgements

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A. Fread

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Surveillance, Risk Assessment and Policy (SRAP) Subgroup

Cost Utility Analysis of HIV, HCV, and HBV Screening of Blood Donations

Project funded by the ISBT TTID Working Party

Brian Custer, Mart Janssen, Rene van Hulst

Working Parties

- Working Parties
- Global Blood Safety
- Quality Management
- Apheresis
- Granulocyte Immunobiology
- Rare Donors

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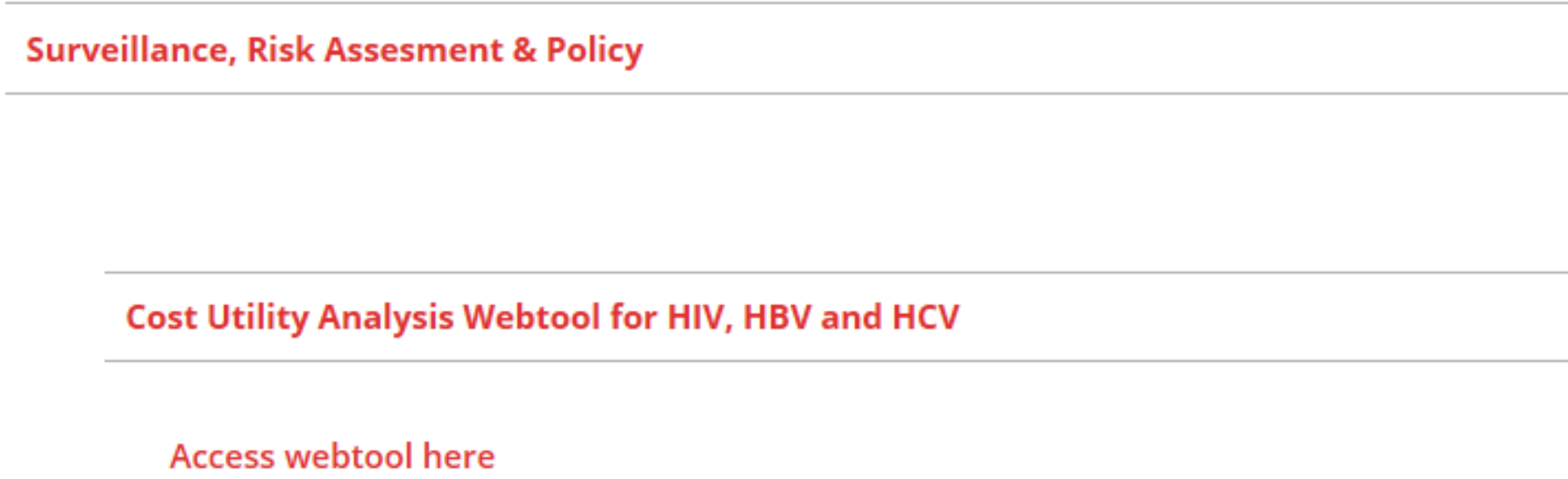
- Parasites
- Virology
- Surveillance, Risk Assesment & Policy
- Transmissible Spongiform Encephalopathy

Update

- The tool is complete and accessible at:

http://www.isbtweb.org/working-parties/transfusion-transmitted-infectious-diseases/



https://interactive.basecase.com/home#!/summary?id=14143

Activities in last year

- Extensive QC of the underlying model and the web interface
- Switch to QALYs
- Addition of new part of Results reporting
- Alliance of Blood Operators (ABO) project
  - Complex issues related to disclosure of results have not been resolved

Introduction

BLOODSAFETY

This tool allows you to perform analysis of blood donation screening strategies for the following test combinations:

- HIV Ab + HCV Ab + HBsAg
- HIV Combo + HCV Combo + HBsAg
- All Mini Pool Multiplex NAT
- All Individual Donation Multiplex NAT
- Do nothing (HIV, HCV, HBV)

You can estimate the cost-effectiveness of screening in
for the data you will need, before you start entering data
data, you will need to register an account. Please se
name, and organization to bcuster@bloodsystems.org.
marinus.van.hulst.transfusion@gmail.com for informati

This application will guide you through the analysis step
are:

Select a country from the list to the right that best matc
country will appear. These values can be replaced with
the default values, you can re-select the country in the

- If you can't provide data for a particular strategy,
- Select the 'Next Step >>' in the lower right of eac
  entry or results page
- On the 'Results' page you will be able to select th
  compare

Predefined Country Scenarios

Scenarios	Save
USA data	
Ghana data	
Brazil data	
South Africa data	
Thailand data	

This tool was developed by the Surveillance, Risk Assessment and ... Infections Diseases Working Party (TTID WP) and BaseCase, and was funded by the ISBT TTID WP and Blood Systems Research Instit

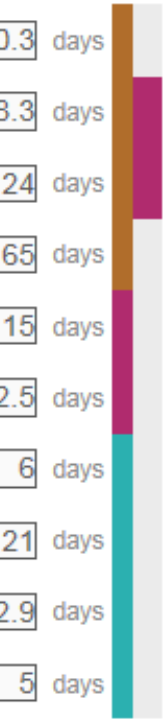
Risk Model ▸

Infectious Window Periods

BLOODSAFETY

If you are interested in Minipool NAT for your setting, please specify a pool size on the right side of the table below. Optionally, you may also adjust the window periods of the tests. However, unless you have specific data on the windows periods of the tests available in your setting, it is better to use the pre-loaded data.

HIV Ab	20.3	days
HBsAg	38.3	days
HBsAg (late stage)	24	days
HCV Ab	65	days
HIV Combo (Ab,p24)	15	days
HCV Combo (Ab,Ag)	12.5	days
HIV ID-NAT, Ab	6	days
HBV ID-NAT, HBsAg	21	days
HBV ID-NAT, HBsAg (late stage)	12.9	days
HCV ID-NAT, Ab	5	days



Multiplex Minipool NAT

For the pool size you select the window periods will automatically be estimated.

Pool Size	12	
HIV MPNAT, Ab	9.59	days
HBV MPNAT, HBsAg	28.75	days
HCV MPNAT	6.97	days
HBV MPNAT, HBsAg (late stage)	13.03	days

Advanced Inputs

HIV Ab + HCV Ab + HBsAg | HIV Combo + HCV Combo + HBsAg | All Mini Pool (x) Multiplex NAT | All Individual Donation Multiplex NAT

Reporting Options - Update

1. Infections remaining, costs (testing and disease) and QALYs

2. Incremental cost effectiveness ratios (ICERs)

3. ICER / GNI per capita

   Ratio ≤ 1 – Cost effective
   1 < Ratio < 3 – Context dependent
   Ratio > 3 – Not cost-effective

4. Cost-effectiveness plane, also known as the Efficiency Frontier

Download report

Results

BLOODSAFETY

Please select the screening strategies you would like to compare for your setting. Results can be viewed in three different ways by selecting the tab for ICERs, Cost-Effectiveness Plane or Totals.

Infections remaining, costs and QALYs | ICER | ICER / GNI per capita | CE Plane

Screening Strategies	HIV	HCV	HBV	Costs	QALYs
HIV Ab + HCV Ab + HBsAg	28.702	163.943	6.128	$4,996,625	5,019.2
HIV Combo + HCV Combo + HBsAg	21.208	35.151	6.128	$9,822,247	5,216.6
All Mini Pool (x) Multiplex NAT	12.353	17.858	3.886	$19,341,662	5,322.4
All Individual Donation Multiplex NAT	7.918	13.779	3.295	$29,319,910	5,370.0
Do Nothing (HIV, HCV, HBV)	417.460	1,103.443	405.372	$4,541,873	0.0

- [x] HIV Ab + HCV Ab + HBsAg
- [x] HIV Combo + HCV Combo + HBsAg
- [x] All Mini Pool (x) Multiplex NAT
- [x] All Individual Donation Multiplex NAT

Please select the screening strategies you would like to compare for your setting. Results can be viewed in three different ways by selecting the tab for ICERs, Cost-Effectiveness Plane or Totals.

Infections remaining, costs and QALYs | ICER | ICER / GNI per capita | CE Plane

AB+HBsAg	Combo+HBsAg	MP Multi NAT	ID Multi NAT	Compared to:
0.0	0.1	0.4	0.6	Do Nothing
	3.3	6.4	9.4	AB+HBsAg
		12.2	17.3	Combo+HBsAg
			28.5	MP Multi NAT

- [x] HIV Ab + HCV Ab + HBsAg
- [x] HIV Combo + HCV Combo + HBsAg
- [x] All Mini Pool (x) Multiplex NAT
- [x] All Individual Donation Multiplex NAT

Risk Based Decision Making Project

Health Economic and Outcomes

Objective: To compare the cost-utility of the same interventions in a list of countries with similar HDIs

Participants: Australia, Canada, Denmark, Finland, France, Netherlands, UK, USA (two other countries have been approached)

- Are patterns of similar cost-effectiveness/utility ratios evident?
- What aspects may exhibit substantial differences?
- Are there broader patterns with respect to blood safety for HIV, HBV, and HCV that can be discerned?

Acknowledgments

ISBT TTID Working Party

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- Cees van der Poel (Honorary)

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- Peter Tomasulo
- Tina Viner

Other collaborators

- Gijs Hubben

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Netherlands – Anton de Weert, Ed Slot, Mart Janssen

UK – Su Brailsford

USA – Ed Notari, Susan Stramer, Roger Dodd

Public Health England

Protecting and improving the nation's health

Welsh Blood Service

NHS Blood and Transplant

The UK Blood Donor Survey OVERVIEW 2015

Prepared by the UK Blood Donor Survey Team
- on behalf of the Steering Group, June 2015

Katy.davison@phe.co.uk

Background

2011 review of UK donor selection criteria related to sexual behaviours

Compliance with ALL donor selection criteria important factor in risk-reduction

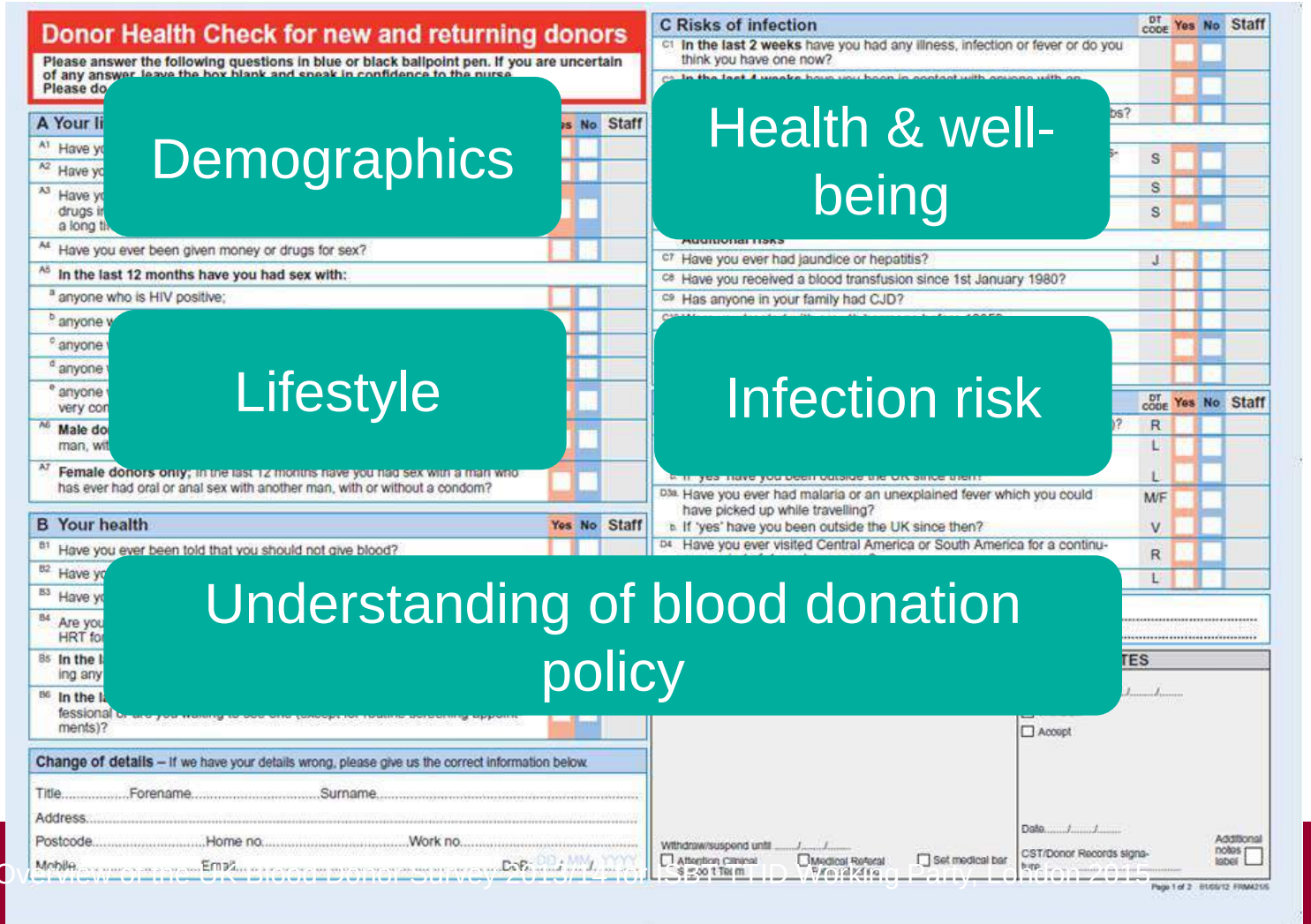
Long established surveillance systems for donors with markers of infection

BUT little known about behaviours in ‘healthy’ donors

Opportunity to ask donors about behavioural risks but also understanding of donor selection guidelines and whether they fully disclose information

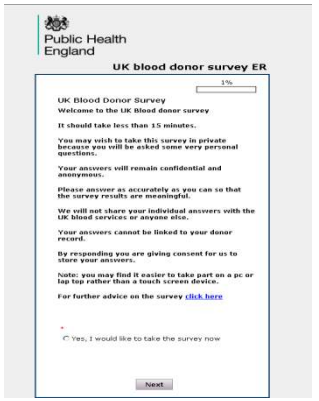
Questionnaire - online, unlinked & anonymous

NHS Blood and Transplant



Survey

Development
- Focus group
- Pilots in 4 UK blood services



Live survey
- November 2013
- Invited via email with URL to questionnaire + 2 reminders

Information for donors
- PHE website
- donorsurvey@phe.gov.uk

Information for staff
- Blood services
- Public Health agencies

Sampling

Each month for one year, all eligible new and an equal number repeat donors from UK blood centres

Eligible

- whole blood donation within previous month
- email address
- donation made at non-static site
- NOT reactive on testing

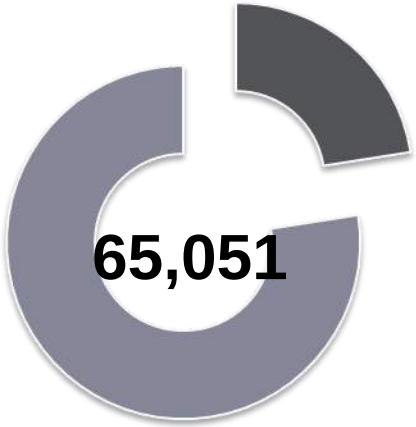
Estimated 60,000 participants (2011)

- fewer new donors → 3 x repeat donor sampling (NHSBT)

Good participation

225,091

UK donors sent anonymous online survey
Nov 2013-Oct 2014

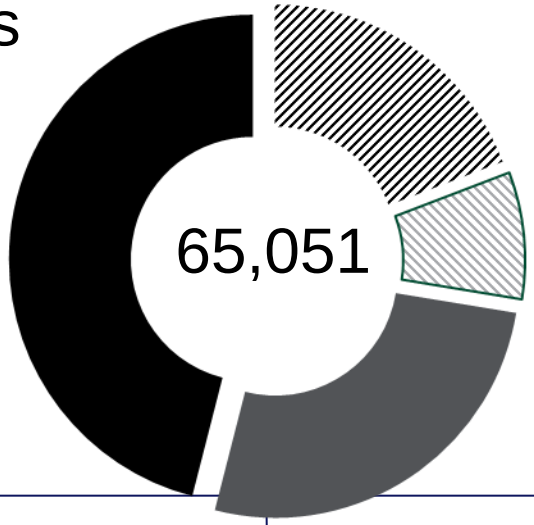


1 in 3

responded
90% completed whole survey

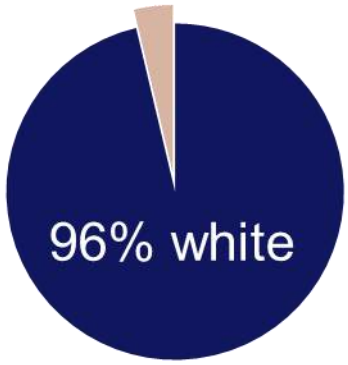
Responders from range of subgroups

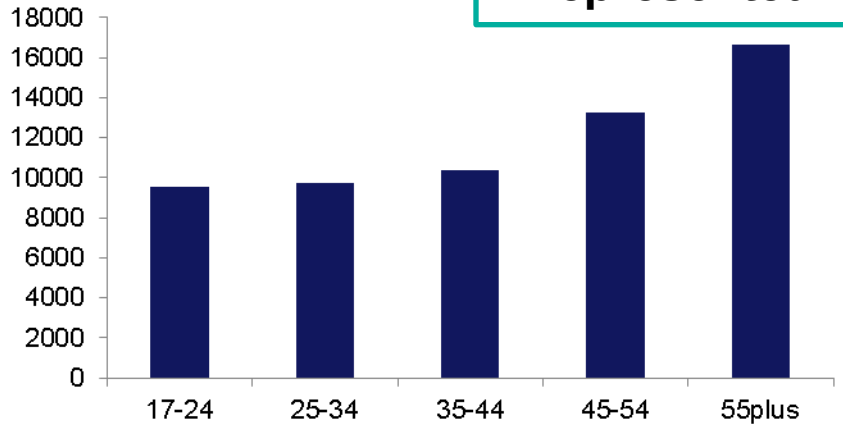
Repeat donors
30,205
17,280



New donors
12,558
5,496

responders
all donors
9%
Males, older, repeat donors
under-represented





Donors disclosed behaviours of a personal nature

Sex

Responses - 63,311 (96.7%)

- 7 in 10 sex in last year
  - more common in males and young donors aged 17-24
- 2 in 10 >= 1 new partner in the last year
- 1 in 10 history of a sexually transmitted infection

Drugs

Responses – 62,157 (95.5%)

- 25 IDU
- 950 intranasal (most 25-34y)

Compliance with the donor selection guidelines was very good

Example – lifestyle deferrals

- exceeded 99% in each category
- small but significant difference between new and repeat donors in some cases
- lower rates of compliance among responders who did not understand the eligibility criteria or did not agree with the rationale for the selection criteria.

MSM

22,065 males who have had sex

1% MSM 

74 were non-compliant (70 <12m)
- 99.7% of all males COMPLIANT

Compliance with lifestyle deferrals

Other aspects of compliance and donor health

Piercings & acupuncture
- Compliance > 99%

19,000 adverse events
>80% bruises
2% delayed faint
- most not reported

2 in 3 travelled outside the UK < 12 months

- Compliance >99.7%

Other stuff:
- Illness/medication/ medical appointments
- Smoking/drinking
- 1 in 2 keep pets!

Summary and next steps

Information of behaviour & lifestyle of > 65,000 donors

Compliance with donor selection guidelines was generally very high

Among those who did not comply, understanding & poor perception of own risk

Findings are limited to responding population – and there is reporting bias

Data about donor well-being still to be reviewed and compared with general population data

Due to report findings to UK Department of Health Expert Committee

- Key areas of interest – sex & drug use

Data will be fed back to each of the UK blood services to be used to support and develop blood donation policies

ISBT 2015

Getting personal with UK blood donors – the findings of a large scale anonymous behavioural survey to assess understanding of, and compliance with, donor selection guidelines

K Davison, C Reynolds, N Andrews and S Brailsford on behalf of The UK Blood Donor Survey Steering Group

ADD AFFILIATIONS

"Highlights on donors' nightlives" – findings on sexual behaviours from the UK blood donor survey

K Davison, C Reynolds, N Andrews and S Brailsford on behalf of The UK Blood Donor Survey Steering Group

ADD AFFILIATIONS

Acknowledgements

Survey Team; Su Brailsford – Principal Investigator (NHSBT/PHE), Katy Davison & Claire Reynolds - Survey co-ordinators (NHSBT/PHE), Nick Andrews – Statistician (PHE)

Steering Group: Harpreet Kohli – Chair (SABTO until November 2014), Gail Miflin NHSBT, Crispin Wickenden NHSBT, Felicity Hay (past NHSBT), Joanne Allan WBS, Stephen Field WBS, Moira Carter SNBTS, Kathryn Maguire NIBTS, John Ratchford PHE

Others: Andrew Reid SNBTS, David Moore NIBTS, Rhian Roberts WBS, Nicola Thomas WBS

Also Clive Seed, Australian Red Cross, for helpful guidance on the questionnaire

Teleperformance for distribution of the email invites from NHSBT AND THE DONORS!!

Final thought from a donor…

"if eligibility issues
were sorted out *beforehand*
then the session experience
would be
more motivational,
about donating blood
rather than reasons **not** to"

Risk of transmission of neurodegenerative disorders through blood transfusions: a retrospective cohort study

Gustaf Edgren, MD PhD (gustaf.edgren@ki.se)
Department of Medical Epidemiology and Biostatistics, Karolinska Institutet,
and Department of Hematology, Karolinska University Hospital

Background

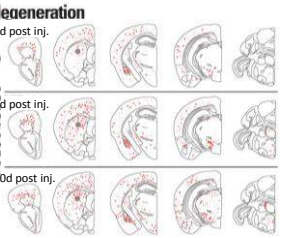
- Since the 1980's, the transfusion medicine community has maintained a strong track record for dealing with new threats to the blood supply
- However, the current approach for detecting and managing emerging TTIs may not be able to manage
  - Diseases with long induction times
  - Poorly understood/recognized diseases
  - Unexpected / unconventional pathogens
  - Common diseases
- Recent data indicates a possible prion-related (and hence possibly transfusion transmitted) etiology for several neurodegenerative diseases – potentially very large consequences

Science 338, 949 (2012);

Pathological α-Synuclein Transmission Initiates Parkinson-like Neurodegeneration in Nontransgenic Mice

Kelvin C. Luk, Victoria Kehm, Jenna Carroll, Bin Zhang, Patrick O'B
John Q. Trojanowski, Virginia M.-Y. Lee*

Parkinson's disease is characterized by abundant α-synuclein (α-Syn) neu as Lewy bodies and Lewy neurites, and the massive loss of midbrain dop cause-and-effect relationship between Lewy inclusion formation and unclear. Here, we found that in wild-type nontransgenic mice, a single in synthetic α-Syn fibrils led to the cell-to-cell transmission of pathologic α- Lewy pathology in anatomically interconnected regions. Lewy pathology a progressive loss of dopamine neurons in the substantia nigra pars compa ventral tegmental area, and was accompanied by reduced dopamine level deficits. This recapitulation of a neurodegenerative cascade thus establishe transmission of pathologic α-Syn and the cardinal features of Parkinso



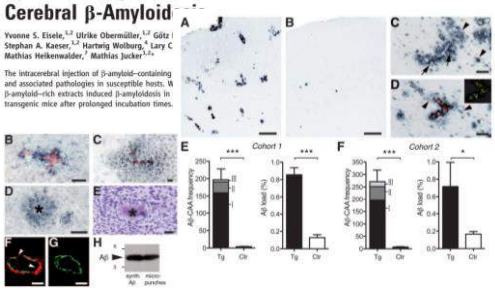
Intracerebral inoculation of α-Syn fibrils → Cell-cell transmission of α-Syn fibrils → Loss of dopamin neurons (Lewy pathology) → Gradual development of motor deficits

Science 330, 980 (2010)

Peripherally Applied Aβ-Containing Inoculates Induce Cerebral β-Amyloid

Yvonne S. Eisele,[1,2] Ulrike Obermüller,[1,2] Götz
Stephan A. Kaeser,[1,2] Hartwig Wolburg,[4] Lary C
Mathias Heikenwalder,[1] Mathias Jucker[1,2]*

The intracerebral injection of β-amyloid–containing and associated pathologies in susceptible hosts. W β-amyloid–rich extracts induced β-amyloidosis in transgenic mice after prolonged incubation times.



CELL BIOLOGY

22 JUNE 2012 VOL 336 SCIENCE

A Unifying Role for Prions in Neurodegenerative Diseases

Stanley B. Prusiner

A profound change in thinking about the etiologies of many neurodegenerative diseases has far-reaching implications for developing therapeutics.

Prion diseases	Precursor proteins	Prion forms	Protein deposits	Self-propagation in mammals	Self-propagation in cultured cells	References
CJDiscrapie	PrP^C	PrP^{Sc}	PrP plaques	inoc apes, monkeys, wt mice & Tg mice	N2a, GT1	(1–13)
Alzheimer's	APP	Aβ	Aβ plaques	inoc marmosets & Tg(βAPP) mice		(14–24)
Tauopathies (FTD, PSP, Pick's, CTE)	tau	tau aggregates	NFTs, Pick bodies	inoc Tg(HuTau), inoc Tg(HuTau,P301S) & inducible Tg(HuTau, ΔK280) mice	C17.2, HEK293	(25–32)
Parkinson's	α-synuclein	α-synuclein aggregates	Lewy bodies	Lewy bodies in grafts & inoc Tg(HuSNCA,H53T) mice	Primary mouse hippocampal neurons	(33–39)
fALS	ΔSOD1, ΔTDP43	ΔSOD1 aggregates	Bunina bodies		N2a, HEK	(40–43)
Huntington's	ΔHtt	ΔHtt aggregates	Nuclear inclusions		Cos7	(44–47)

Abbreviations: CJD, Creutzfeldt-Jakob disease; PrP, prion protein; inoc, intracerebral inoculation; wt, wild-type; Tg, transgenic; APP, amyloid precursor protein; Aβ, amyloid beta; FTD, frontotemporal dementia; PSP, progressive supranuclear palsy; CTE, chronic traumatic encephalopathy; NFTs, neurofibrillary tangles; fALS, familial amyotrophic lateral sclerosis; ΔSOD1, mutant superoxide dismutase; ΔHtt, mutant huntingtin.

Reason to worry?

Lancet 356, 999-1000 (2000)

RESEARCH LETTERS

Research letters

Transmission of BSE by blood transfusion in sheep

F Houston, J D Foster, Angela Chong, N Hunter, C J Bostock
See Commentary page 955

Lancet 363, 417-421 (2004)

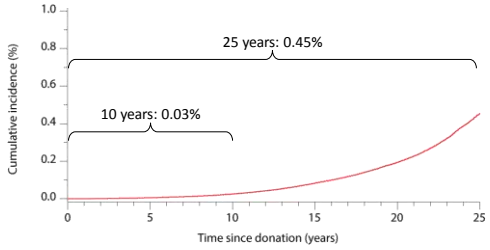
Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report

Stephen I Wroe, Suvankar Pal, Dunmanjit Siddique, Harpreet Hyare, Rebecca Macfarlane, Susan Joiner, Jacqueline M Linehan, Sebastian Brandner, Jonathan D F Wadsworth, Patricia Rowcliffe, John Collinge

Conceptual TTI risk model

Clinical consequence ≡ [Prevalence of agent in blood donors] × [Infectivity/ transmissibility] × [Probability that recipient lives long enough]

Alzheimer's disease



Results

Clinical consequence ≡ [Prevalence of agent in blood donors] × [Infectivity/ transmissibility] × [Probability that recipient lives long enough]

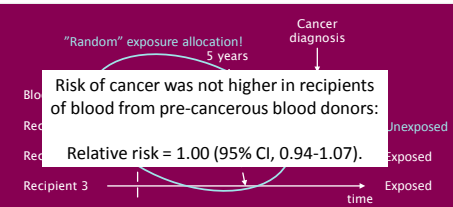
Disease	10 yr. cumulative incidence	Expected 10 yr. survival	Expected cases per 100,000 transfusions (5% infect.)	Expected cases per 100,000 patients (5% infect.)
Alzheimer's disease	0.03%	0.3	0.5	2.2
Parkinson's disease	0.03%	0.3	0.4	1.9
Amyotrphic lateral sclerosis	0.02%	0.3	0.3	1.7
Dementia, unspecified	0.08%	0.3	1.2	4.7

Example: Cancer as a TTD?

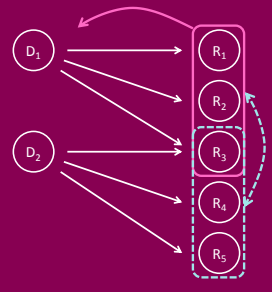
The Lancet 2007; 369:1724-30

Risk of cancer after blood transfusion from donors with subclinical cancer: a retrospective cohort study

Gustaf Edgren*, Henrik Hjalgrim*, Marie Reilly*, Trung Nam Tran, Klaus Rostgaard, Agneta Shanwell, Kjell Tillestad, Johanna Adami, Agneta Wikman, Cesar Jerald, Gloria Gridley, Louise Wideroff, Olaf Nyrén, Mads Melbye



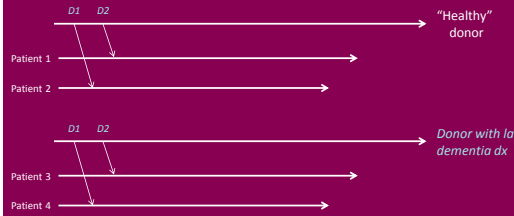
Transmission analyses (1)



Approach 1:
Are recipients risk increased if their donors develop disease?

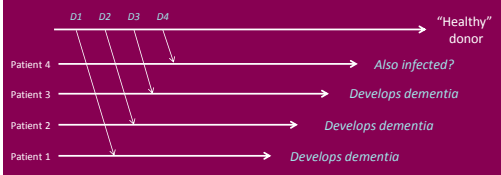
Approach 2:
Do all recipients of blood from one specific donor have a shared increased risk?

Transmission analyses (2)



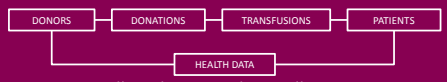
Are patients 3&4 at inreased risk compared to patients 1&2?

Transmission analyses (3)



Do patients 1-4 have a "shared" increased risk?

SCANDAT 2



- Data on 1.7 million donors and 2.1 million patients in Sweden and Denmark since 1960's and 1980's, respectively
- Ability to track transfusions between donors and their respective recipients
- Linkages with a range of health outcome registers providing follow-up for various health outcomes through 2012

Methods

- Retrospective cohort analysis based on SCANDAT2 database
- All patients followed from first transfusion until death or diagnosis of neurodegenerative disease (Dementia, Alzheimer's, Parkinson's, or ALS)
- Two sets of analyses:
  - →Transmission analyses, assessing effect of receiving blood from diseased donor
  - →Cluster analyses, assessing if certain donors' blood increases risk (without donor necessarily becoming ill)
- Methods validated using chronic hepatitis

Validation analyses: transmission of chronic hepatitis

- Relative risk before 1992 = 8.36 (95% CI, 7.25-9.63)
- Relative risk after 1992 = 1.19 (95% CI, 0.72-1.95)

Number of patients with a later hepatitis diagnosis the donor has donated blood to	RR of chronic hepatitis in "next" recipient (before 1992)	RR of chronic hepatitis in "next" recipient (after 1992)
No prior recipients	1.0 (ref)	1.00 (ref)
1-4 recipients	1.32 (1.19-1.46)	1.07 (0.97-1.20)
≥5 recipients	3.33 (2.55-4.36)	1.29 (0.76-2.22)

Overall dementia transmission

- Overall relative risk, relative risk = 1.04 (95% CI, 0.99-1.09)
- <5 year latency, relative risk = 1.05 (95% CI, 0.89-1.22)
- Young onset in donor (<65 yrs), relative risk = 1.05 (95% CI, 0.97-1.14)

Number of patients with later dementia the donor has donated blood to	Relative risk of dementia in "next" recipient
No prior recipients	1.00 (ref)
1-4 recipients	1.01 (0.99-1.03)
5-9 recipients	1.03 (0.98-1.07)
≥10 recipients	1.06 (0.87-1.30)

Alzheimer's disease transmission

- Overall relative risk, relative risk = 0.99 (95% CI, 0.85-1.15)
- <10 year latency, relative risk = 0.73 (95% CI, 0.38-1.41)
- Young onset in donor (<65 yrs), relative risk = 0.79 (95% CI, 0.56-1.11)

Number of patients with later AD the donor has donated blood to	Relative risk of AD in "next" recipient
No prior recipients	1.00 (ref)
1-3 recipients	1.01 (0.98-1.04)
≥4 recipients	1.14 (0.81-1.60)

Parkinson's disease transmission

- Overall relative risk, relative risk = 0.94 (95% CI, 0.78-1.13)
- <10 year latency, relative risk = 1.10 (95% CI, 0.83-1.47)
- Young onset in donor (<65 yrs), relative risk = 0.88 (95% CI, 0.66-1.16)

Number of patients with later PD the donor has donated blood to	Relative risk of PD in "next" recipient
No prior recipients	1.00 (ref)
1-2 recipients	1.01 (0.98-1.04)
≥3 recipients	1.14 (0.81-1.60)

ALS transmission

- Overall relative risk, relative risk = 1.83 (95% CI, 0.87-3.88)
- <10 year latency, relative risk = 2.25 (95% CI, 0.84-6.05)
- Young onset in donor (<65 yrs), relative risk = 1.21 (95% CI, 0.39-3.79)

Number of patients with later ALS the donor has donated blood to	Relative risk of ALS in "next" recipient
No prior recipients	1.00 (ref)
1 recipient	0.95 (0.69-1.31)
2 recipients	0.00 (n.e.)

Conclusions

- Analyses based on SCANDAT2 indicate that even with (speculatively) high transmission rates, possible consequences on transfusion safety are limited
- Although recent animal model data suggest a prion-related etiology behind a range of neurodegenerative diseases, we find no sign of such transmission

Acknowledgements

- Funding from Svenska Sällskapet för Medicinsk Forskning (SSMF), Swedish research council, Swedish Heart-Lung foundation, and NHLBI
- SCANDAT group (Olof Nyrén, Henrik Hjalgrim *et al*)
- BSRI/UCSF group (Mike Busch)

The Danish Blood Donor Study and transfusion transmitted diseases

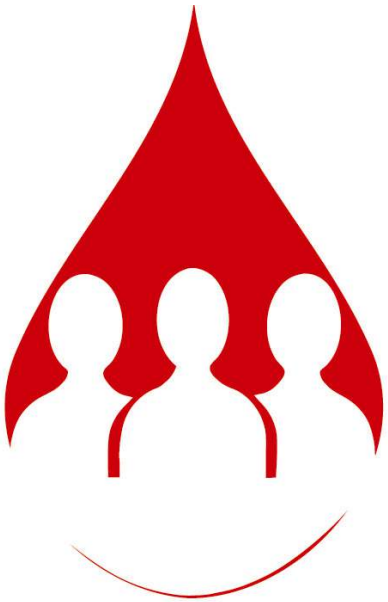
Christian Erikstrup

Chief physician, Associate Professor

Head of Blood Production, HIV and Hepatitis Testing

Dept. of Clinical Immunology

Aarhus University Hospital, Denmark



Introduction - The Danish Blood Donor Study

Initiated in 2010

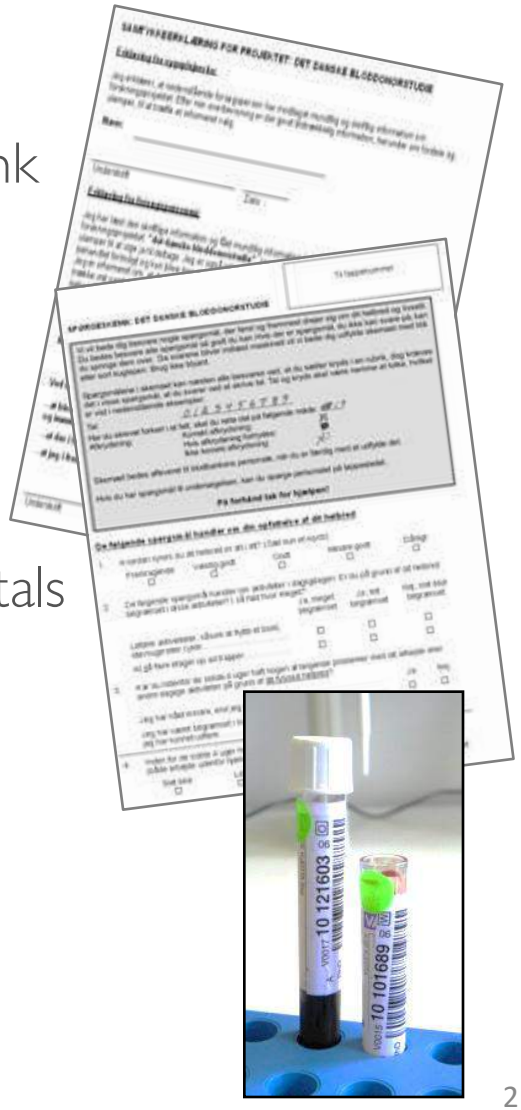
National multicenter public health study and biobank (plasma and DNA)

Questionnaires collected at inclusion

Permission to collect data from public registers
National Patient Register
ICD-10 codes from all contacts with hospitals
National Prescription Register
ATX codes from all filled prescriptions
Socioeconomic data

Permission to contact donor again

Access to recipient data through SCANDAT and national registers



Status

97,000 blood donors have been included

Current work dataset, merged and uploaded to Statistics Denmark:

81,898 participants

256,097 person-years of follow-up by Dec 31 2014

All baseline samples transferred to automated sample management system

>500,000 plasma archive samples from every donation available for research

New electronic, flexible questionnaire is being introduced

Research questions related to infection

- No DBDS substudy has yet addressed transfusion transmitted diseases
- Examples of substudies on donors and infection risk
- Demonstration of the statistical power when using diagnosis codes vs. filled prescriptions as the end point

Obesity and risk of infection

Obesity is associated with the metabolic syndrome, cardiovascular diseases, type 2 diabetes

Obesity is associated with surgical-site infections.

No studies on obesity related risk of all-cause infection among otherwise healthy individuals

Aim - To examine the association between obesity and risk of infection

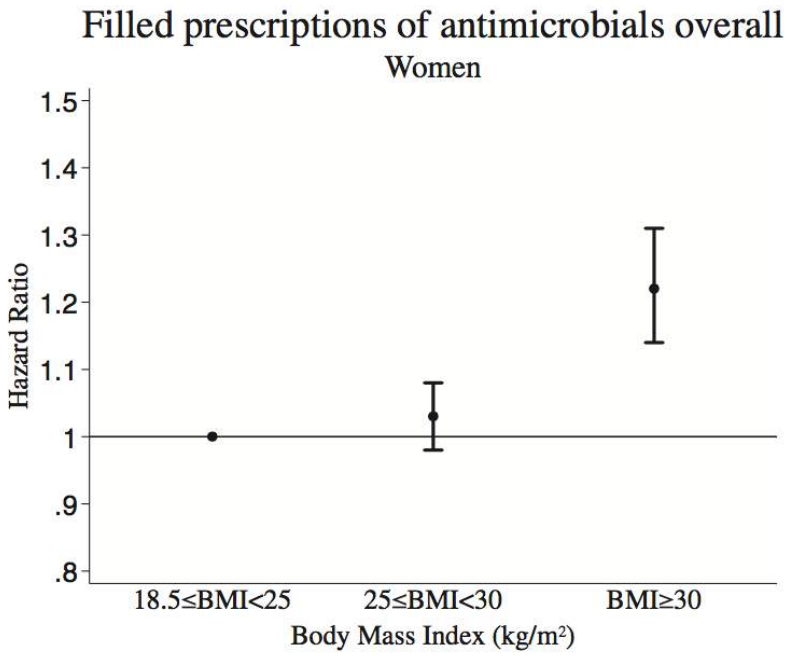
Methods: 37,808 donors; 106,609 person-years

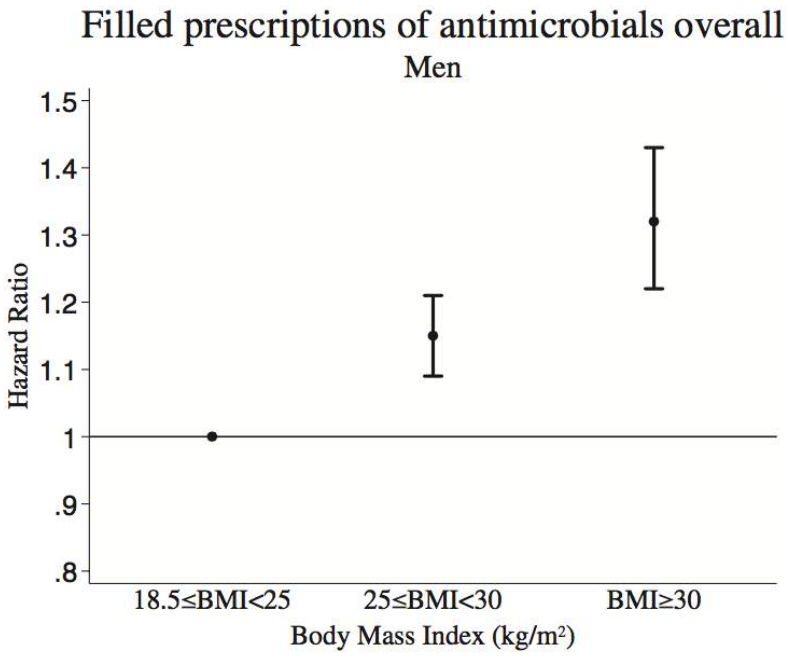
Results

1,233 participants had hospital contact due to for infection during 106,609 person-years of observation; adjusted for age, sex, smoking

	Women			Men		
Site of infection	**N**	**HR (95% CI)**	**P**	**N**	**HR (95% CI)**	**P**
Infections overall	**575**	**1.44 (1.13-1.84)**	**0.003**	**658**	**1.53 (1.23-1.91)**	**<0.0001**
Abscesses	**105**	**2.28 (1.40-3.70)**	**0.001**	**139**	**2.33 (1.54-3.54)**	**<0.0001**
Infections of the skin and subcutaneous tissue	87	0.85 (0.39-1.85)	0.69	**201**	**2.24 (1.57-3.18)**	**<0.0001**
Respiratory tract infections	**144**	**1.60 (1.00-2.55)**	**0.05**	143	1.27 (0.78-2.09)	0.34

15,856 participants filled a prescription of antimicrobials during 58,834 person-years of observation


Filled prescriptions of antimicrobials overall
Women
Hazard Ratio
1.5
1.4
1.3
1.2
1.1
1
.9
.8
18.5≤BMI<25
25≤BMI<30
BMI≥30
Body Mass Index (kg/m²)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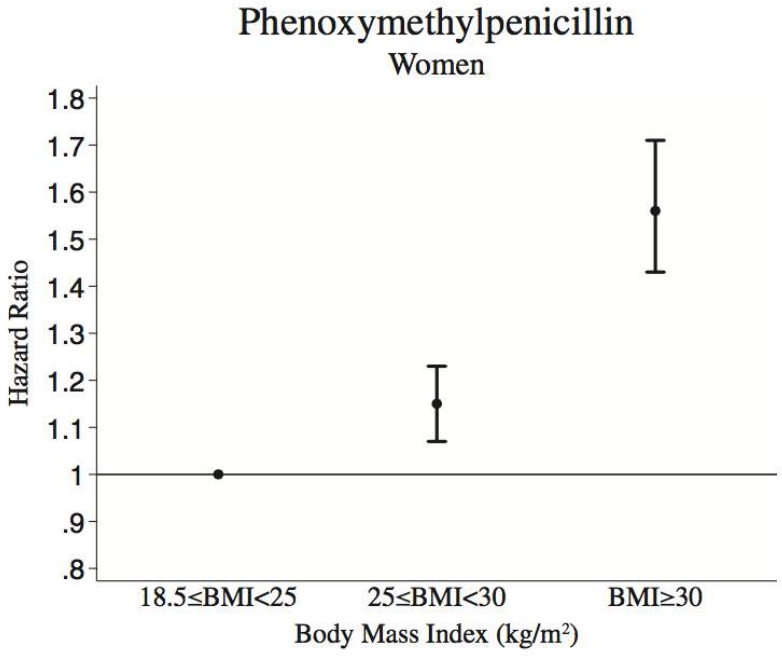
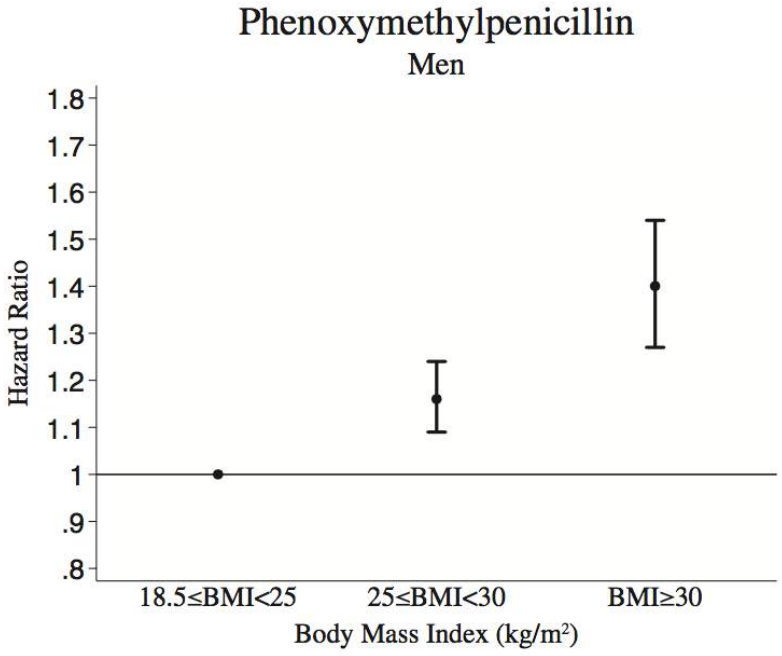

Phenoxymethylpenicillin
Women
Hazard Ratio
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1
.9
.8
18.5≤BMI<25
25≤BMI<30
BMI≥30
Body Mass Index (kg/m²)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.8
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25≤BMI<30
BMI≥30
Body Mass Index (kg/m²)

Obesity – increased risk of infection

Obesity was associated with both hospitalization for infection and use of antimicrobials overall. Specifically:

- Abscesses (both sexes)
- Respiratory tract infections (women)
- Dicloxacillin/flucloxacillin (both sexes)
- Penicillin V (both sexes)

Could prescriptions serve as a feasible proxy for infectious donors?

Epidemiology
July 2015

Obesity and Risk of Infection

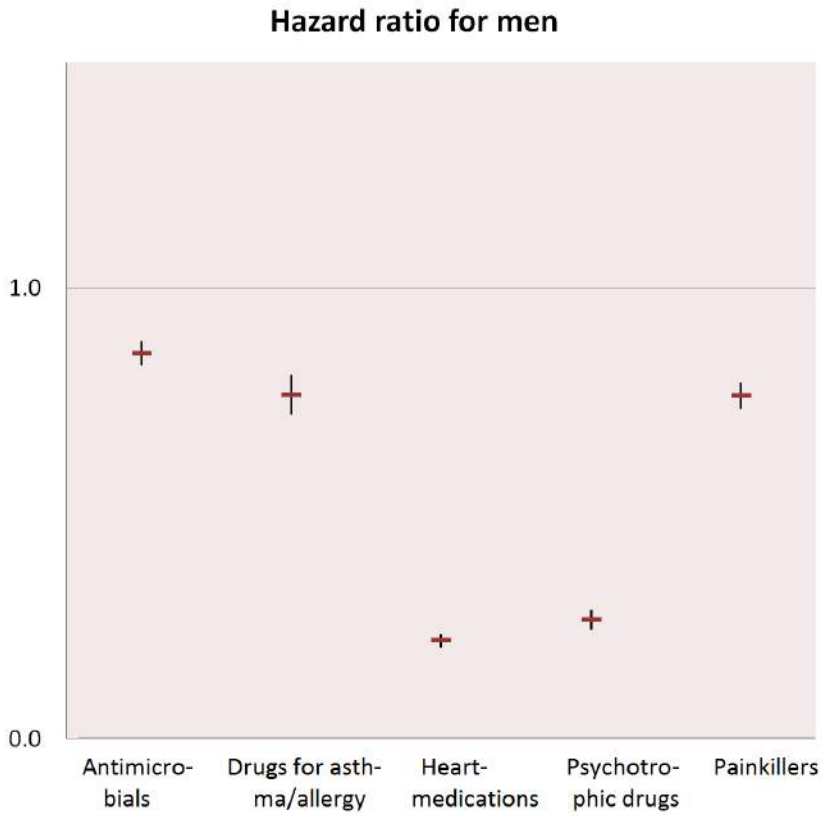
Results from the Danish Blood Donor Study

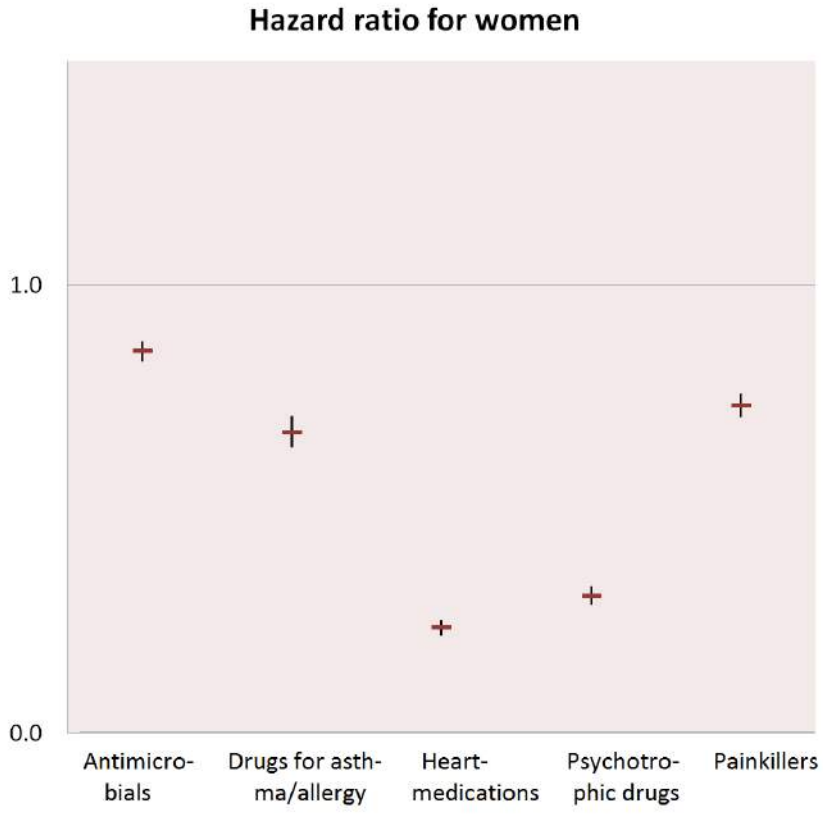
Kathrine Agergård Kaspersen,[a] Ole Birger Pedersen,[b] Mikkel Steen Petersen,[a] Henrik Hjalgrim,[c] Klaus Rostgaard,[c] Bjarne Kuno Møller,[a] Cecilie Juul-Sørensen,[a] Sebastian Kotzé,[a] Khoa Manh Dinh,[a] Lise Tornvig Erikstrup,[d] Erik Sørensen,[e] Lise Wegner Thørner,[e] Kristoffer Sølvsten Burgdorf,[e] Henrik Ullum,[e] and Christian Erikstrup[a]

Infections and the healthy donor effect

37,808 participants and 44,917 randomly chosen controls from the general population matched for age, sex, and region of Denmark.

22,198 donors received at least one prescription during 48,492 person-years





Conclusion

- Incidence rate of at least one prescription among donors:
  Any prescription: 0.46 prescriptions/year
  Antimicrobials: 0.27 prescriptions/year
- Incidence of antimicrobial prescriptions only 15% lower among blood donors than non-donors
- Antimicrobial prescriptions within 2 weeks of donation => 1/88 donations
- New study: association between post-donation prescription and recipient risk of infection

DBDS and transfusion transmitted diseases

Imagine if an association had been found between neurodegenerative diseases in donors and recipients:

- Identification of agent in patients with disease
- Identification of donors with subsequent disease
- Locate and test sequential donor samples

Among 81,898 donors: 10 donors with ALS, 3 with PD, 1 with AD during 256,097 person-years

Donor microbiome and recipient outcome

- A nasal swab has been obtained from 2,050 donors; aim 10,000
- Primary aim: to study the associations of *S. aureus* colonisation with morbidity (infections, metabolic disorders, autoimmune diseases)
- Secondary aims:
  Nasal microbiome and donor morbidity
  S. aureus/nasal microbiome and recipient outcome
- First finding: *S. aureus* colonisation more prevalent than previous studies: 50%
- Fecal microbiome:
  Demand for donors for fecal transplantation

Blood donor study – research infrastructure

Research questions:

Blood donor health questions

Transfusion medicine questions

Generic health research questions

Infrastructure:

Donor and recipient database

National health registers

Questionnaire database

Biobank

Give blood, save lives, create knowledge

The Danish Blood Donor Study:
now part of the strategy for the Danish Blood Donor Organisation to use in the recruitment and adherence of donors

The Danish Blood Donor Study

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NHS
Blood and Transplant

Update on TT vCJD investigations in UK

Patricia Hewitt
Consultant in Transfusion Medicine/ Clinical Transfusion Microbiology
NHS Blood and Transplant Colindale

Definite or probable vCJD cases (UK n=177)

NHS Blood and Transplant

Mean age at death:	30 (range 14-75)
Median age at death:	28
Mean age at onset:	29 (range 12-74)
Median age at onset:	26
Median duration of illness:	14 months (range 6-114)
101 males:	75 females

160 cases tested: all MM at codon129 of the PrP gene

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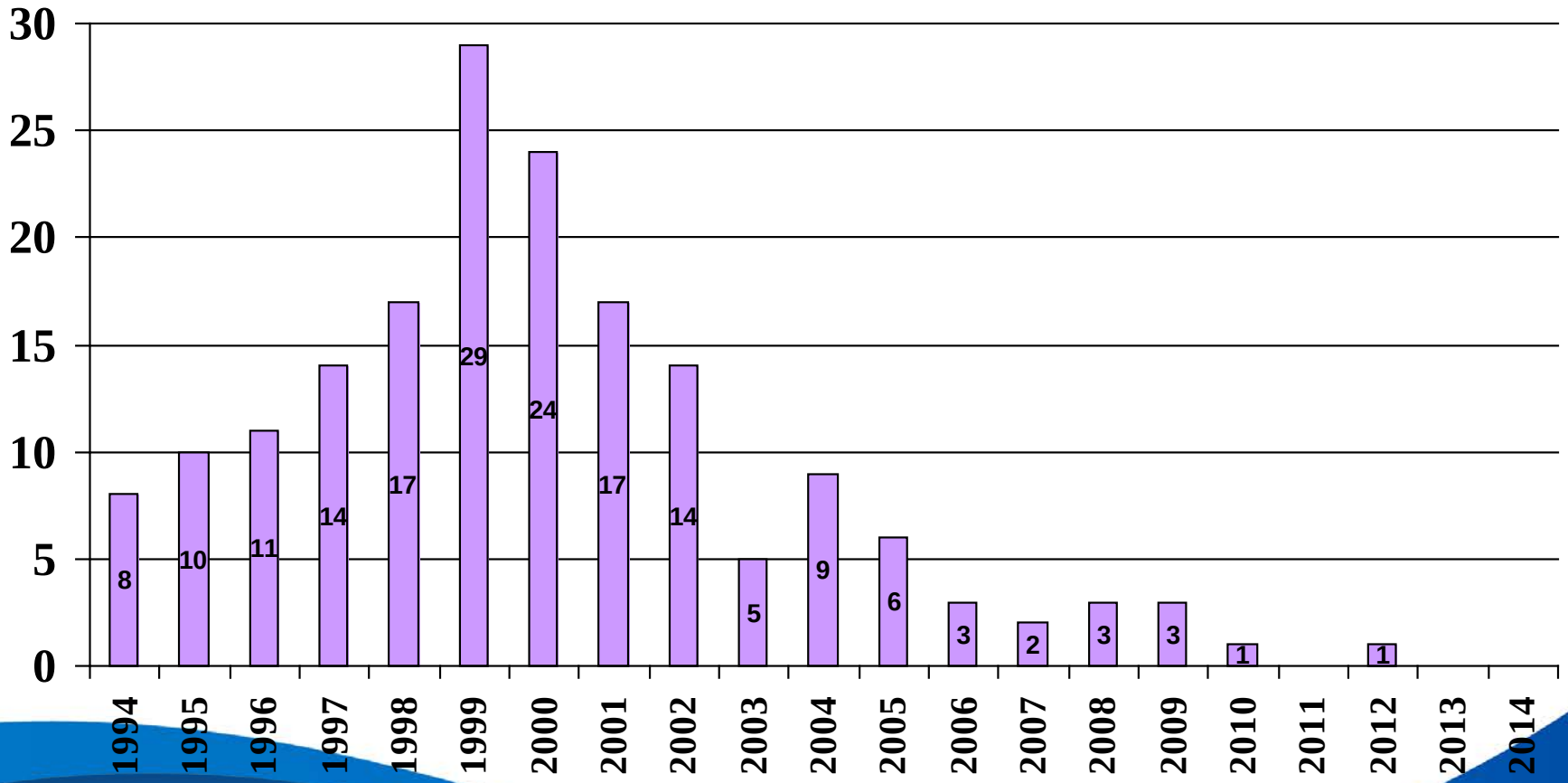
UK vCJD Cases

- 122 neuropathologically confirmed
- 55 no post mortem

NHS Blood and Transplant

Number of onsets per annum of vCJD in the UK



Number of vCJD cases by 10-year age group

NHS Blood and Transplant

Age at death	Number of vCJD cases
10-19	22
20-29	78
30-39	52
40-49	9
50-59	11
60-69	3
70+	2
TOTAL	177

NHS Blood and Transplant

Follow up of donations from individuals with CJD

(Transfusion Medicine Epidemiology Review)

Dr Patricia Hewitt
Dr Charlotte Llewelyn
Professor R Will
Jan McKenzie

NHS Blood and Transplant, UK
National CJD Research and Surveillance Unit

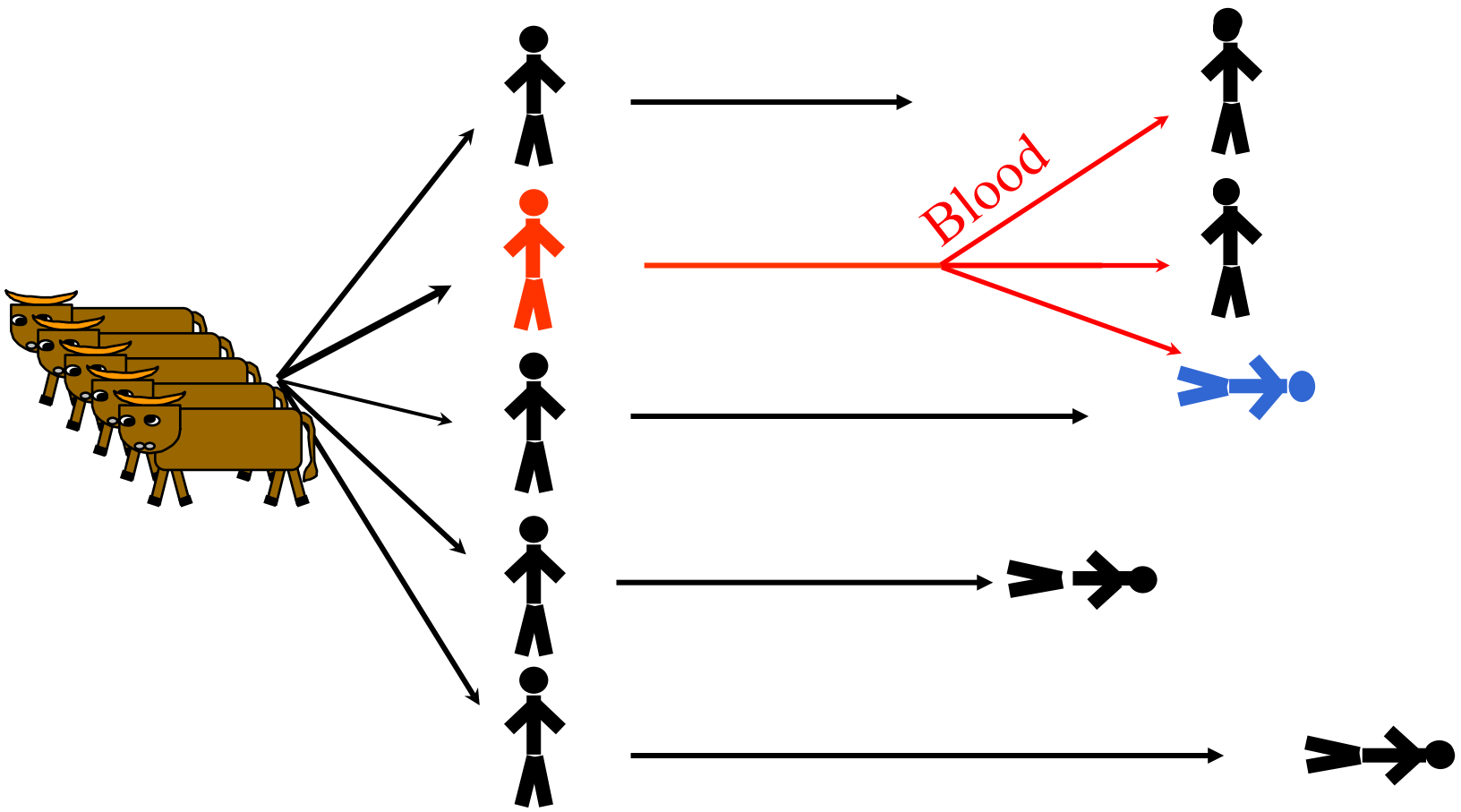
NHS Blood and Transplant

Study outline

- TMER (Transfusion Medicine Epidemiology Review) links databases of UK Blood Services and NCJDRSU
- cases of CJD are actively investigated for history of blood donation/ transfusion
- blood donations are traced through to names of recipient/donors: lookback and traceback
- passive surveillance of those identified: death certificates examined

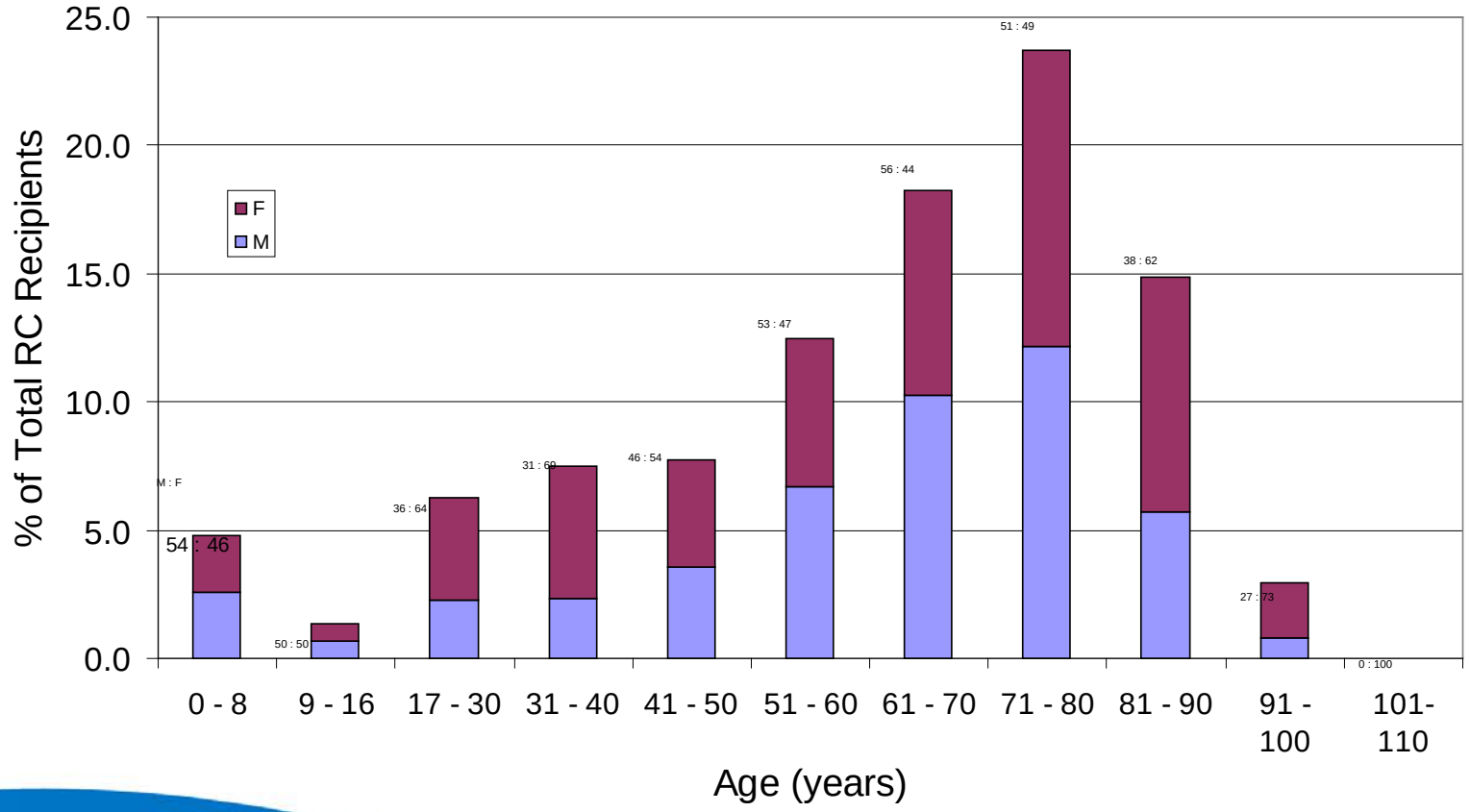
TMER forward arm: lookback

NHS Blood and Transplant



(after M.Busch)

Age distribution for red cell recipients
National Study (24 hospitals) (n=10080)



(Williamson, Murphy, Llewellyn et al, '03)

NHS Blood and Transplant

vCJD – BLOOD DONORS

total number of vCJD cases in the UK	177
number who were eligible to donate (ie aged ≥ 17)	167
number reported by relatives to have been blood donors	32
number of cases where donor records have been traced	24*
number of cases from whom components were actually issued	18
number of recipients identified from 18 cases where recipient and component information is available	67***

* donor records were traced on four cases where the relatives had reported the case not to be a donor; one of these had donated while the other 3 were registered as donors but never donated

*** some other recipients not identified

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TMER forward arm: lookback recipient outcome

- 34/67 recipients < 5 years survival since transfusion
- 14/67 recipients currently alive
- all living recipients have survived > 10 years

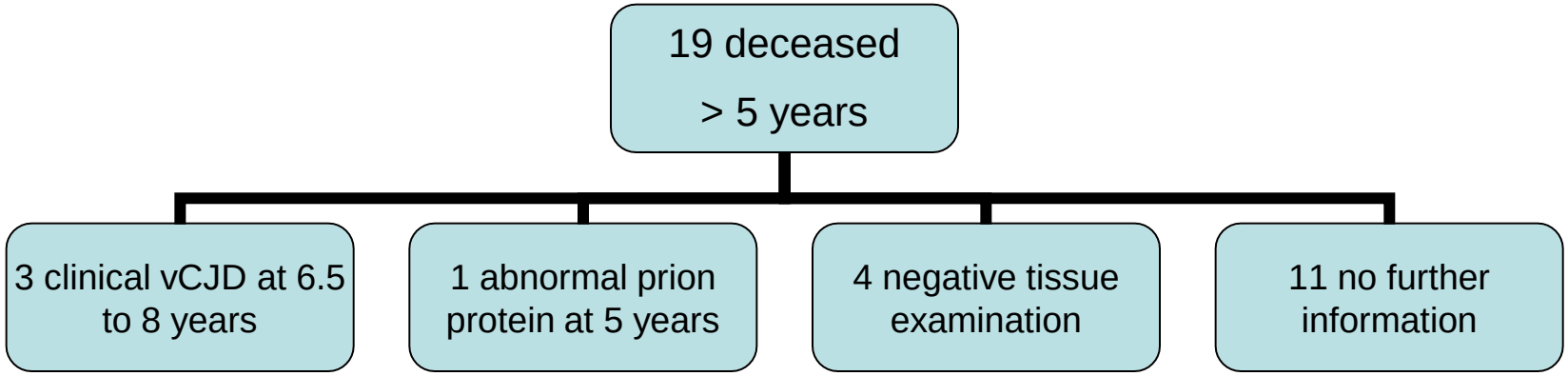
NHS Blood and Transplant

Decesed recipients with < 5 year survival (n = 34)

- cause of death known; none suggest prion disease
- none had post-mortem/ tissue examination

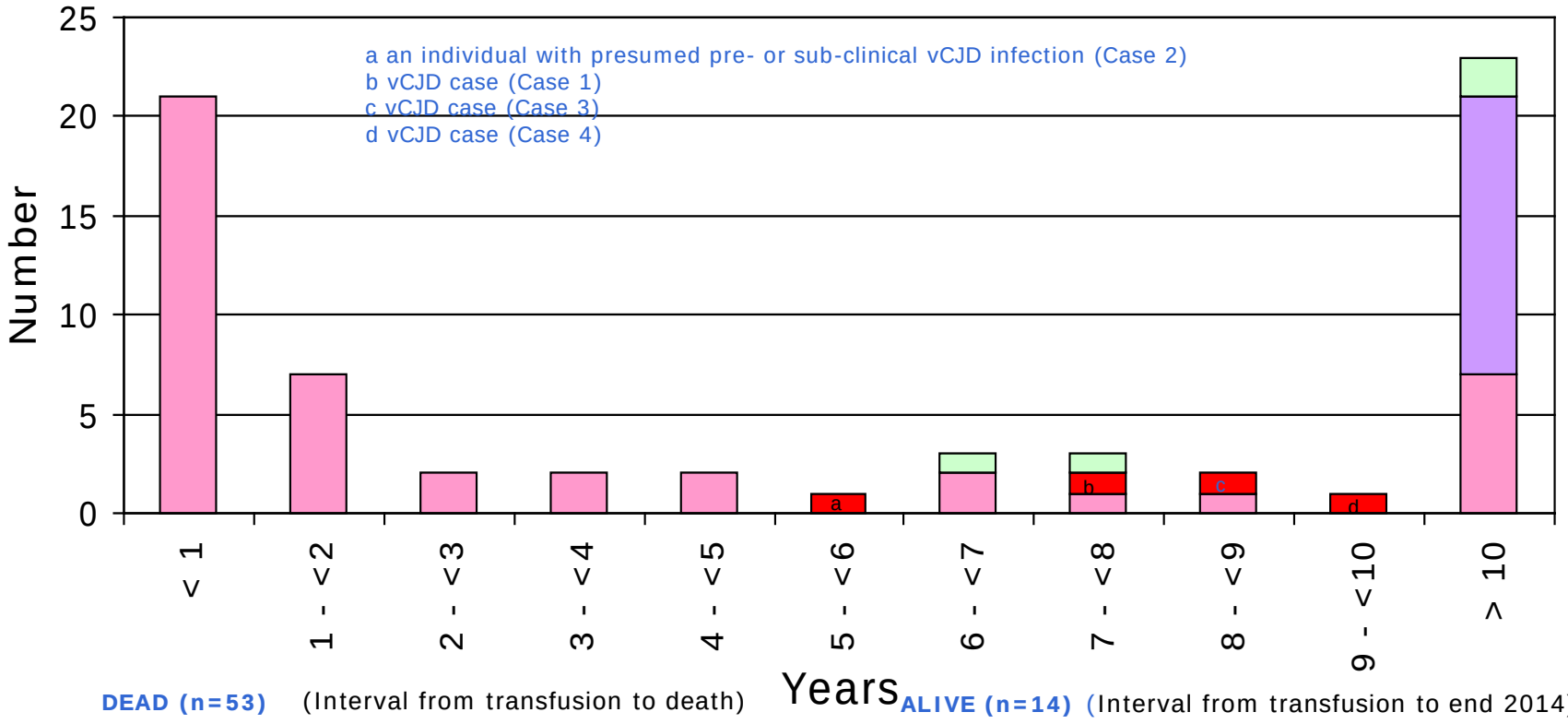
NHS Blood and Transplant

Deceased recipients with > 5 years survival (n =19)



Recipients (n=67) of labile blood components donated by donors who developed vCJD

NHS Blood and Transplant



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Living recipients

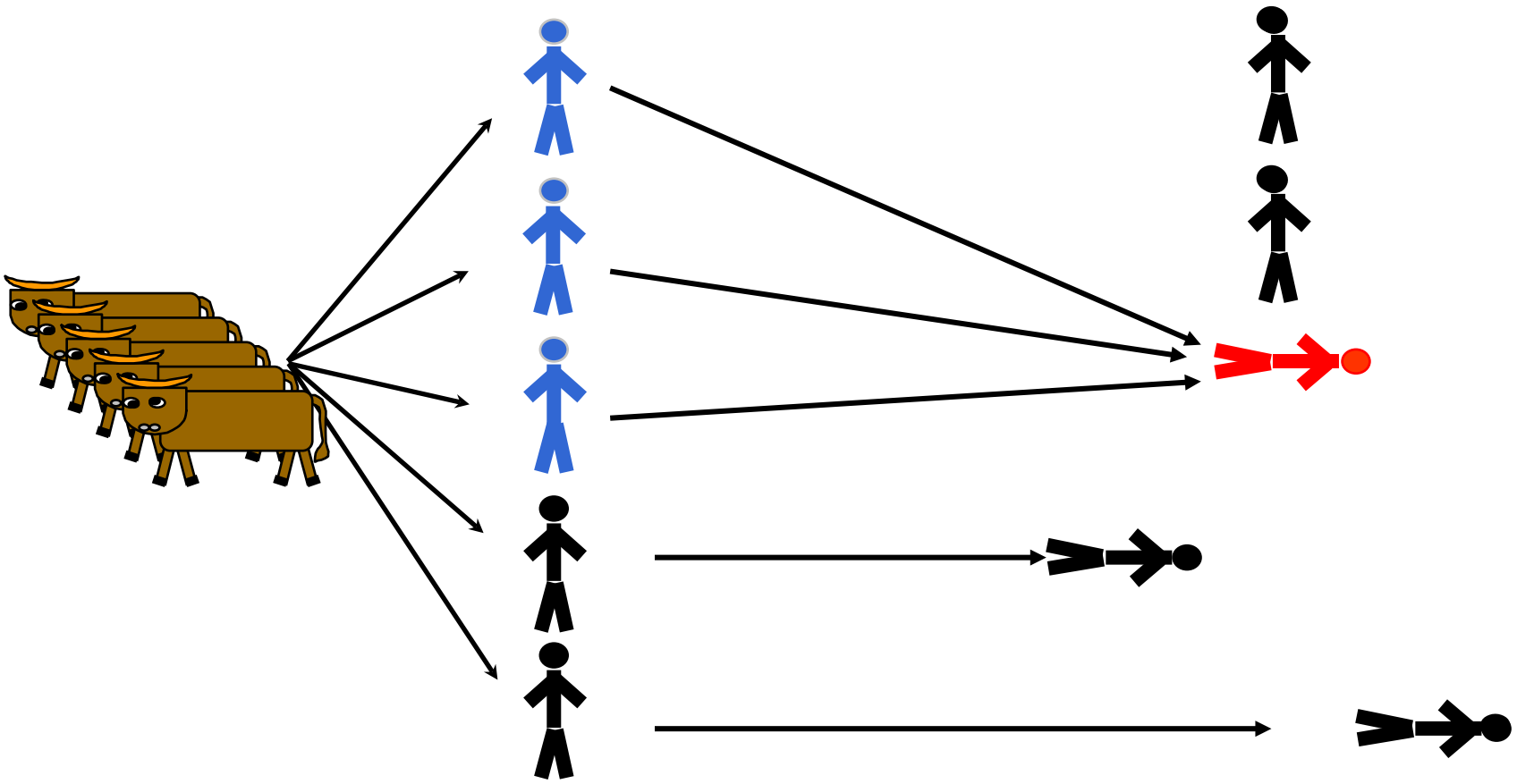
Recipients of blood from donors who later developed vCJD

NHS Blood and Transplant

Number of years lived following exposure for recipients currently alive, n=14

Number of years since exposure	Current age group of living patients										Total alive by years since exposure
	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	≥90	
0-4											
5-9											
10-14					1	1	2	1			5
15-19				1	2	1		1	2		7
≥ 20						1		1			2

TMER reverse arm: traceback



(after M.Busch)

NHS Blood and Transplant

Blood Transfusion in vCJD cases: traceback

Total number of vCJD cases in the UK	177[1]
No. of vCJD cases reported to have received a blood transfusion	15[2]
▪ Number not transfused: 1 ▪ Number predating available records: 4 (transfused 1962, 1969, 1971, 1976) ▪ Transfusion records found: 10 (transfused 1982, 1983+1993, 1993, 1994, 1996, 1997, 1997, 1999, 2002)	
Number of donors identified who gave blood to 10 vCJD cases	193
Number of donors already listed on the NCJDSU register as vCJD cases	2[3]

1 Note: recipient with pre-clinical infection (Case 2) is not included in this slide as this patient did not have a diagnosis of vCJD.
2 An additional case received a transfusion after onset of symptoms of vCJD and therefore is not included in the table.
3 two donors diagnosed with vCJD, one with one red cell recipient (Case 1 transfused in 1996), the other with two red cell recipients (Cases 3 and 4, both transfused in 1997).

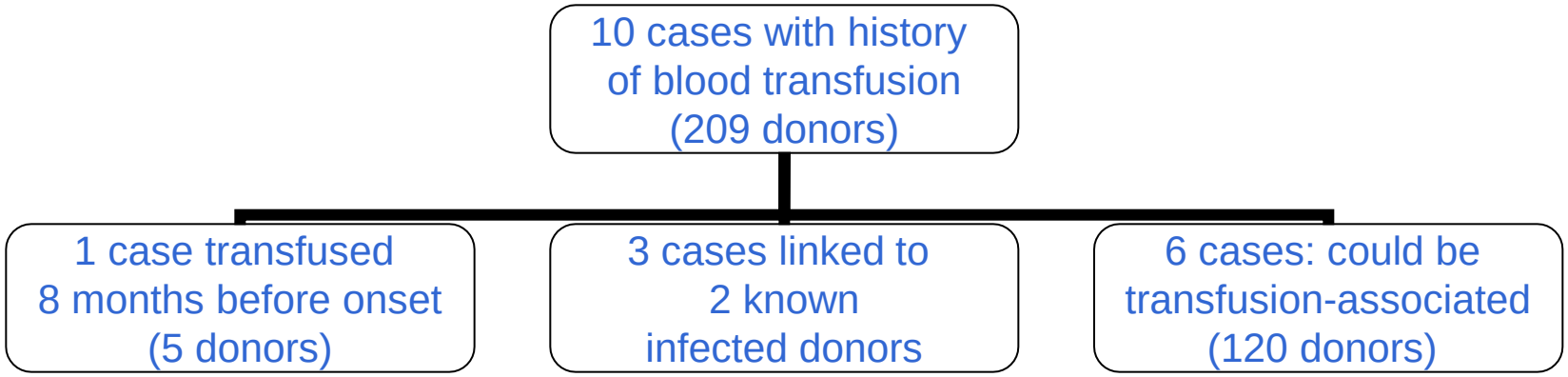
vCJD CASES WHO RECEIVED BLOOD TRANSFUSION(S) IN THE PAST

NHS Blood and Transplant

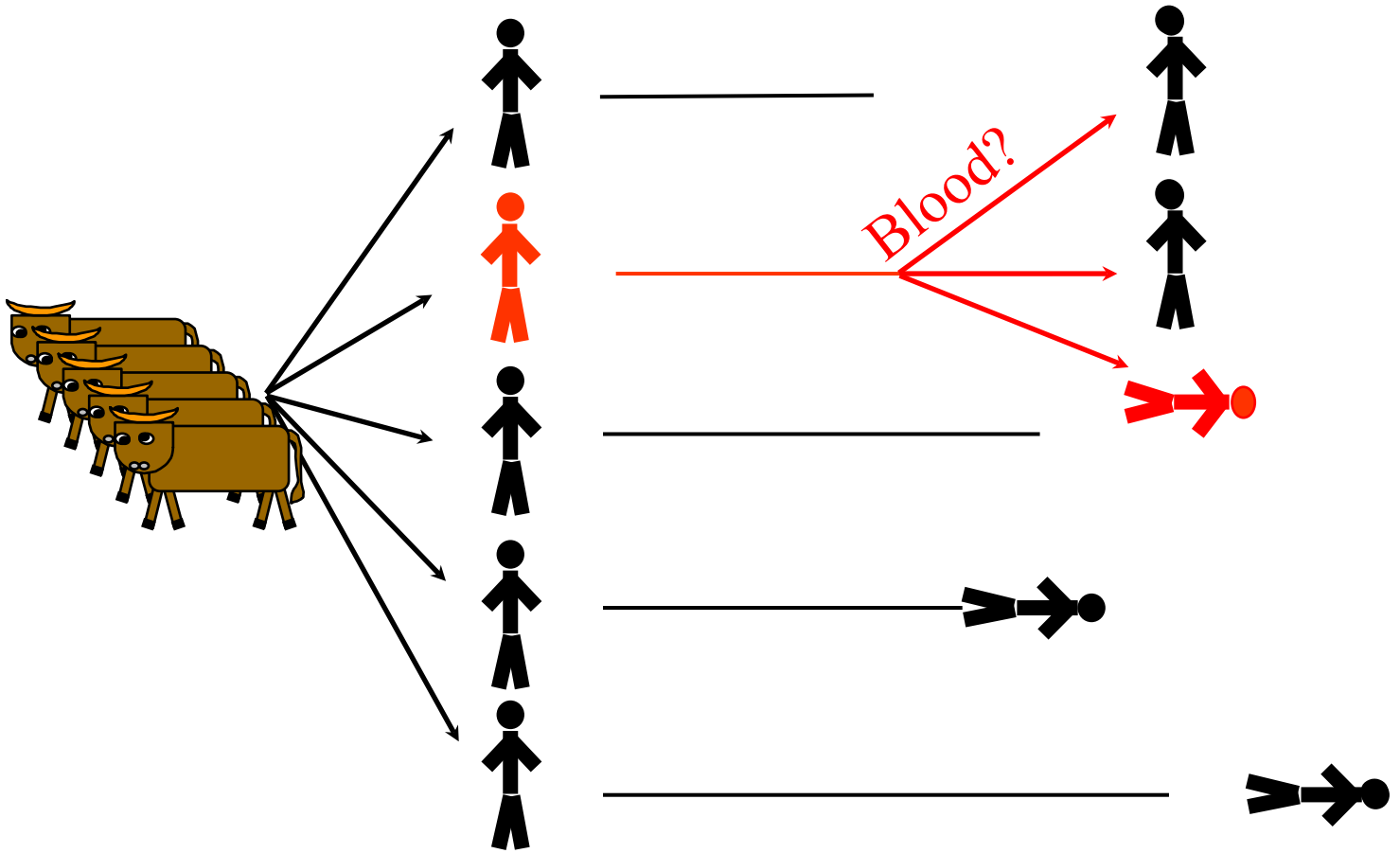
Recipient	Transfusion	Number of donor exposures	Interval from transfusion to onset of illness
1	1	38	4 years, 9 months
1	2	65	4 years, 6 months
2	1	2	15 years, 11 months
2	2	3	6 years, 3 months
3	1	4	5 years, 4 months
4	1	5	8 months[1]
5 (Case 1)	1	5[2]	6 years, 6 months
6 (Case 3)	1	56[2]	7 years, 10 months
7	1	2	13 years, 11 months
8	1	4	16 years, 9 months
9 (Case 4)	1	21[2]	8 years, 4 months
9 (Case 4)	2	2	7 years, 8 months
10	1	2	5 years, 11 months

[1]timing of clinical illness excludes blood transfusion as the source of infection in one case.
[2]one donor developed vCJD.

vCJD in transfusion recipients



TMER reverse arm: case 1



(after M.Busch)

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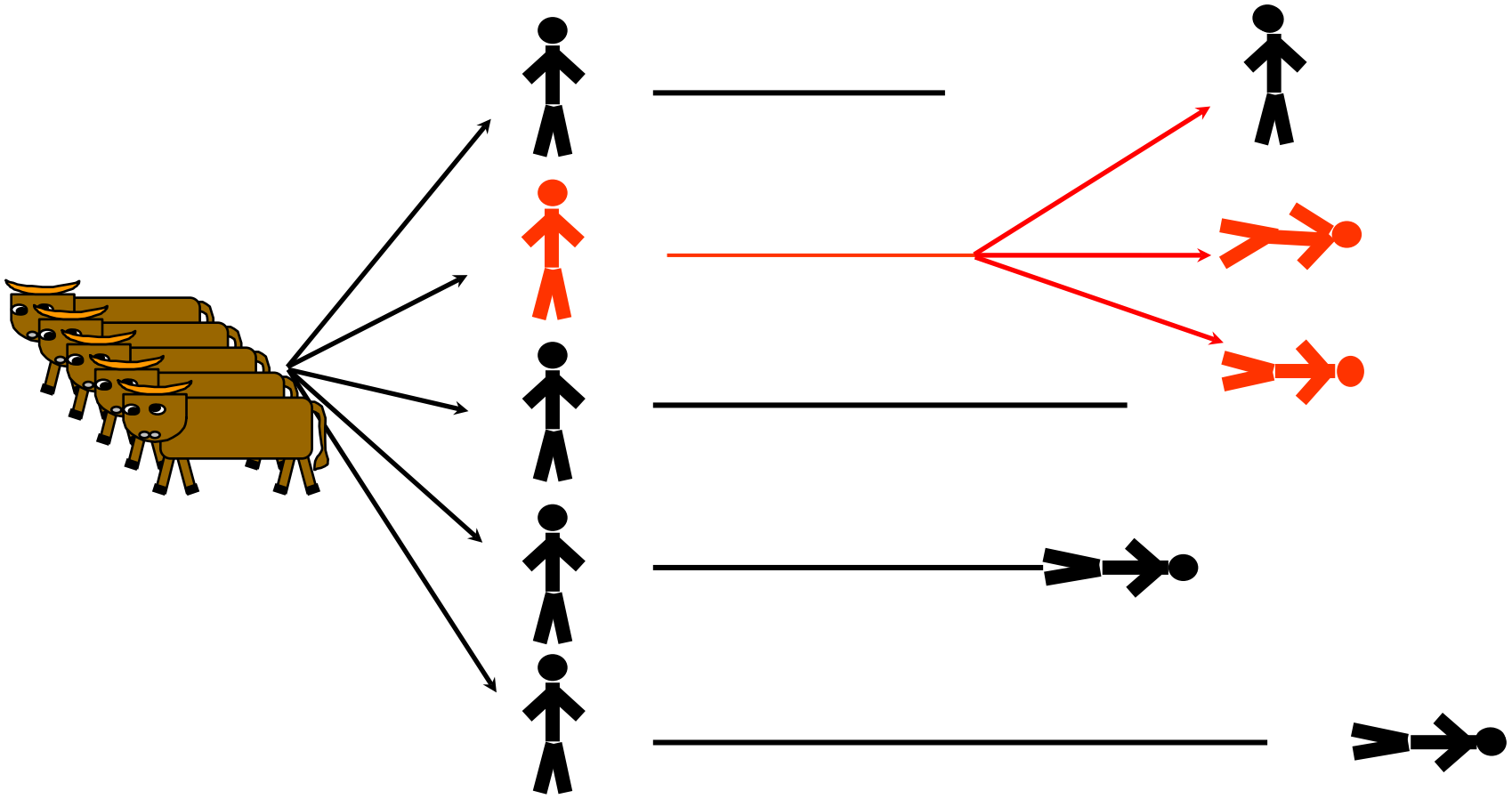
TMER Reverse arm: cases 3 and 4

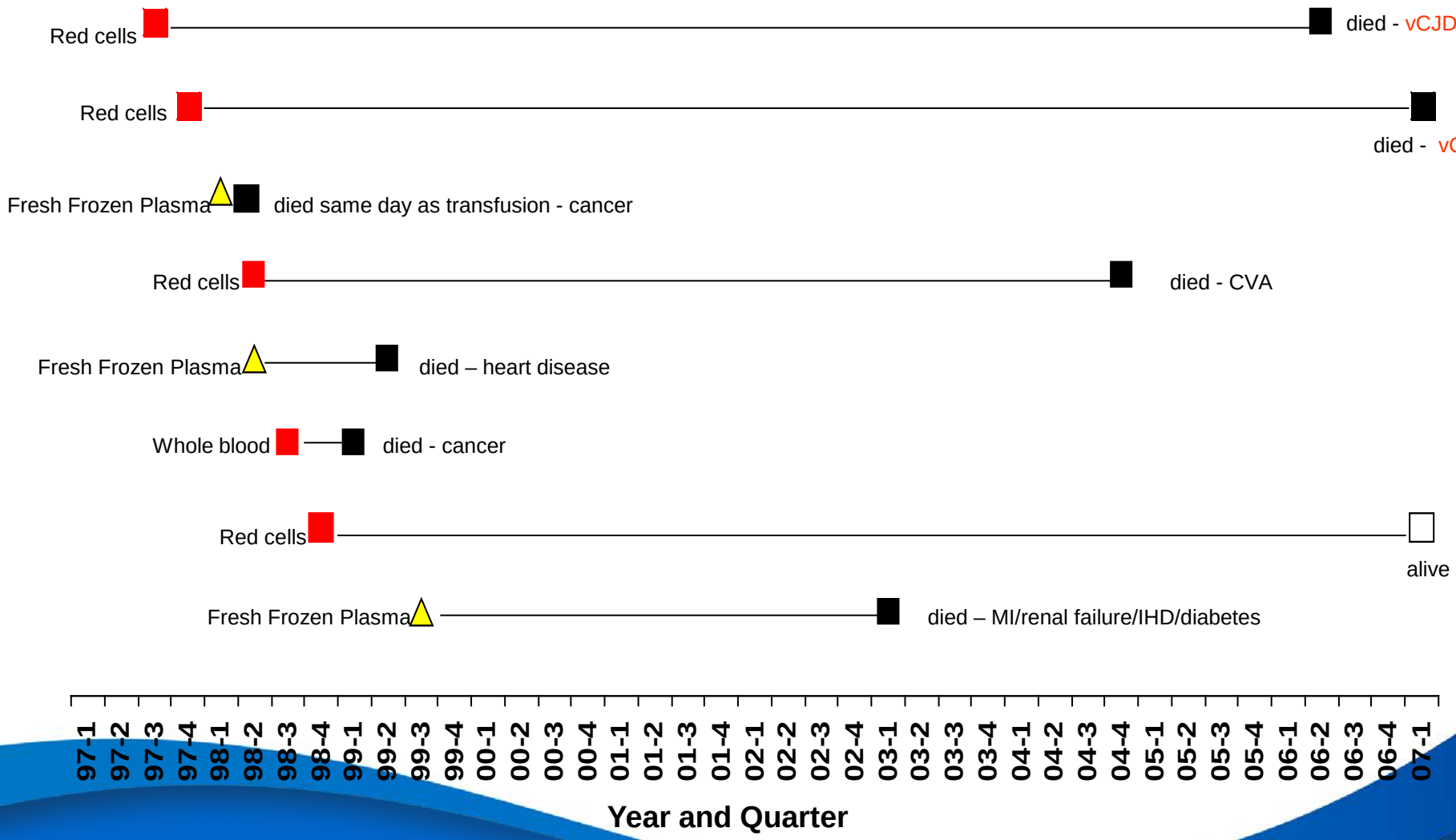


BSE vCJD infection incubation (10-20 years) death

(after M Busch)

DONOR TO CASES 3 AND 4 AND OTHER DONATIONS MADE

NHS Blood and Transplant



NHS Blood and Transplant

TMER reverse arm

- 209 donor exposures, 193 identified donors traced of whom 2, already known to have developed vCJD, donated to 3 recipients
- remaining donors to recipients 5, 6, and 9, with already identified infected donor: no further action
- remaining donors in cases with no identified infected donor: notified “at risk of vCJD for public health purposes” and continue under passive surveillance

vCJD CASES WHO RECEIVED BLOOD TRANSFUSION(S) IN THE PAST

NHS Blood and Transplant

Recipient	Transfusion	Number of donor exposures	Interval from transfusion to onset of illness
1	1	38	4 years, 9 months
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2	1	2**	15 years, 11 months
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3	1	4	5 years, 4 months
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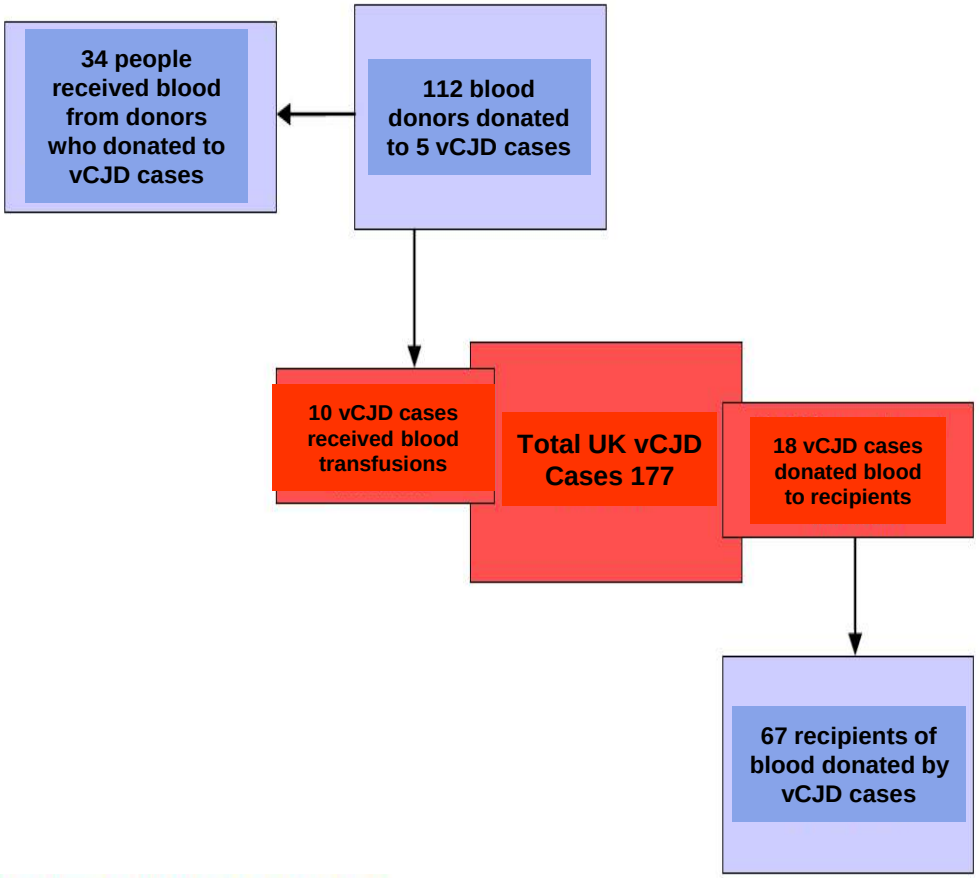
8	1	4**	16 years, 9 months
9 (Case 4)	1	21[2]	8 years, 4 months
9 (Case 4)	2	2	7 years, 8 months
10	1	2	5 years, 11 months

**donors not traced

[1]timing of clinical illness excludes blood transfusion as the source of infection in one case.

[2]one donor developed vCJD.

Patients at increased risk traced to a variant Creutzfeldt-Jakob disease (vCJD) case through blood donations.
Data source: Transfusion Medicine Epidemiology Review (TMER) study.



Journal of Hospital Infection 88 (2014) 22–27

Public Health England

Enhanced surveillance of people at increased risk of Creutzfeldt-Jakob Disease
Biannual Report, February 2015

NHS Blood and Transplant

Summary of groups identified as at increased risk of CJD on which data are collected (Data correct as at 31st December 2014)

'At risk' Group	Identified as 'at risk'	Number notified as being 'at risk'		Cases	Asymptomatic infections [a]
		All	Alive		
Recipients of blood from donors who later developed vCJD	67	27	14	3	1
Blood donors to individuals who later developed vCJD	112	108	104	0	0
Other recipients of blood components from these donors (reverse risk recipients)	34	32[b]	18	0	0
Plasma product recipients (non-bleeding disorders) who received UK sourced plasma products 1980-2001 [c]	2	2	2	0	0
Certain surgical contacts of patients diagnosed with CJD	196	163 [d]	139[e]	0	0
Highly transfused recipients [f]	3	3	3	0	0

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Follow-up surveillance is conducted by the CJD team at Public Health England, based on data provided by the TMER

P-447

Ten years on–follow up of cohorts with an increased risk of variant CJD through donating or receiving blood

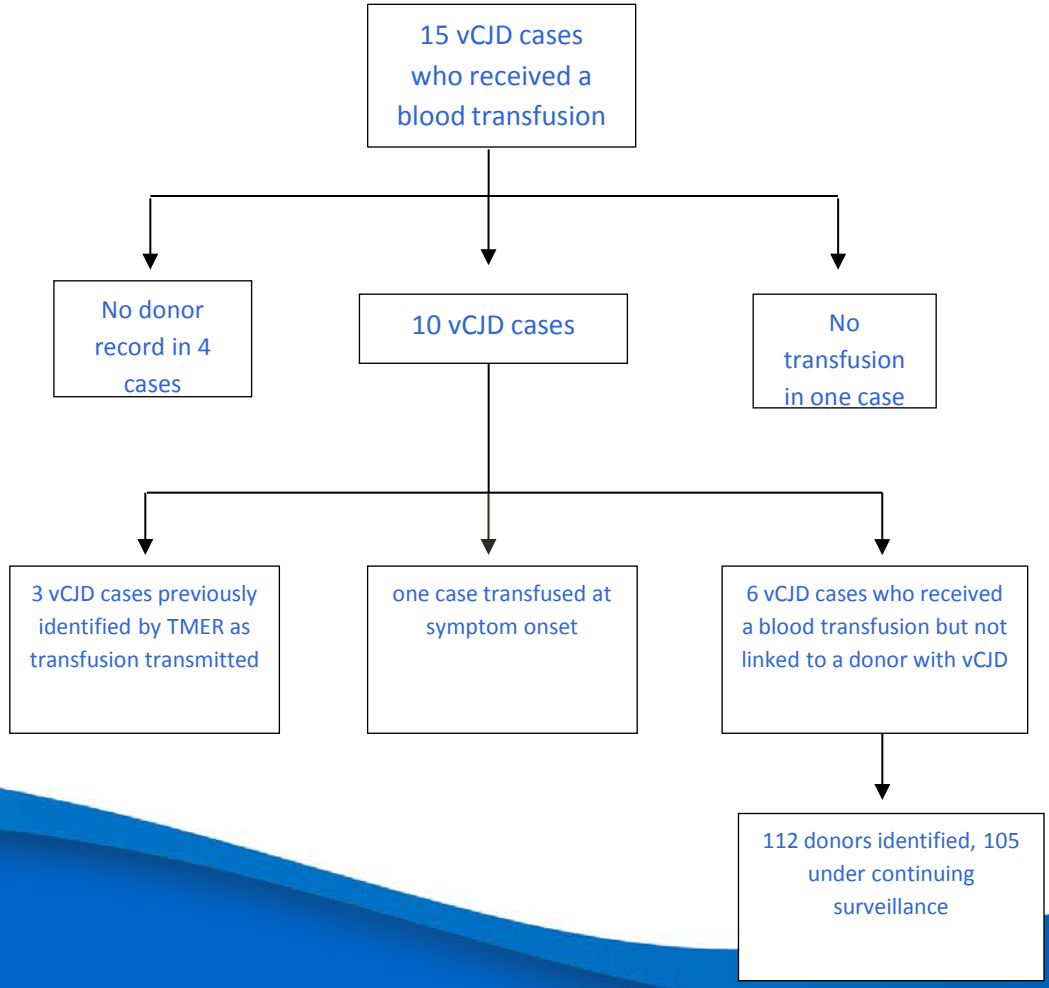
Poster prepared by Katy Sinka and Marta Checchi of the CJD team at PHE

Variant CJD and Blood Transfusion: are there additional cases?

NHS Blood and Transplant

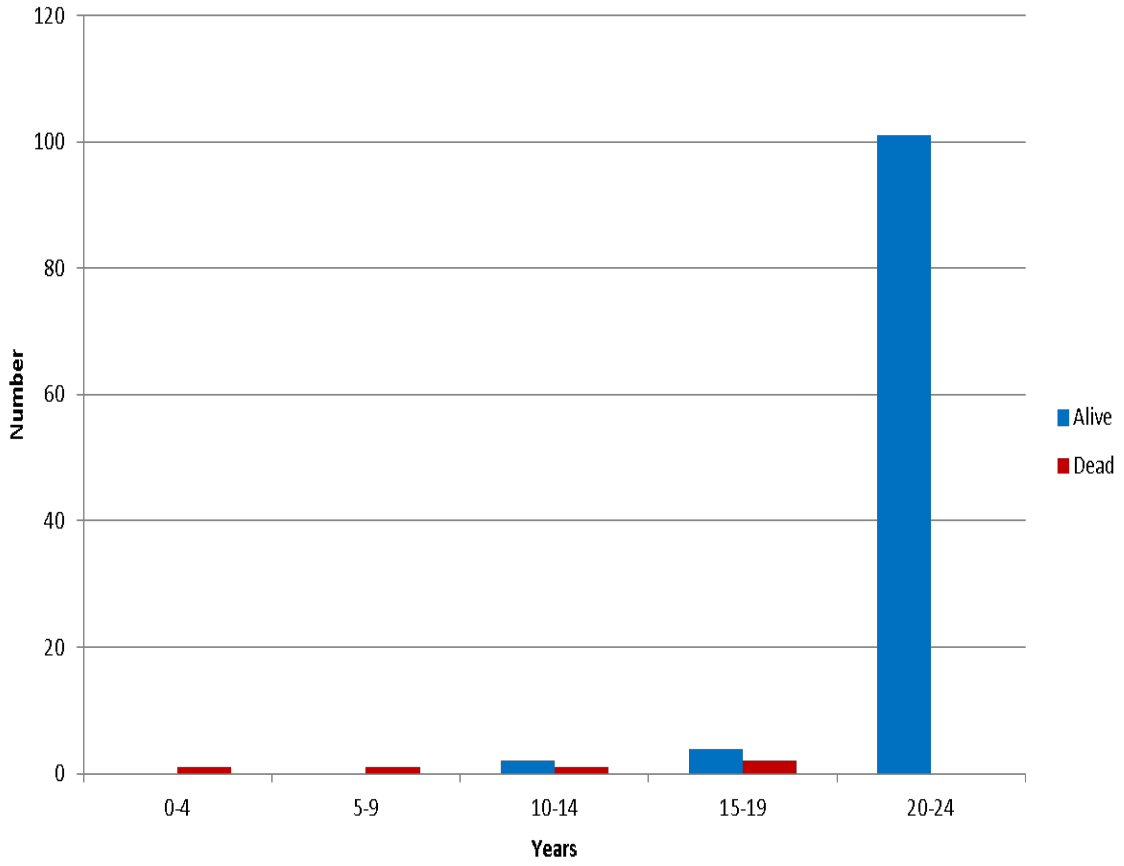
LRR Davidson, CA Llewelyn, JM Mackenzie, PE Hewitt, RG Will: Vox Sanguinis 2014 107 220-225

National CJD Research and Surveillance Unit and NHS Blood and Transplant



Donor survival from transfusion in index case (n=112)

NHS Blood and Transplant



Variant CJD and Blood Transfusion: are there additional cases?

LRR Davidson, CA Llewelyn, JM Mackenzie, PE Hewitt, RG Will

Cause of death among 112 donors to the 5 vCJD cases under review

NHS Blood and Transplant

Year of Death	Interval from transfusion in index case to death in donor	Cause of death in donor
1994	1 year	Injury to abdominal aorta causing haemorrhage Verdict: Death by Misadventure
2001	8 years	Hypertensive heart disease (Coroner's post mortem without inquest)
2006	13 years, 4 months	Pulmonary embolism/Deep vein thrombosis/ ischaemic heart disease (Coroner's post mortem without inquest)
2008	15 years, 2 months	Bronchopneumonia/disseminated sigmoid colon carcinoma, pulmonary embolism
2012	18 years, 8 months	Complications of heart valve surgery

Variant CJD and Blood Transfusion: are there additional cases?

LRR Davidson, CA Llewelyn, JM Mackenzie, PE Hewitt, RG Will

NHS
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Age at onset in variant CJD cases

- Mean age at onset in **primary** vCJD cases
  28.4 years

- Mean age at onset in **3 transfusion transmitted** cases
  57.6 year

- Mean age at onset in **6 recipients** unlinked to an affected donor **35.5** years

VoxSanguinis
The International Journal of Transfusion Medicine

NHS
Blood and Transplant

Conclusion: In conclusion, it is possible that one or more of the vCJD cases that received a blood transfusion derived from an individual not known to have vCJD were infected by the blood transfusion. However, the evidence for this is weak, and the absence of a past history of transfusion in most cases of vCJD excludes a large number of unrecognised transfusion-transmitted cases.

LRR Davidson *et al*, 2014 107 220-225

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Blood and Transplant

VoxSanguinis
The International Journal of Transfusion Medicine
ISBT International Society of Blood Transfusion
Vox Sanguinis (2015) 108, 432–433
© 2015 International Society of Blood Transfusion
DOI: 10.1111/vox.12241

LETTER

Variant CJD and blood transfusion

J. P. Wallis

Older patients with clinical vCJD are more likely to have been transfused, and the mean age will be higher than the whole cohort. Based on the age-adjusted transfusion prevalence, the mean age of cases that might have received an unlinked prior transfusion is 33.4 years. This compares with the observed figure given by Davidson *et al*. of 35.5 years.

NHS Blood and Transplant

TMER summary

- TMER has used standard blood transfusion lookback and traceback procedures
- and linked blood service and NCJDRSU records
- to investigate any linkage between donors and recipients with vCJD

NHS Blood and Transplant

TMER conclusions

- 4 cases of prion transmission by transfusion (3 fatal) have been identified from lookback on transfusions in 1996 – 1999
- no further cases of transfusion-transmissions have been identified through traceback from infected recipients
- continued surveillance will be necessary for many years

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Blood and Transplant

Acknowledgements

Jan MacKenzie
Prof Bob Will
Charlotte Llewelyn

Staff in all four UK blood services and in hospital blood transfusion laboratories

The TMER is funded by the Department of Health

HEV and interventions: UK perspective

Patricia Hewitt NHS Blood and Transplant

ISBT TTID Working Party June 2015

NHS Blood and Transplant

NHSBT Hepatitis E study 2012-13

- screened 225,000 blood donations over a 12 month period
- 79 (1 in 2850) donations HEV RNA positive
- overall transmission rate 42%
- all recipients eventually cleared infection

NHS Blood and Transplant

SaBTO HEV sub-group

- UK-wide, with representation from all 4 UK blood services
- examining options, operational and financial considerations

NHS Blood and Transplant

HEV and blood donations: options

- no screening
- universal screening
- screening for selected recipients (cf HCMV)

NHS Blood and Transplant

Donor management?

- follow-up testing before return to donation, if so, when?

2013: 5/37 had low level detectable viraemia at 4 weeks after pick-up

- return to donation after set period, if so, when?

- special considerations for “valuable” component (platelet) donors?

NHS Blood and Transplant

Donor management: workload

- within NHSBT, extrapolating from previous data, universal HEV screening would yield 386 confirmed positive donations in first year, assuming 2012/13 incidence levels

- this is greater than for all other infections combined: 2014: approx 177 in total

NHS
Blood and Transplant

Outcome?

- report to extraordinary meeting of SaBTO in July 2015
- SaBTO make recommendations to Ministers

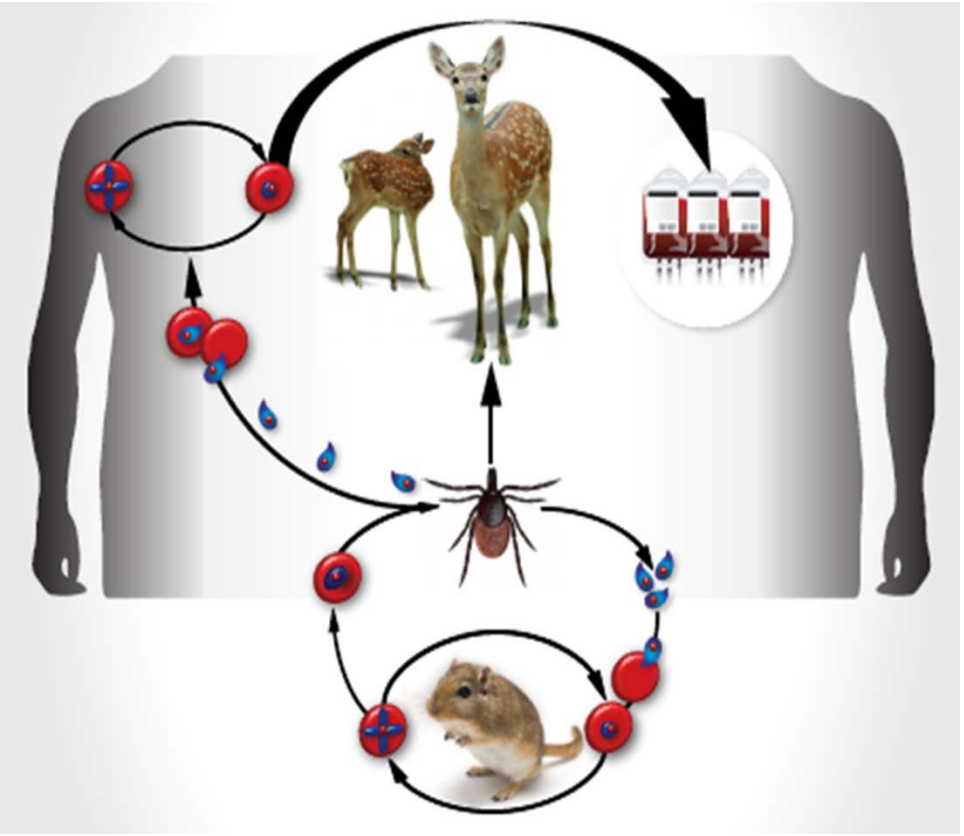
Strategies for Implementation of Antibody and Nucleic Acid-based Testing for *Babesia microti* in Blood Donations: Summary of May 13th 2015 Blood Product Advisory Committee Meeting

Hira L. Nakhasi, Ph.D.

CBER/USFDA

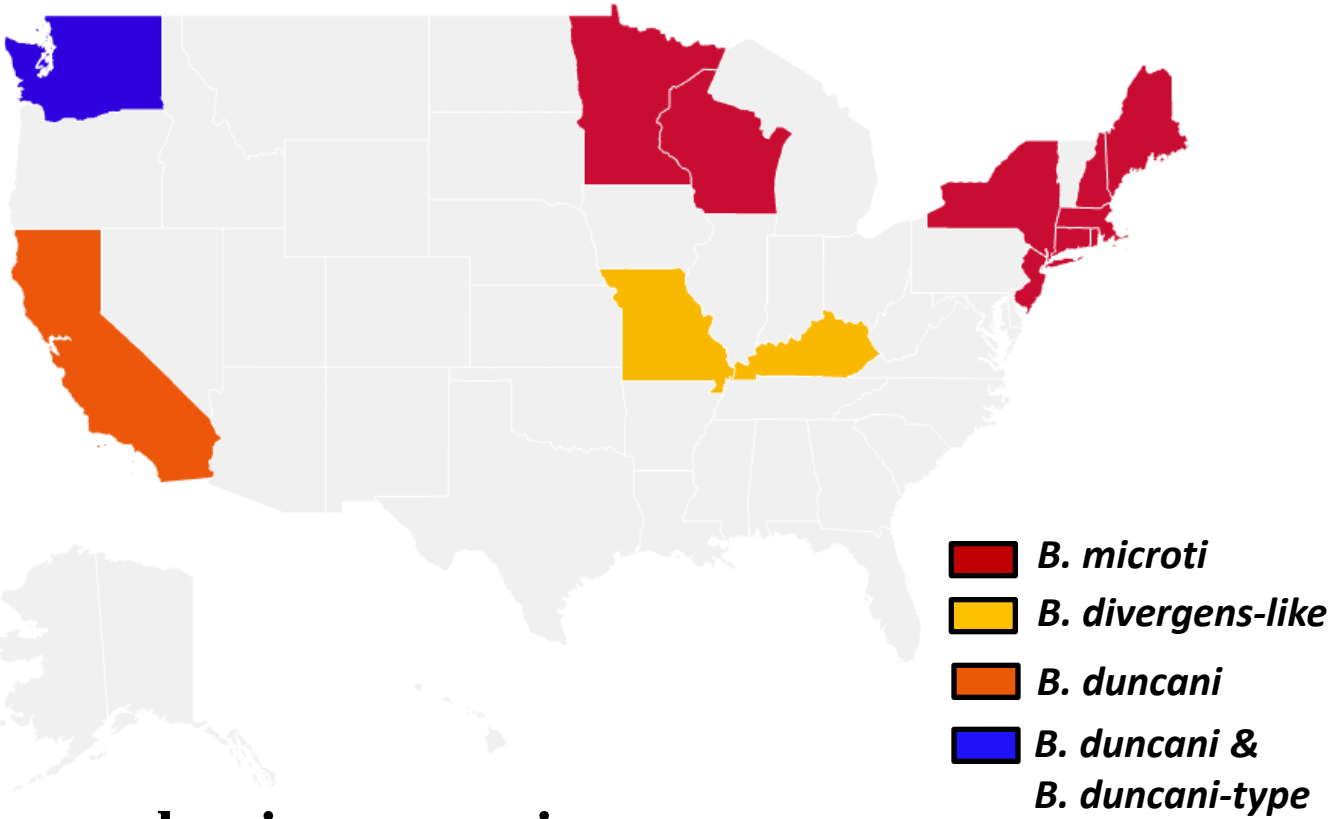
July 3rd 2015

Life Cycle of *B. microti*



- **Enzootic transmission**
- **Sylvatic reservoir**
- **Human is incidental host**
- **Chronically infected asymptomatic individuals cause TTB**

Babesia Species Prevalent in United States



- ***B. microti* – predominant species**
- ***B. duncani* and *B. duncani*-type**
- ***B. divergens*-like**

Assays designed for *B. microti* may fail to detect the other *Babesia* species prevalent in U.S.

Epidemiology of Babesiosis

- **Endemic transmission is reported mostly in Northeastern, Mid-Atlantic and Upper Midwestern states**
- **Area of endemic transmission is reported to be expanding, particularly into the states adjoining the endemic states**
- **Several other states without recognized endemic areas also report babesiosis cases due to infections acquired during travel to endemic areas**

Babesia Transmission is Regional While TTB Risk is Systemic

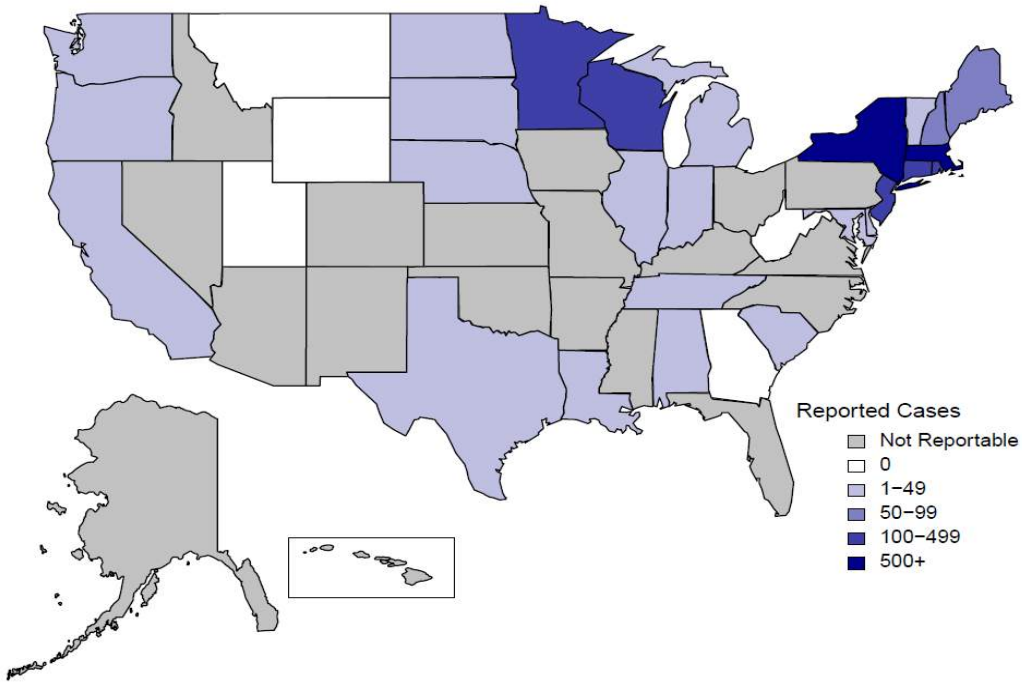
- **TTB risk is nationwide, because**
  - **Donors from non-endemic areas travel to endemic areas and acquire infection**
  - **Donors who normally reside in endemic areas may donate elsewhere**
  - **Blood products are often shipped between widely separated regions across the U.S.**

- **Therefore, screening is needed where blood is collected**

Assessment of Babesiosis Risk in the United States based on the following data sets

- **National Babesiosis Surveillance Program, CDC 2011-2013**
- **Transfusion-Transmitted Babesiosis Cases 1979-2009 (CDC)**
- **Center for Medicare & Medicaid Services (CMS) health records for beneficiary claims for diagnosis of babesiosis in persons 65 and older 2006-2013**

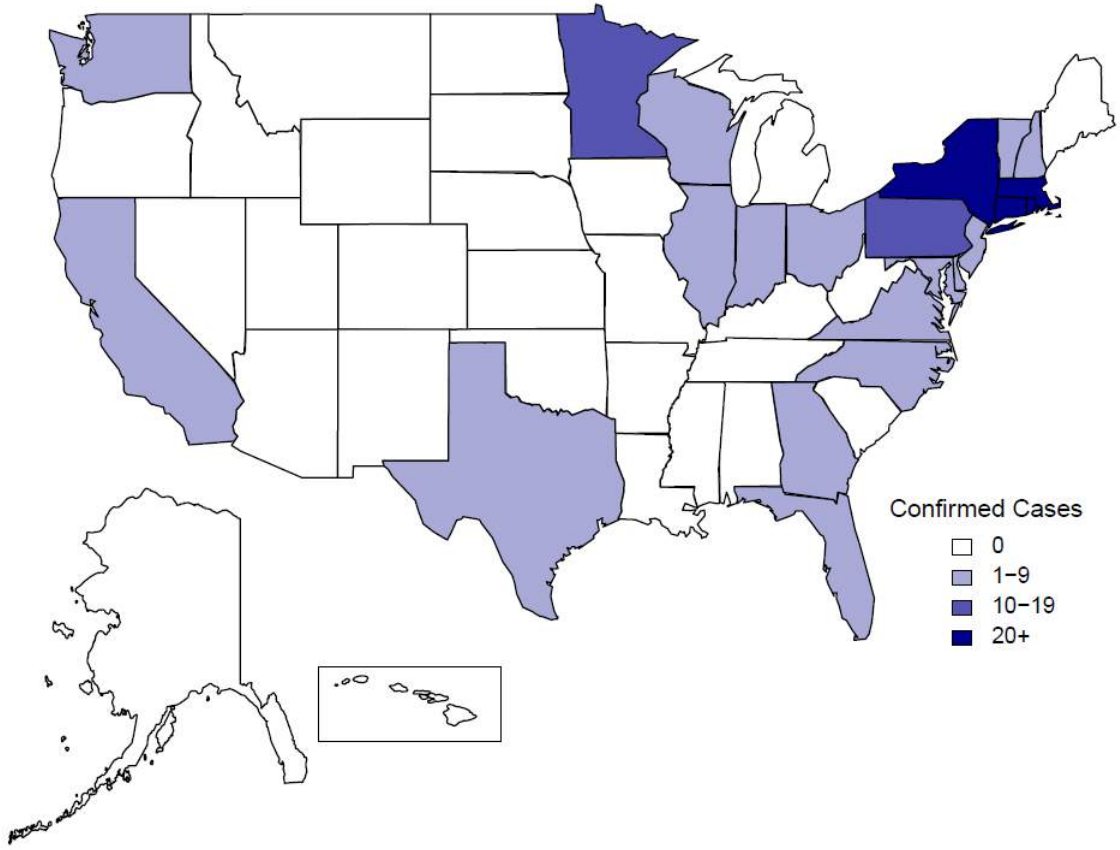
Clinical Babesiosis Cases by State*



- **Notifiable disease since of 2011. Cases observed in 26 states**
- **<u>2013</u>**
  - **22 states,1,792 cases**
- **98.5% of all cases in 9 endemic states**

***Likely underreported due to nondiagnosis or misdiagnosis of clinical and asymptomatic infections**

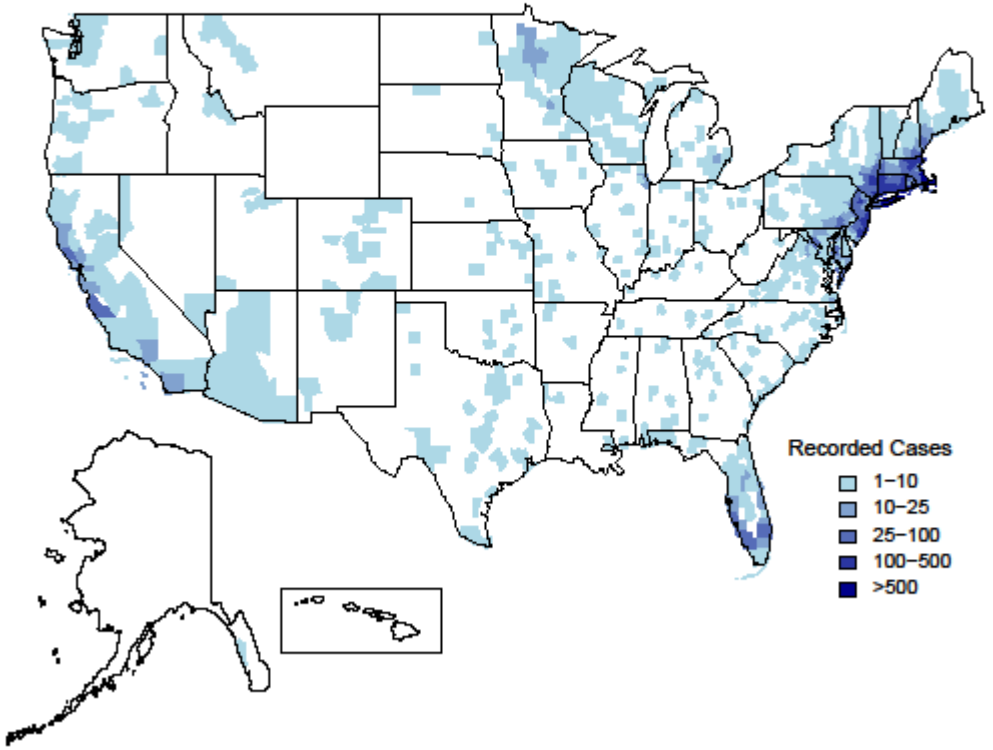
Distribution of TTB by State



- **Since 1979, 205 cases, for whom state of donation was known, were reported from 22 states**
  - **About 87% of cases in 9 endemic states**

Nationwide Prevalence of Babesiosis (CMS)

- **2006-2013**
  - **10,301 unique diagnoses of babesiosis**
- **Cases reported from all states and Washington D.C., except Wyoming**



Issue for BPAC Discussion

Sought advice on donor testing strategies for evidence of *Babesia microti* infection

a. Should antibody testing be nationwide and year round

b. Should NAT be limited to certain high risk states

c. Should alternative approaches be considered based on geographic and seasonal risk

d. What should be the appropriate donor deferral time?

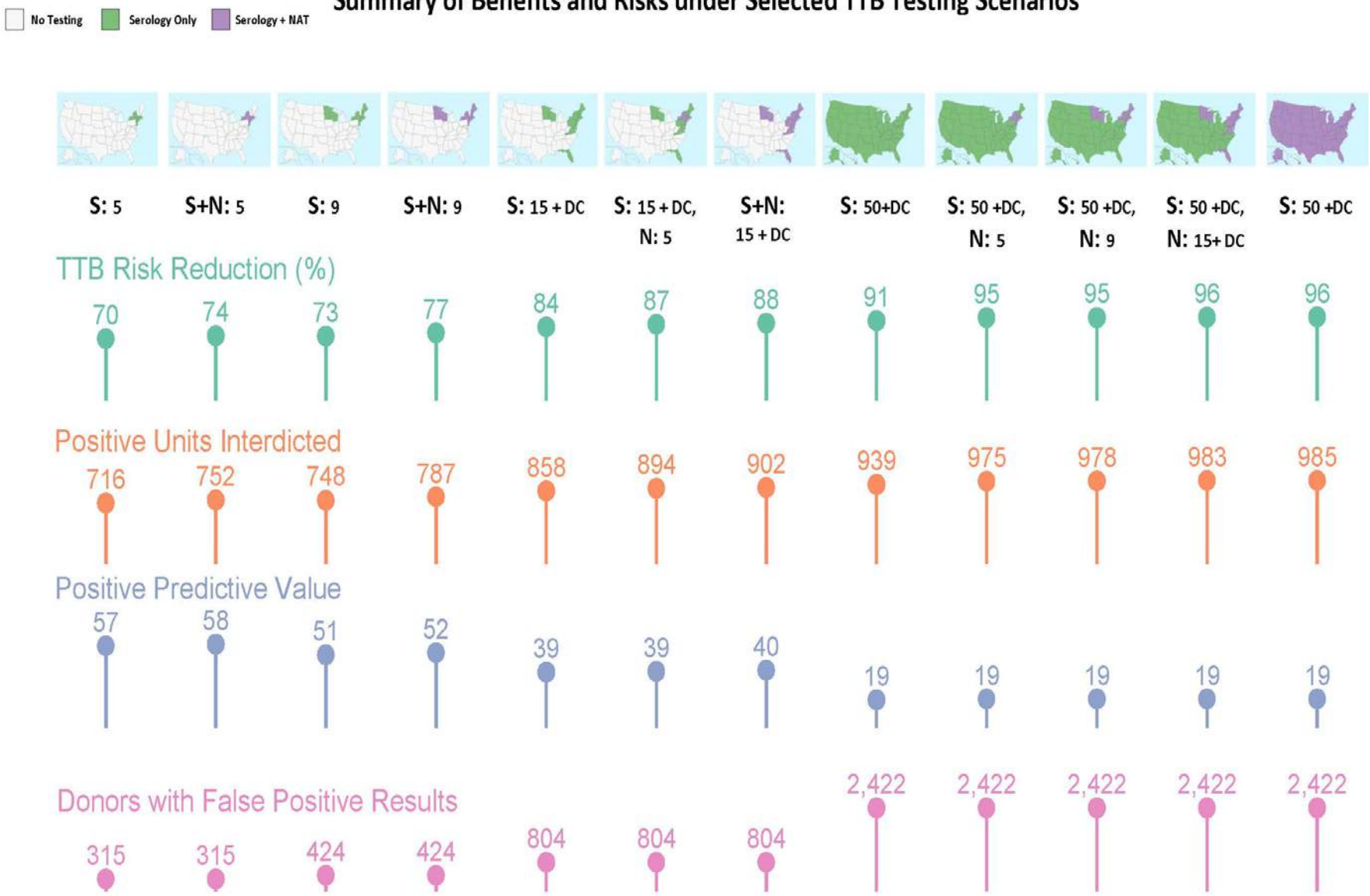
FDA Benefit-Risk Model for *B. microti* Testing of Blood Donations

FDA model using the CMS dataset to estimate:

- **Potential risk of babesiosis in U.S. blood donors**
- **Potential reduction in TTB risk under various testing strategies**
  - **Antibody-only testing in selected states or nationwide**
  - **Testing with both antibody and NAT in selected states or nationwide**
- **Potential blood unit loss due to false positive test results**
- **Positive predictive value of testing for markers of infection**

Testing Scenario	Percent TTB Risk Reduction	Positive Predictive Value	Units From Positive Donors Interdicted	False Positive Donor Test Results
No Donor Testing	**0**	0	0	0
5 States CT, MA, RI, NY, NJ	**73.7**	58.3	752	315
9 States CT, MA, RI, NY, NJ, WI, MN, NH, ME,	**77.1**	52.2	787	424
13 States + DC CT, MA, RI, NY, NJ, MD, NH, ME, DC, MN, VT, PA, DE, WI	**82.9**	45.8	847	589
14 States + DC CT, MA, RI, NY, NJ, MD, NH, ME, DC, VA, MN, VT, PA, DE, WI	**84.9**	43.9	868	652
15 States + DC CT, MA, RI, NY, NJ, MD, NH, ME, DC, VA, MN, VT, PA, DE, WI, FL	**88.3**	39.7	902	804
50 States + DC	**96.0**	19.3	985	2422

Summary of Benefits and Risks under Selected TTB Testing Scenarios



Blood Products Advisory Committee Meeting, May 13, 2015

Questions for the Committee (I)

1. **Do the available scientific data and FDA analysis support the concept of nationwide, year round testing of blood donations for *Babesia*-risk by an antibody-based test?**

   1a. If not, please comment on alternative options that FDA should consider, including limitation of antibody testing to specific states.

The committee agreed that the scientific data and FDA analysis support the concept of nation-wide, year round testing of blood donations for *Babesia*-risk by an antibody-based test. 11 yes votes. 3 no votes, 0 abstained.

Questions for the Committee (II)

2. Does the Committee agree that NAT-based testing should be performed in blood donations in certain high-risk states?

The Committee voted unanimously for NAT-based testing in blood donations in certain high-risk states. (Vote 14 yes, 0 no).

a. If so, please advise whether year round NAT testing should be considered in the following:

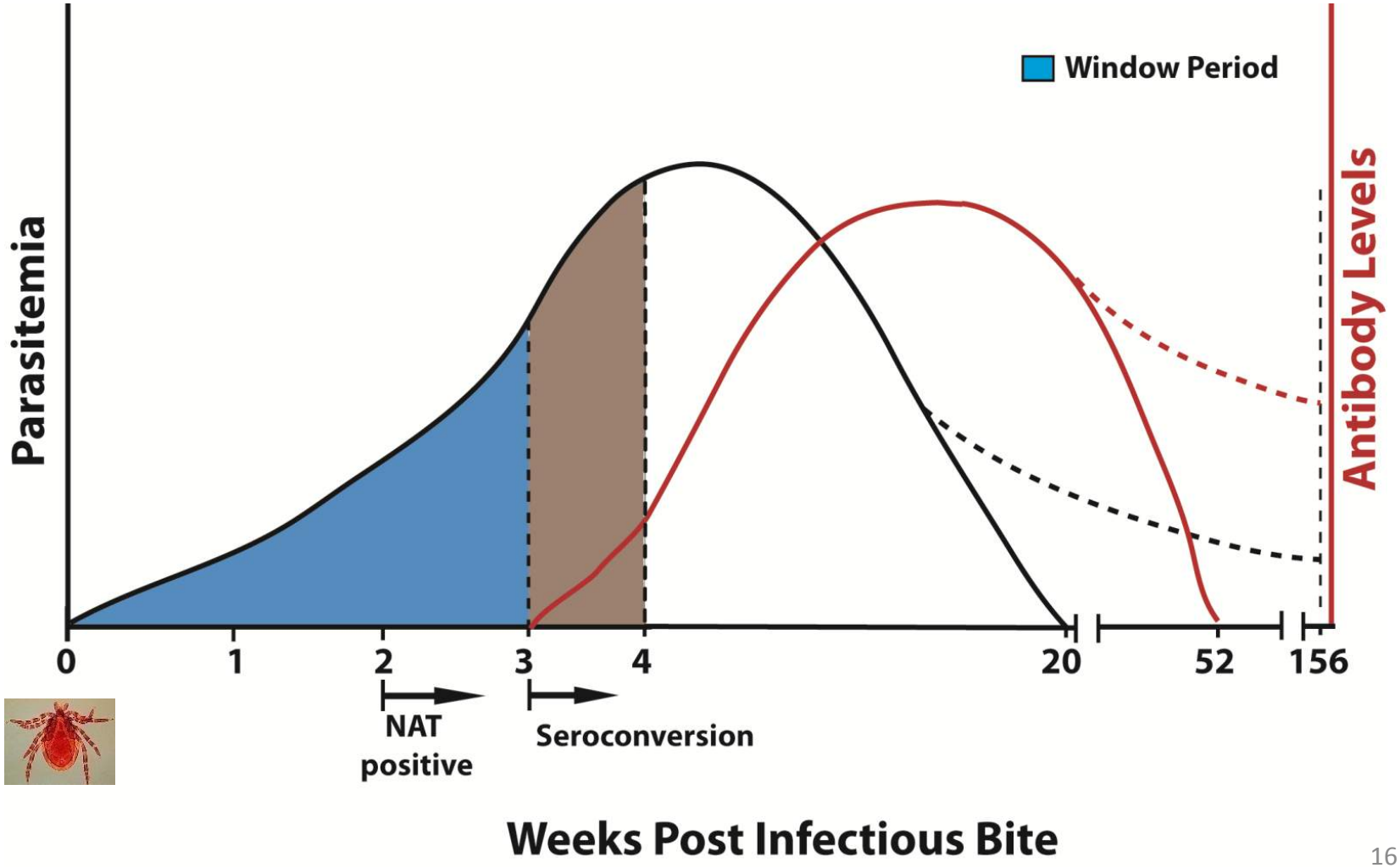
i) 5 states (highest endemic): CT, MA, RI, NY and NJ

ii) 9 states (all known endemic): CT, MA, RI, NY, NJ, MN, WI, NH and ME

iii) 15 States plus DC (largest risk capture with the smallest number of states): CT, MA, RI, NY, NJ, MN, WI, NH, ME, MD, DC, VA, VT, PA, DE and FL

The majority of the Committee voted in favor of the 9 states testing option (8 votes). The remaining Committee members (6 votes) supported the 15 states, plus D.C. testing option. Some members commented that PA should be added to the 9 states option.

Window Period, Seroconversion, Duration of Parasitemia and Antibody Response: Implications for NAT and Antibody Testing for *B. microti*



Questions for the Committee (III)

3. Please comment whether it would be appropriate to apply a time-based deferral for those donors who have *B. microti*-positive test result(s)?

3a. If so, please advise on a suitable deferral period for donors who had *B. microti*-positive test results?

Members supported a deferral period of at least two years and that a reentry algorithm should include antibody and NAT testing.

Acknowledgements

- Sanjai Kumar
- Richard Forshee
- Mikhail Menis
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- John Peyton Hobson
- Jennifer Scharpf
- Ginette Michaud
- Peter Marks
- Jay Epstein

Survey for Bacterial Testing in Platelet Concentrates in Latin America

Sandra Ramirez-Arcos, Carl McDonald and Richard Benjamin, for the ISBT Working Party Transfusion-Transmitted Infectious Diseases (WP-TTID), Subgroup on Bacteria

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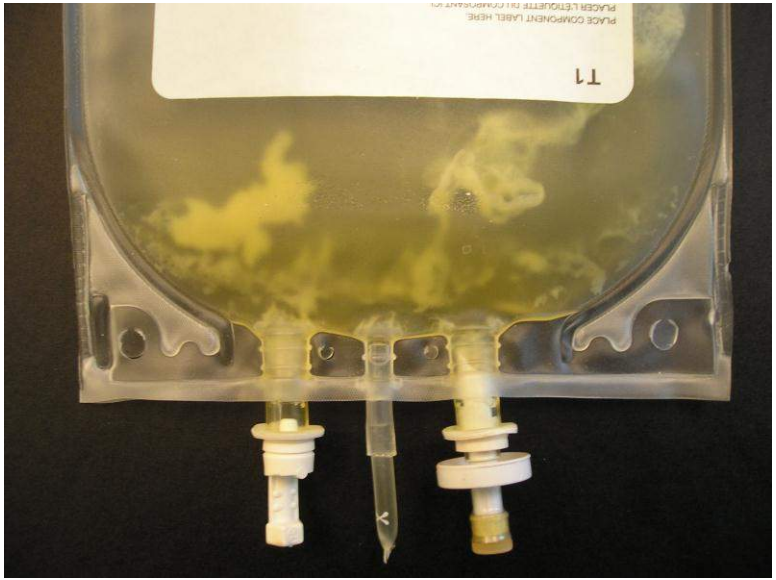
June 26, 2015

Bacterial Contamination in Platelet Concentrates

- **Bacterial contamination of platelet concentrates (PCs) poses the highest post-transfusion infectious risk in developed countries.**
  - ***There is not extensive information about similar strategies implemented in developing countries.***
    - ***As part of the initiatives of the ISBT WP-TTID, Latin American blood banks were surveyed.***



Methods

- A Survey Monkey with 10 comprehensive questions was sent to 43 blood banks in five countries: Argentina, Brazil, Colombia, Honduras and Mexico.

- The centers were asked about the type(s) of PCs produced, platelet shelf-life and strategies used to improve platelet safety.
  - Centers performing bacterial testing were questioned regarding
    - the percentage of PCs tested
    - quarantine period after sampling
    - screening system(s)
    - definitions to interpret testing results
    - haemovigilance data on septic transfusion reactions and
    - implementation of pathogen reduction technologies

- Respondents were further surveyed about annual PC production and distribution.

Respondents

- One of the 43 centers does not perform bacterial testing in PCs
- Seven out of the remaining 42 centers (16.7%) (2 from Argentina, 2 from Mexico and 3 from Brazil) answered all survey questions.
  - Reported annual PC production/distribution varies within centers: 3,000-13,800 (Mexico) and 3,300-19,200 (Brazil).

Question 1: Which type(s) of platelets are produced at your center?

Answer Options	Response Percent
Apheresis	0.0%
Whole-blood derived prepared by the platelet-rich-plasma method	0.0%
Whole-blood derived prepared by the buffy coat method	14.3%
Apheresis and Whole-blood derived prepared by the platelet-rich-plasma method	71.4%
Apheresis and Whole-blood derived prepared by the buffy coat method	14.3%

Which percentage?

Question 2

2. What is the platelet shelf life at your center?

- Five days ← 100% respondents
- Seven days
- Other

Other (please specify)

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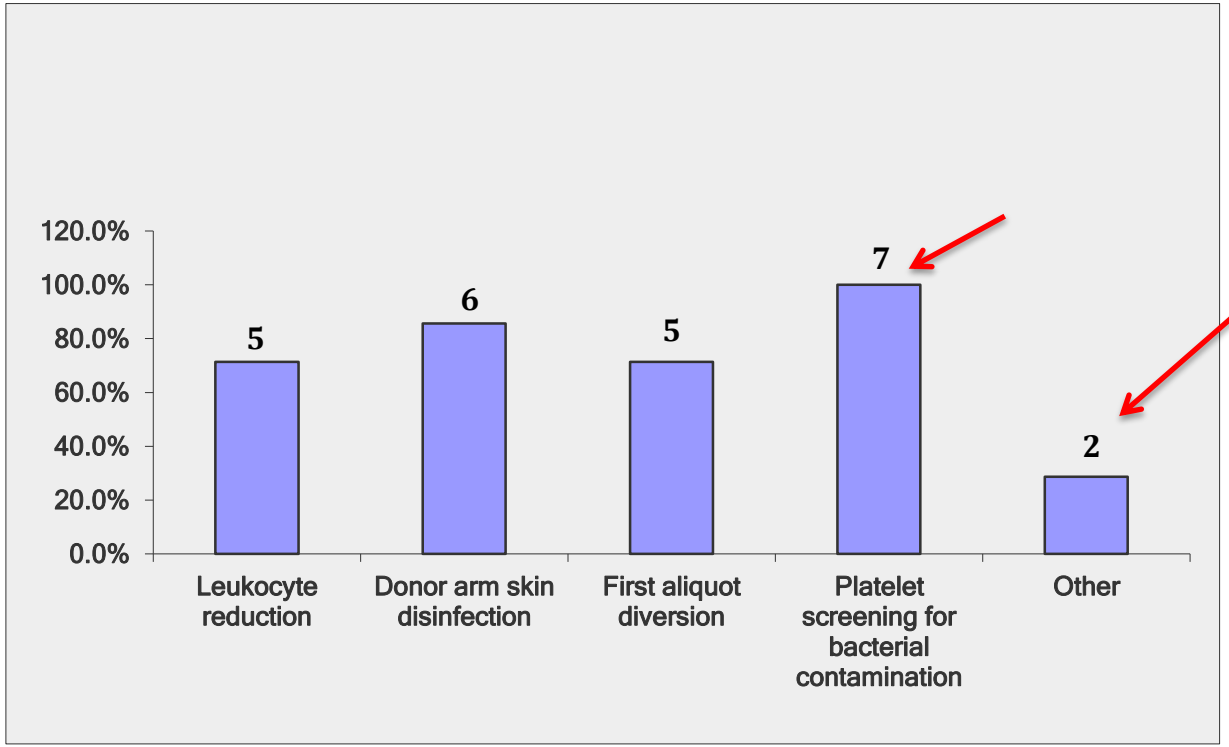
Question 3: Which of the following strategies are implemented at your center ?

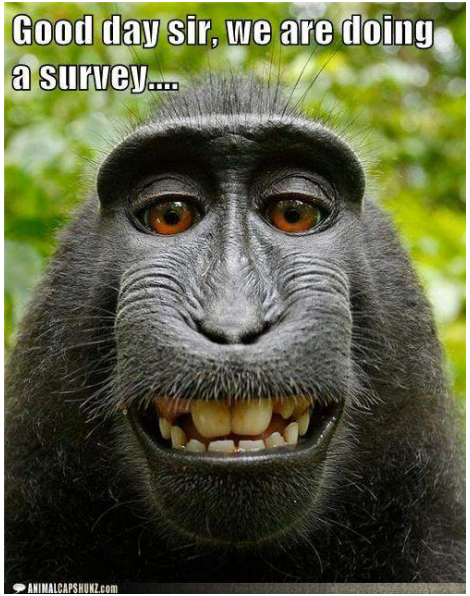


Question 4: If you are screening platelets for bacterial contamination, which proportion of the collection is screened? How long after collection is the sample taken?

Center	Response
1	One per cent in the expiration date
2	100% - 24 hours
3	100%
4	1% of our monthly inventory (at least 4 units per month). Samples are taken at the end of the shelf life.
5	100% - 20 hours after collection
6	Screen 100% - Sample taken 24 hs after collection.
7	1% (It is mandatory)

Question 5: If you test platelets for bacterial contamination, is there a mandatory quarantine period prior to platelet release to inventory once the sample is taken?

- **Yes (3 centers, 42.9%)**
  - ***Two respondents: quarantine for 24 hours***
- **No (4 centers, 57.1%)**



Question 6: If you perform screening for bacterial contamination as part of routine testing, which system do you use?

Testing system	Percentage	Number
Culture method	85.7%	6
Rapid test	0.0%	0
pH/Glucose	0.0%	0
More than one of the above	0.0%	0
Other (please specify)	14.3%	1

- 100% use a culture method

Question 7: If you perform screening for bacterial contamination with a culture method, which type of culture bottle do you use?

Testing system	Percentage	Number
Culture method	85.7%	6
Rapid test	0.0%	0
pH/Glucose	0.0%	0
More than one of the above	0.0%	0
Other (please specify)	14.3%	1

- 4 centers: BacT/ALERT
- 2 centers: BACTEC
- *All aerobic and anaerobic culture bottles*

eBDS

Question 8: If you perform platelet screening for bacterial contamination with a culture method, during the analysis of your results how do you define (if applicable):

Center	Confirmed (true) positive cultures?	False positive results?	Indeterminate results?	False negative results?
1	automated test			
2	Send to reference lab	Send to reference lab	Send to reference lab	Send to reference lab
3	Full pathogen identification as per Clinical Lab			
4	second sample confirmed positive in another lab	second sample negative in another lab	N/A	negative screening sample (48 hs) but positive after release of unit to inventory
5	Perform the test of sample again	Perform the test of sample again	Perform the test of sample again	

Question 9: Do you have haemovigilance data on adverse transfusion reactions due to bacterially-contaminated platelets? If yes, is data available to the public?

- Yes (3 centers, 42.9%)
  - *No data available to the public*
- No (4 centers, 57.1%)

Question 10: Have you implemented or considered implementing pathogen reduction at your center?

- **Yes (2 centers, 28.6%)**
  - ***Two centers have considered implementation***
    - ***One center is at a preliminary phase of consideration***
    - ***For the second center, the technology is not available in their country***
- **No (5 centers, 71.4%)**

Table 1
Summary of publications reporting routine bacterial screen testing with the BacT/ALERT culture system

Reference	Year published	Country	AP platelets	BC platelets	PRP platelets	Diversion	Skin preparation	Leukoreduced	AP technology	PAS	Delay before sampling (h)	Volume per bottle (mL)	Laminar flow hoods
Jenkins et al	2011	Canada	X			100%	IPA/TI Chloro (1)	Yes	MCS+, Spectra, Trima	No	24-48	4-10	Yes
Souza et al	2012	USA	X			>90%	IPA/TI Chloro (1)	Yes	MCS+, Spectra, Trima, Amicus	No	24-36	4	No
Souza et al	2012	USA	X			100%	Chloro (1)	Yes	MCS+, Spectra, Trima, Amicus	No	24-36	8	No
Su et al	2008	USA	X			91%	IPA/TI Chloro (1)	Yes	MCS+, Spectra, Trima, Amicus	No	24-36	4-5	No
Benjamin et al	2013	USA	X			100%	PI (2) Chloro (1)	Yes	Amicus, Trima	No	24-36	8-10	Yes
Eder et al	2009	USA	X			100%	PI (2)	Yes	Amicus, Trima	No	24-36	8-10	Yes
Eder et al	2007	USA	X			39%	PI (2)	Yes	Spectra, Trima, Amicus	No	24-36	4-5	Yes
Su et al	2008	USA	X			100%	Chloro (1)	Yes	MCS+, Spectra, Trima,	No	24-36	4-5	No

What is next?

Expand the survey to Asia and Middle East

- **Need participants !!!**

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Acknowledgements

- **Dr. Silvano Wendel for providing the list of participants.**
- **Survey participants.**
- **Funding to upgrade the Survey Monkey was provided by Canadian Blood Services.**

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Thank you

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ARBOVIRAL RISKS TO BLOOD SAFETY IN AUSTRALIA

Clive Seed

Australian Red Cross Blood Service

ISBT TTD-WP meeting 26 June, 2015

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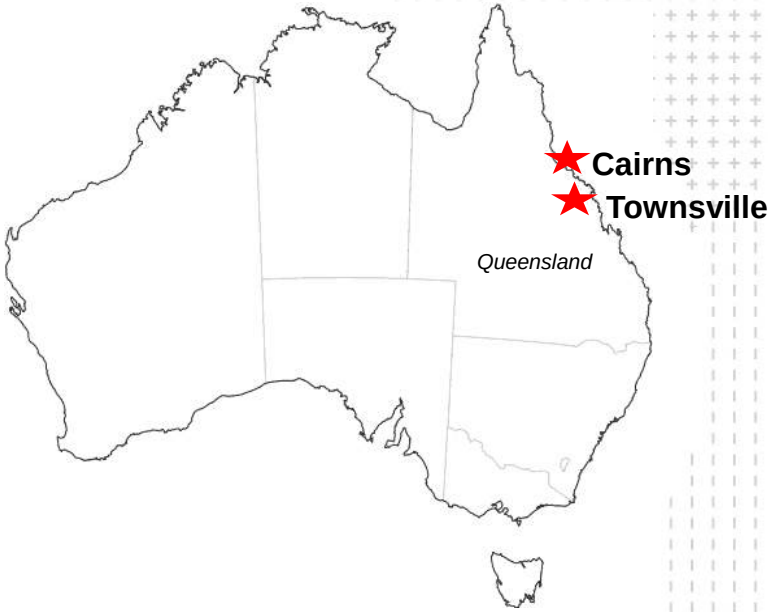
Transfusion significant arboviral threats

- **Dengue - epidemic**
- **Ross River virus - endemic/epidemic**
- West Nile virus Kunjin strain – endemic, low virulence/transmission
- ? Other endemic Australian arboviruses (Barmah Forest virus, Murray Valley encephalitis virus etc) - endemic/epidemic, low virulence/transmission
- ? chikingunya virus - occasional imported cases; vector present
- ? Zika virus - occasional imported cases; vector present

Dengue in Australia

- Seasonal outbreaks in NE Australia
  - Vary from <50 to >1,000 cases
- All four DENV types can occur
  - Occasionally together (last in 2009)

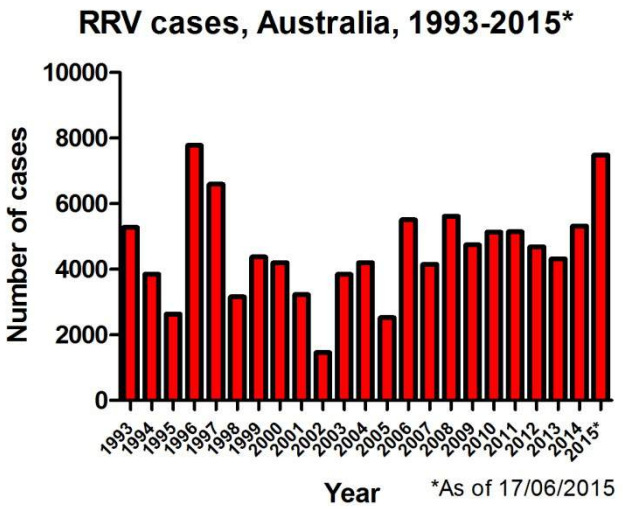


- Rapid public health response -> Very effective in minimising impact
- Transfusion risk
  - Implement supplementary donor questioning
    - Restriction to plasma for fractionation only for residence in or travel to outbreak area
  - Restrictions lifted 28 days after last case onset date

Faddy HM, Seed CR, Fryk JJ, et al.: Implications of dengue outbreaks for blood supply, Australia. Emerg Infect Dis. 2013;19: p. 787-789.

Ross River virus (RRV)

- Alphavirus (*Togaviridae*)
  - Same antigenic family as CHIKV
- Most common arboviral disease in Australia
  - ~5,000 cases notified annually



- Endemic throughout coastal regions of northern and central Australia; epidemic throughout rest Australia
- Causes non-fatal epidemic polyarthritis or RRV disease
  - Asymptomatic/mild infections in 50-75% of cases
- Incubation period 2-21 days – average 7-9 days

RRV - transfusion transmission risk

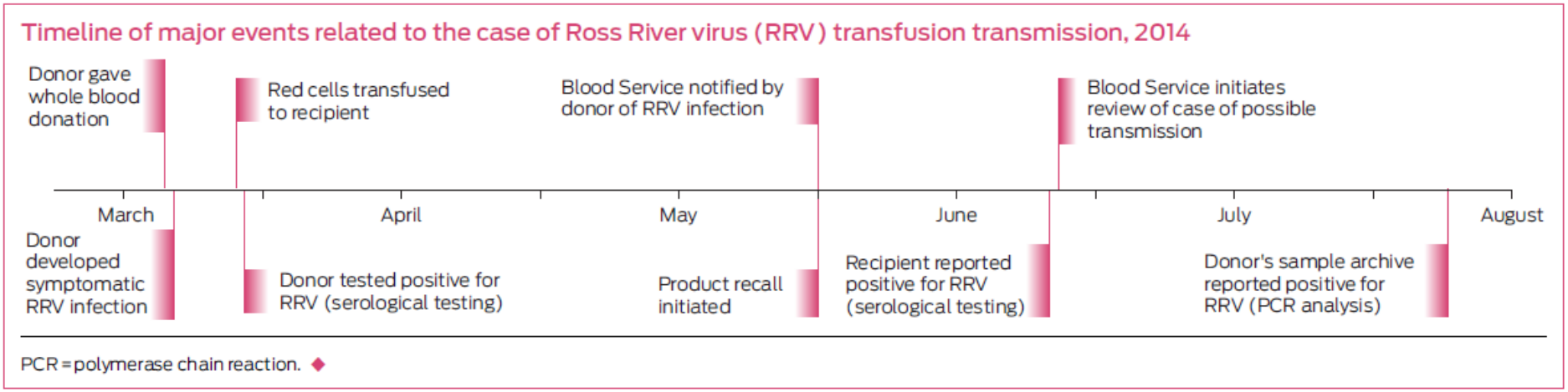
- Virus first isolated in early 1970's – TT-RRV suggested in mid 1990's
- Asymptomatic viraemia (mouse model) - typically 5, but up to 9 days[1]
- Potential TT-RRV risk estimated:
  - For 2004 outbreak in Cairns -> ~1 in 13,000 [1]
  - After increased rainfall -> ~1 in 7,333 [2]

  } Similar to DENV TT-risk for contiguous outbreak

- Maintain close watching brief

1. **Shang G, Seed CR, Gahan ME, et al.: Duration of Ross River viraemia in a mouse model-implications for transfusion transmission. Vox Sang. 2012;102: p. 185-192.**
2. **Faddy H, Dunford M, Seed C, et al.: Seroprevalence of Antibodies to Ross River and Barmah Forest Viruses: Possible Implications for Blood Transfusion Safety After Extreme Weather Events. Ecohealth 2014. (Epub ahead of print).**

First probable case of TT-RRV



Hoad VC, Speers DJ, Keller AJ, Seed CR et al.: First reported case of transfusion-transmitted Ross River virus infection. Med J Aust. 2015;202: p. 267-270.

- RBC recipient - symptoms consistent with RRV
  - IgM detected
  - Haemagglutination inhibition (HI) positive

Imputability and risk assessment

- Imputability - probable case
  - No molecular matching BUT RNA positive donation transfused to recipient who later developed symptoms consistent with RRV
  - No other RRV notifications in recipient's public health unit
  - Recipient had no recollection of mosquito bites & spent majority time indoors

- EREEID* risk framework
  - Escalate from 'yellow' to 'red' status
  - Notify regulator (TGA) & conduct risk assessment

** Emerging, Re-emerging & Emerged Infectious Disease*

Risk analysis

- Risk Analysis (Western Australia [residence of case], Jan – Mar 2014)
  - Blood Service model: 1 in 26,177 (7,729 to 103,628)
  - EUFRAT: 1 in 14,943 (5,094 to 48,593)

  [predicted issue of 1 (0.3-2.9) infectious donation (WA, Jan-Mar 2014), or 11 (4-39) annually, Australia-wide]

- <u>Key risk considerations</u>
  - Transmission risk from transfusion very minor when compared to ~5,000 vectorial notifications annually
  - High proportion of asymptomatic infections
  - Clinical illness generally mild and self-limiting
    - No mortality
  - Scope and continuity of RRV outbreaks

Risk management options

1. Enhanced donor education/post-donation illness reporting

Recommended

2. Geographically based fresh component restrictions during high transmission periods (as per the current strategy for local dengue outbreaks)

Not recommended – donor/product sufficiency concern

3. RRV donor testing

No licensed blood screening tests available

4. Pathogen reduction for clinical plasma and platelets (assuming future licensing of PRT)

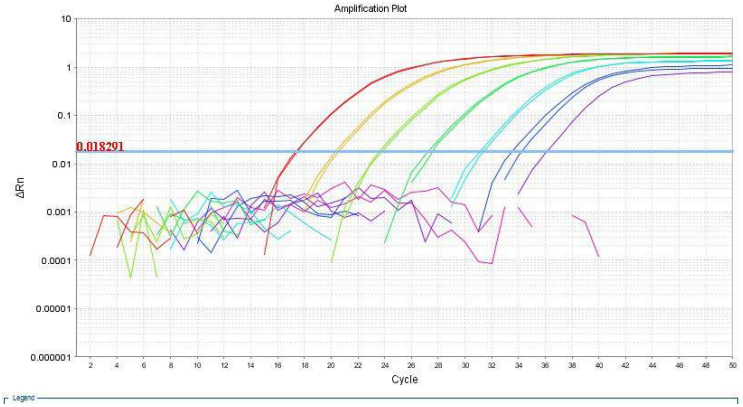
Not currently available

Research - RRV

- Risk is proportional to rate of RRV viraemia among donors – unknown

AIM: Determine rate of RRV RNA carriage among Australian donors

- Samples (n=7,500) from high-risk areas, during higher risk seasons
- RT-PCR (based on pathology laboratory methods)
  - MS2 phage (extraction and amplification control)
  - QIAsymphony (automated RNA extraction and RT-PCR plate set-up)
  - TaqMan chemistry; StepOnePlus Real-Time PCR System



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Conclusions

- Australia has a number of arboviral threats to blood safety
- Of these dengue, WNV proven TT and now strong evidence for RRV
- Dengue TT risk effectively minimised by rigorous public health response and activating supplementary donor measures during local outbreaks
- RRV TT recently confirmed
  - Very low risk compared to vectorial transmission given 5,000+cases per year
  - Contrasting dengue - lacks severe clinical consequences for recipients
  - Scope and size of outbreaks precludes geographical deferral strategy
- RRV risk management – enhanced post-donation symptom reporting messaging (under development)

Acknowledgements

Australian Red Cross Blood Service

- Dr Veronica Hoad
- Dr Anthony Keller
- Dr Helen Faddy

Australian governments fund the Australian Red Cross Blood Service to provide blood, blood products and services to the Australian community

Enlargement of WHO Repository PC Transfusion Relevant Bacteria Reference Strains

WP-TTID
chair: Michael Busch

Subgroup on Bacteria
chairs:
Carl P McDonald, England
Richard J Benjamin, USA

Presentation

ISBT WP-TTID,
London, June 26th, 2015

Eva Spindler-Raffel

Paul Ehrlich Institut
Federal Institute
for Vaccines and Biomedicines
Division Microbial Safety
Germany

Definition TRBRS

Transfusion-Relevant Bacteria Reference Strains (TRBRS)

- **are deep frozen bacterial suspensions**
- **are ready to use, stable and shippable**
- **are defined in identity**
- **are defined in count [CFU/ml]**
  …allow “real life” spiking of blood components
  (i.e. artificial contamination with ~10 CFU/bag corresponding to 0.03 CFU/ml…)
- **are defined in growth characteristics in platelet concentrates**
  …grow up in PCs independent on donor properties
  …tested in PCs from at least 100 different donors

➢**TRBRS are dedicated to objective validation and assessment of both Pathogen Reduction Methods and Screening Methods.**

First WHO Int. Repository of TRBRS

Paul-Ehrlich-Institut
Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

A WHO Collaborating Centre
for Quality Assurance of Blood Products and
in vitro Diagnostic Devices

1st WHO International Repository of Platelet-Transfusion Relevant Bacterial Reference Strains
PEI code 8483/13
(Version 1.0 December 2012)

1. INTENDED USE

Bacterial contamination of platelet concentrates remains significant problem in transfusion with potential important clinical consequences, including death.

Until now, there have been no transfusion relevant bacterial reference strains available. The repository of platelet transfusion relevant bacteria is a microbiological reference material containing a precise number of viable bacterial cells. It is intended for use as a quantitative quality control sample for the standardization of validation and assessment of methods for improvement of microbial safety of platelet concentrates (PCs). The repository consists of 4 bacterial strains (*Staphylococcus epidermidis* PEI-B-P-06, *Streptococcus pyogenes* PEI-B-P-20, *Klebsiella pneumoniae* PEI-B-P-08, and *Escherichia coli* PEI-B-P-19) which were selected for their ability to replicate in PCs under routine storage conditions used in transfusion medicine. The panel members are prepared using a specially developed procedure which guarantees defined bacterial suspensions (deep frozen, ready to use, stable, shippable, defined in count of living cells). The microbiological identification of each batch of repository strains is confirmed by 16S rDNA sequencing. The panel is designed to allow objective validation of methods for Bacterial Screening in PCs under "real life" conditions, i.e. inoculating the PCs with a very low bacteria count (0.03 to 0.3 CFU/mL) followed by growth in the bag.

The repository has been evaluated in an international validation study which was organized by the International Society of Blood Transfusion (ISBT) Working Party on Transfusion-Transmitted Infectious Diseases (WP-TTID), Subgroup on Bacteria. The WHO Expert Committee Biological Standardization (WHO ECBS) approved the adoption of preparations of the four bacteria strains mentioned above as a Repository for Platelet Transfusion Relevant Bacteria Reference Strains (RPTRBRS) during the annual meeting of 2010 (WHO/BS/10.2154).

2. UNITAGE

A defined unitage is assigned to the individual repository members; the details depend accessorily on the lot of the bacterial preparation. Each vial is labelled with complete information as demonstrated in Table 1.

* XX = lot number

Explanation of code:
- PEI: Paul Ehrlich Institute
- B: Blood (strain regards blood components)
- P: Platelets (strain is intended for the use in platelet concentrates)
- first number: number of bacterial strain
- second number: number of lot

(Example: PEI-B-P-06-08 stands for lot 8 of *Staphylococcus epidermidis* PEI-B-P-06)

Table 1 Unitage of bacterial suspensions / Labelling of the vials

Bacterial Strain	Lot
Staphylococcus epidermidis	PEI-B-P-06-XX*
Streptococcus pyogenes	PEI-B-P-20-XX*
Klebsiella pneumoniae	PEI-B-P-08-XX*
Escherichia coli	PEI-B-P-19-XX*

The mean value of bacterial count [CFU/mL] and the 95% confidence interval depends on the lot and will be provided with the product insert.

3. CONTENTS

Each vial closed with a screw cap contains 1.5 mL of living deep frozen bacteria suspended in tryptic soy broth and 10 % human serum albumin in saline (150 mM NaCl). The strains were characterized regarding their ability to grow up to high counts in PCs after low count spiking independent of donor's immune system.

3.1. IDENTITY

Results of genome sequencing using the MicroSeq 16S rDNA Bacterial Identification System are shown in table 2 (Appendix)

3.2. GROWTH IN PLATELET CONCENTRATES

The figures 1 -4 (Appendix) show the growth characteristics of the bacterial strains in pooled PCs (n = 4) at + 22 °C ± 2 °C after inoculation with < 10 CFU per bag (< 0.03 CFU/mL). The kinetics may be used for experiments to calculate the bacterial count at a defined time point.

4. STORAGE

The material is supplied deep frozen on dry ice and should be stored immediately below - 70 °C ± 5 °C after arrival. Check the vials immediately after arrival. If the samples show any sign of thawing, they must be discarded.

5. CAUTION

THIS PREPARATION IS NOT FOR ADMINISTRATION TO HUMANS.

The material is supplied on dry ice. Always handle dry ice with care and wear protective cloth or leather gloves whenever touching it. Avoid prolonged contact with the skin because it will cause injury similar to a burn.
The preparation contains viable, pathogenic bacteria and may lead to infections of personnel and/or microbial contamination of material and surrounding area. Therefore the samples should only be handled by

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Paul-Ehrlich-Str. 51-59
63225 Langen, Germany

Email: whoccvul@pei.de
Web: http://www.pei.de

1st WHO International Repository of Platelet Transfusion Relevant Bacteria Strains
PEI code 8483/13
Illustration of dilution of repository strains before spiking

Procedure of dilution:

1. Label n (n = number of tubes, depends on the calculated dilution steps in order to receive a final dilution of around 10 CFU per sample) tubes for dilution of the repository strain (e.g. *Staphylococcus epidermidis* PEI-B-P-06-XX; 1 vial for Dilution 1 = D1, 1 vial for D2, 1 vial for D3.....).
2. Prepare the dilution tubes with 9 mL each of s
3. Vortex the thawed vial of the repository st seconds immediately after unfreezing (as des
4. Transfer 1 mL of the stock (vial of reposit dilution 10^{-1}).
5. Discard the tip; cap the tube and vortex for 15
6. Take a new tip and transfer 1 mL out of the tube (D2: dilution 10^{-2}).
7. Vortex the dilution D2 for 15 seconds at highe
8. Continue this procedure up to the final dilution

Series of 10-fold dilutions:

Vortex stock (vial of repository strain) for 15 s
Start: 1 mL of stock
Add: + 9 mL NaCl
} Yield: 1

Vortex dilution above (10^{-1}) for 15 seconds at
Carry-over: 1 mL of 10^{-1} (D1)
Add: + 9 mL NaCl
} Yield: 10

Continue up to the final dilution (calculat containing around 10 CFU per sample for low spiking.

Dilution series

et cetera if necessary

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Paul-Ehrlich-Institut
Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

A WHO Collaborating Centre
for Quality Assurance of Blood Products and
in vitro Diagnostic Devices

1st WHO International Repository of Platelet Transfusion Relevant Bacterial Reference Strains

Mean value of bacterial count [CFU/mL] and the 95% confidence interval

Bacterial Reference Strain		CFU/mL	
		Mean value	95 % confidence interval
Staphylococcus epidermidis	PEI-B-P-06-02-01	9,68E+05	9,43E+05 – 9,93E+05
Streptococcus pyogenes	PEI-B-P-20-02-01	2,49E+08	2,43E+08 – 2,55E+08
Escherichia coli	PEI-B-P-19-02-01	6,47E+06	6,24E+06 – 6,71E+06
Klebsiella pneumoniae	PEI-B-P-08-02-01	1,15E+06	1,13E+06 – 1,17E+06

Result of stability testing, 2015_01_27/JB/AS

Dr. Eva Spindler-Raffel

Scope of collaborative study

- **Bacterial growth in platelet concentrates has to be demonstrated for 11 new candidate strains**
- **4 WHO strains as reference (comparability)**
- **Under real-life conditions**
  -> Low spiking directly into PC-bags: 10 to 25 cfu/bag
  (Tested in 3 PC bags per strain, 14 labs)
- **3 sampling days (2, 4, 7) -> growth kinetics**
- **Growth independent of donor influence (WHO-regions, up to 130 different donors per strain)**

Enlargement of WHO Repository: Candidates

Selected candidate bacteria for Enlargement study

Validation Study 2008/2009	
1.	*Staphylococcus epidermidis*
2.	*Streptococcus pyogenes*
3.	*Escherichia coli*
4.	*Klebsiella pneumoniae*

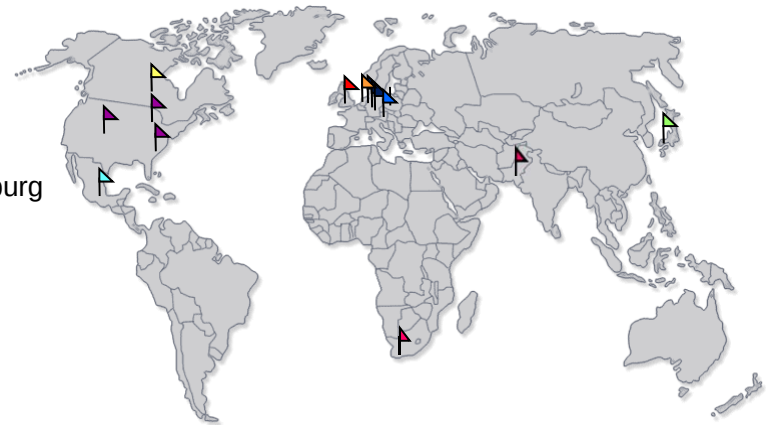
Enlargement Candidates	
5.	***Bacillus thuringiensis* spores**
6.	***Bacillus cereus* spores**
7.	***Enterobacter cloacae***
8.	***Morganella morganii***
9.	***Proteus mirabilis***
10.	***Pseudomonas fluorescens***
11.	***Salmonella choleraesuis***
12.	***Serratia marcescens***
13.	***Staphylococcus aureus***
14.	***Streptococcus dysgalactiae***
15.	***Streptococcus bovis* (reclassified: *Streptococcus gallolyticus*)**

International Validation Study: Participants

Austria	**Christian Gabriel, Susanne Süßner** Austrian Red Cross, Blood Centre Linz
Canada	**Dana Devine, Sandra Ramirez-Arcos** Canadian Blood Service, Ottawa
England	**Carl McDonald, Kate Aplin** NHS Blood and Transplant, London
Germany	**Erhard Seifried, Kai Hourfar** German Red Cross, Frankfurt/Main
	Birgit Gathof, Melanie Stoermer University Hospital Cologne, Transfusion Medicine
	Axel Seltsam, Bernd Lambrecht German Red Cross Blood Service NSTOB, Springe
Japan	**Masahiro Satake, Hideto Nagumo** Japanese Red Cross Kanto-Koshinnetsu Block Blood Center, Tokyo
México	**Julieta Rojo, Dr. Gabriela Ibañez- Cervantes** Centro Nacional de la Transfusion Sanguínea
South Africa	**Charlotte Ingram, Truscha Niekerk** South African National Blood Service, Weltevreden Park
The Netherlands	**Dirk de Korte, Jan Marcelis** Sanquin Blood Supply Foundation; Elisabeth Hospital, Tilburg
USA	**Susanne Marschner, Shawn Keil** Terumo BCT Biotechnologies, BCT, Lakewood
	Richard Benjamin, Stephen J. Wagner American Red Cross, Blood Component Dep. Rockville
	Roslyn Yomtovian†, Michael R. Jacobs Case Western Reserve University, Cleveland *Louis Stokes Cleveland Veterans Affairs Medical Center*
Pakistan	**Zainab Mukhtar, Shaheen Sharafat** Dow Safe Blood Transfusion Services, Dow Medical College, DUHS Karachi

Steering committee

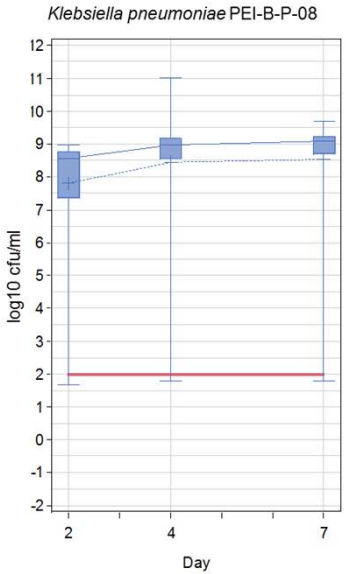
Carl McDonald
Richard Benjamin
Melanie Störmer
Eva Spindler-Raffel
(corresponding address)

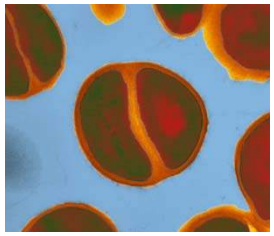


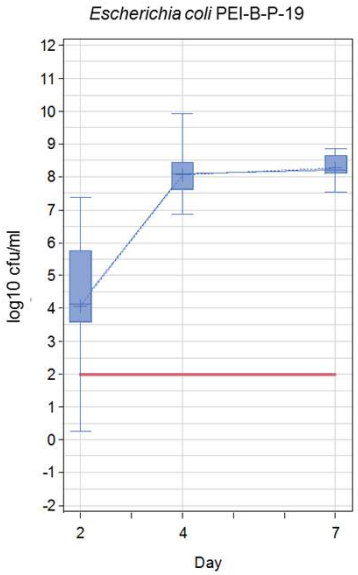
Lot of Lab-Work

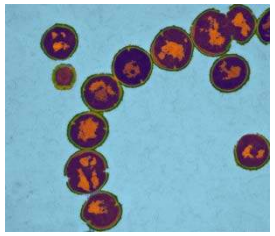
Photo: Section 1/3 Microbial Safety, PEI

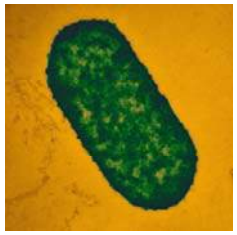
WHO strains confirmed

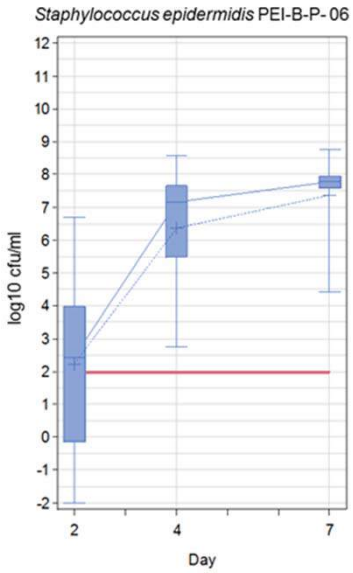


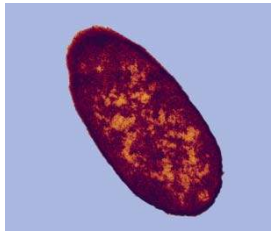


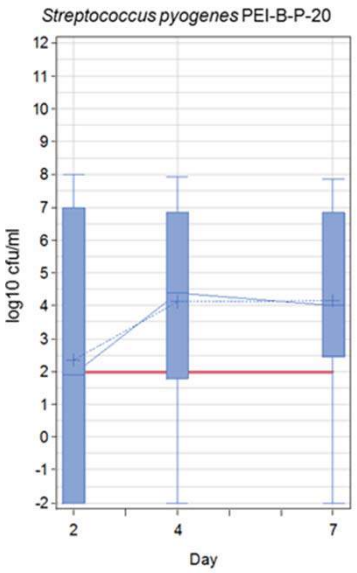






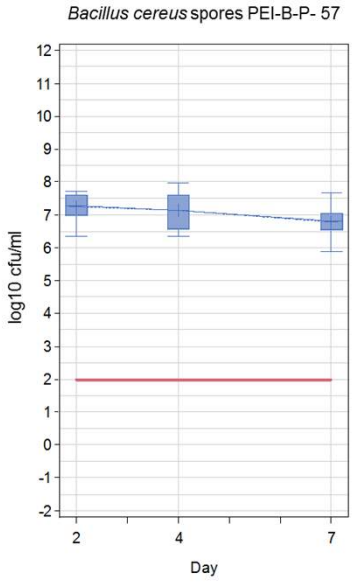


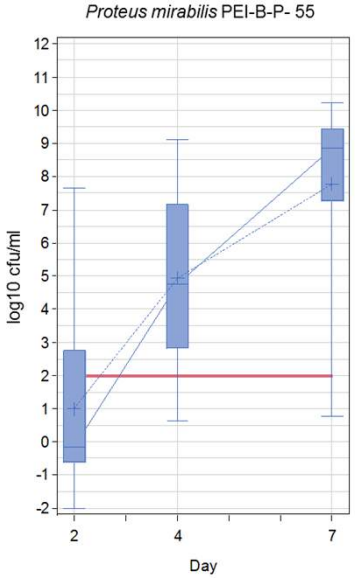


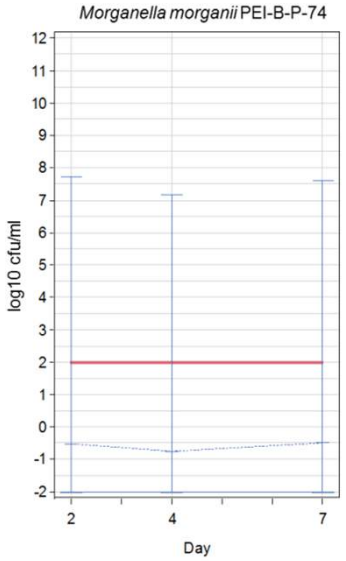


Electron microscopy: Klaus Boller, Regina Eberle, PEI

Different growth kinetics



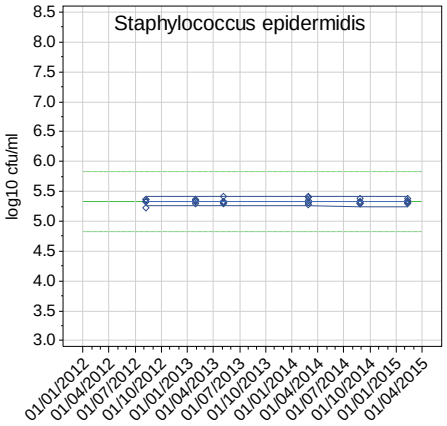


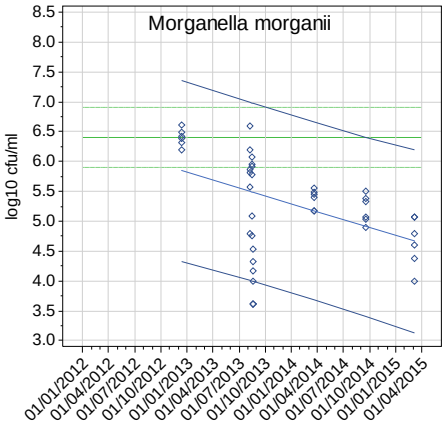


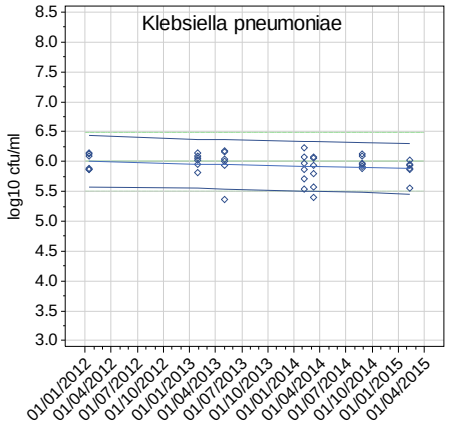
Box-and-Whisker plots for growth:
continuous line connecting the median values per day; dotted line connecting mean values

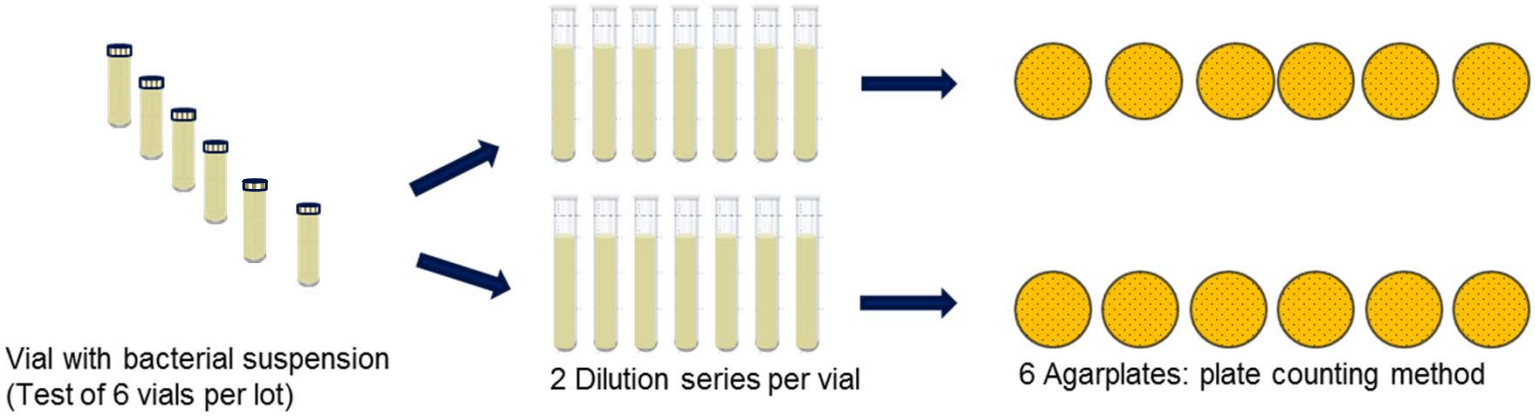
Poster Presentation P-421 and P-432

Test of stability

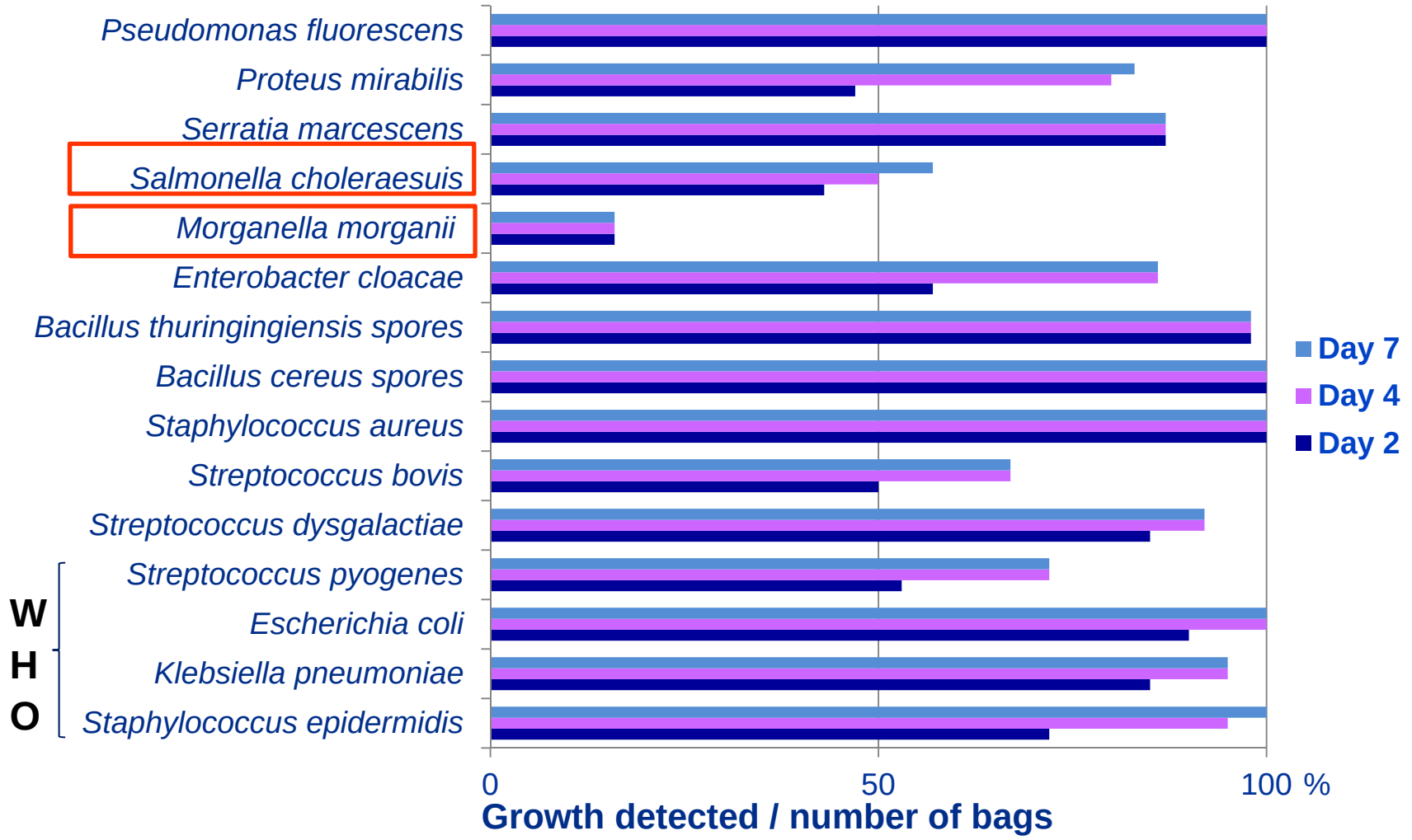








Growth rates per Sampling Day



Summary and Outlook

- **All participants received the deep frozen bacteria strains in good condition without any complaint. As in the first study deep frozen, pathogenic bacteria strains could be shipped worldwide without any difficulties.**
- **The tested inocula proliferated well and were successfully used for spiking. The bacterial identification performed by the study partners complied with the ID of PEI. The results of bacteria counting of all participants are homogenous since the measured divergence factors represent an acceptable value in the estimation of high bacteria cell counts.**
- **The results of the four strains of the existing WHO Repository are equivalent to the first study. (spiking of 10 to 25 CFU per PC unit)**
- **Growth for *Salmonella choleraesuis* was lower than for other strains and showed a high variability among participants**
- **Morganella morganii failed to grow beyond that amount of bacteria in the initial inoculation.**

Next steps:

- **Final report and proposal for strain selection to WHO**
- **Paper in Vox sang**

Acknowledgements

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Sanquin Blood Supply Foundation
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Elisabeth Hospital, Tilburg, The Netherlands

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Thank you very much for your attention !

Prof Paul Ehrlich

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Donor Health Care (DoHeCa)

ISBT Working Party TTID
London, June 26, 2015

Peter J.M. van den Burg, MD, PhD
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prof. Hans L. Zaaijer, MD, PhD
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Education and Culture
Lifelong Learning Programme
ERASMUS

EUROPEAN BLOOD ALLIANCE

Motivation for DoHeCa

- Education for donor professionals hardly exists
- Separated professional area's (blood, cells, tissues and organs)
- Not all countries/institutions are compliant with legislation
- Donor care attracts/needs more attention

The DoHeCa project

- Target groups: professionals in medical care of donors
- Area: donors who donate 'Substances of Human Origin' (SoHo)
- Development of a master program (University of Amsterdam)
- EU grant Life Long Learning, October 2013-2016

Donor Health Care project

European Commission -
Education, Audiovisual & Culture
Executive Agency

Project Leader

WP7 WP8 WP9 WP10

Sanquin Blood Supply

Project Management Team
Peter van den Burg, Wim de Kort, Rosa de Groot

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NHSBT
Nicky Anderson

Members:
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WP2
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Karin Magnussen

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Aurora Navarro
Hans Vrielink

WP5
Leader:
Université Jean Monnet
Olivier Garraud

Members:
Ramadan Jashari
Alex Pruß
Beate Mayer

WP6
Leader:
CITM
Tomislav Vuk

Members:
Alex Pruß
Beate Mayer

Associated partners

Quality Board

ISBT / Roger Dodd, (Chair)
AABB / Joy Fridey
Ted Eastlund

Advisory Board

Jeroen de Wit (Chair)
Erhard Seifried
Lorna Williamson
Axel Rahmel
Pierre Tieberghien

DoHeCa and WP TTID

If you are interested in this matter,
please read the outline of the TTID module,
and give us your opininion:

- is outline of TTID study material adequate?
- are the assignments relevant ?
- what would you add or drop?

your remarks are wellcome, eg. via e-mail:
p.vandenburg@sanquin.nl , h.zaaijer@sanquin.nl

thank you...

Sanquin
Blood Supply

DONOR
HEALTH
CARE

Education and Culture
Lifelong Learning Programme
ERASMUS

ISBT International Society of Blood Transfusion

eba EUROPEAN BLOOD ALLIANCE

project number: 538986-LLP-1-2013-NL-ERASMUS-EQR

ISBT TTID Research Young Investigator Training

Development of a new initiative within the ISBT TTID working party

Marion Vermeulen, Michael Schmidt, Brian Custer

ISBT

TTID

RESEARCH

YOUNG

INVESTIGATOR

TRAINING

TTID WP | Attracting New Investigators

- Aims and Objectives:
  - Teaching in TTID
    - Technologies and Methods
    - Algorithms
    - Designing Research
  - Support of research
  - Networking
  - Transfer of technology/methods
  - Improving safety of blood world-wide
  - Mentoring concept
  - Increase publications in *Vox Sanguinis*/ Transfusion
  - Develop a mechanism for support of best projects/ studies (minigrant concept) - corporate funding of small research grants?

Proposed Training Initiative | Rationale and Scope

- Vision
  - The training would focus on research skills development in TTID and provide a path to bring young investigators in developing/transitional country settings into the TTID WP on a more sustained basis
- Objectives
  - Project-based learning (how to plan, conduct, analyse and report research in TTID)
  - Skills development in algorithms and other laboratory based issues
  - Donor, donation screening, or recipient focused research projects

Proposed Training Initiative | Approach

- Three Aspects
  - Online didactic coursework (how to design and write a research protocol)
  - In person meetings attached to regional and/or global congresses (half day to 2-day meetings) for further didactic development and direct mentoring (review, critique, and revision of protocols)
  - Continued distance mentoring to promote the completion of the research, analysis and reporting of findings
    - Expectation that abstracts would be submitted to ISBT congresses
    - Manuscript development with target journals of *Vox Sanguinis*/Transfusion

Source Material for Training Content

- BSRI / UCSF Investigators have an existing workshop curricula used for Training in Clinical Research that has been tailored to the Transfusion Medicine setting
- Course/Educational materials drawn from existing curricula
- Further tailoring would be undertaken to make the content highly applicable to the target audience
  - e.g. WHO and NAT algorithms

Title of Lecture	Date and Time	Lecturer
Lecture 1 - Conceiving the Research Question	22th April 2015 5am UTC	Custer
Lecture 2 - Background and Study Plan	26th May 2015 5am UTC	Schmidt
Lecture 3 - Basics of measurement: variable types, precision and accuracy	17th June 2015 5am UTC	Vermeulen
Lecture 4 - Introduction to statistics and estimating sample size & power	15th July 2015 5am UTC	Custer
Lecture 5 - Overview of study designs	5th August 2015 5am UTC	Vermeulen
Lecture 6 - Designing studies of medical tests, including sensitivity and specificity	19th August 2015 2015 5am UTC	Schmidt
Lecture 7 - Data validity, cause and effect, issues of bias	23rd September 2015 5am UTC	Custer
Lecture 8 - Research ethics, data management, quality control and big data	7th October 2015 5am UTC	Schmidt

July – Dec 2014	• Development and Approval of TTID Training Proposal
Nov 2014 - Jan 2015	• Announcement and promotion of initiative and application procedures
March 2015	• Applicant selection and notification
April - October 2015	• Online course lectures; research protocol development

June 2015	• Half-day in person meeting linked to ISBT London – initial review and discussion the proposed research
November 2015	• Two day satellite meeting linked to ISBT Bali
Late 2015 and Early 2016	• Abstract writing and submission, including online didactic sessions on writing and mentorship
Late 2016	• Manuscript writing ongoing mentorship

Selection Process and Applicants |

We focused on promoting the initiative in the Asia-Pacific Region

Applicants from any country, recruitment materials were widely distributed

Selection process: Review of applicants CV, research idea and geographic location by each of the three trainers. Summary average score determined

30 formal applications with additional interest from others

8 Participants selected

3 Observer participants

Name	Current Position	Institute	Country
Ashish Shrestha	PhD Student	University of Queensland	Australia/ Nepal
Amit Agrawal	Junior Medical Consultant	Fortis Escorts Hospital	India
Pairaya Rujirojindakul	Chief of Blook Bank and Transfusion Medicine	Prince of Songkla University	Thailand
Adriu Sepeti	Lecturer in Transfusion Medicine	Fiji National university	Fiji
Puneet Ashok Jain	Junior Medical Resident	Tata Memorial Hospital	India
Souaad Boulai	Medical Specialist/Dir of Donation and Donor Unit	Centre of Biologic Hematology and Blood Bank, Oran	Algeria
Elizebeth Mah	Scientific Officer	National Blood Centre	Malaysia
Dina Ekram	Head of Serology Dept	National Blood Transfusion Centre	Egypt
Ni Ni Aung	Transfusion Medicine Specialist	Australian Red Cross Blood Service	Australia
Kate Ellen Marie Aplin	Biomedical Scientist Team Manager	National Bacteriology Laboratory	UK
Jennifer Allen	Biomedical Scientist Team Manager	National Bacteriology Laboratory	UK

International Society of Blood Transfusion

Lectures are available to registered participants through the ISBT Academy

http://academy.isbtweb.org/isbt/#!*menu=6*browseby=6*sortby=1*ce_id=852

Acknowledgements

TTID Organizing Committee
- Mike Busch
- Tony Hardiman
- Emma Castro
- Ravi Reddy

BSRI
- Erin Bickler

ISBT Central Office
- Judith Chapman
- Monique van Dorp

ISBT Executive and Academy
- Diana Teo
- Erica Wood
- Roger Dodd

Budget in USD

Budget Item	Per Person	Per Day	Total for 4 instructors and 8 trainees
Curriculum Development and Electronic Distribution			1000
½ Day Meeting ISBT London*			
Travel	1600		12,800
Venue		1000	1000
Catering	70		840
Accommodation	250		3000
2 Day Meeting ISBT Bali*			
Travel	1600		19,200
Venue		850	1700
Catering	100		2400
Accommodation	150		3600
IT and Teleconference Infrastructure to Support Online Training			2500
London congress attendance for trainees (8 x 1581)			12,648
Administrative Support			1500
Small grants for three proposals with highest merit (3 x 5000)			15,000
Total Cost			Approved budget **77,188 (64,689€)**
*Includes trainee and trainer travel costs			

	London*	Bali**	Total by Category
Registration (US$)	400 x 8	-	3200
Room and board (US$)	264 x 8 x 4 days	200 x 5 x 3 days	11,448
Additional travel expenses (UD$)	1000	1500 (airfare) x 3	5500
Total	12,648	7,500	20,148 (16,880 Euro)

* Trainee additional cost
** Trainer costs to attend

TTID WP Young Investigators Satellite Meeting | Bali

- Day 1| Education
  - Review of research protocol components
  - Keynote lectures in TTID research methods and algorithms
    - Invited SMEs (?)
  - Networking at evening dinner
- Day 2| Research
  - Presentation of projects/studies by young investigators
  - Peer review and discussion of the projects
  - 1 on 1 mentorship

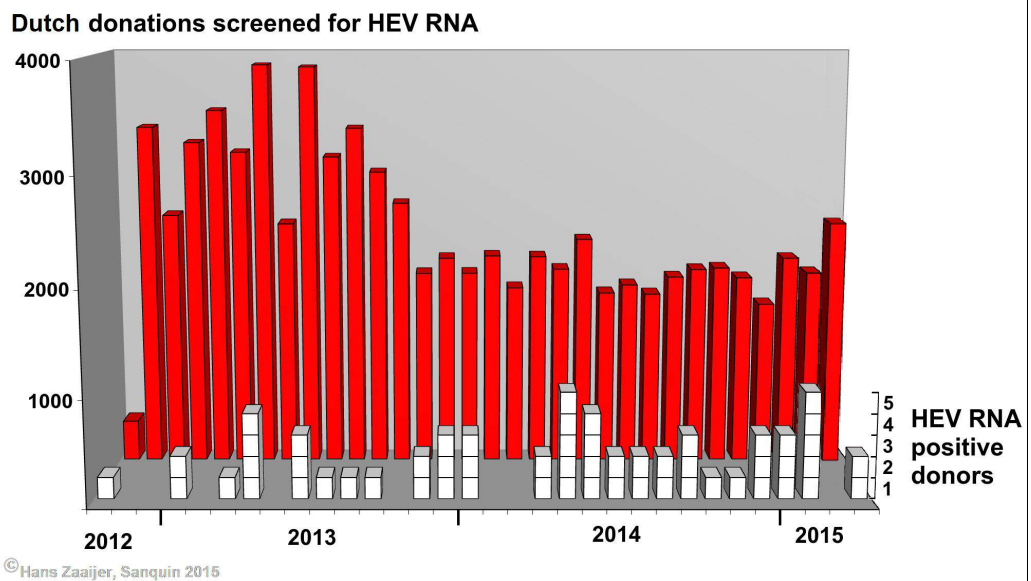
Hepatitis E virus *genotype 3*, the Dutch experience

TTID - WP June 26th 2015

Hans L. Zaaijer MD PhD
Sanquin - Blood-borne Infections &
Academic Medical Centre - Clinical Virology
Amsterdam NL

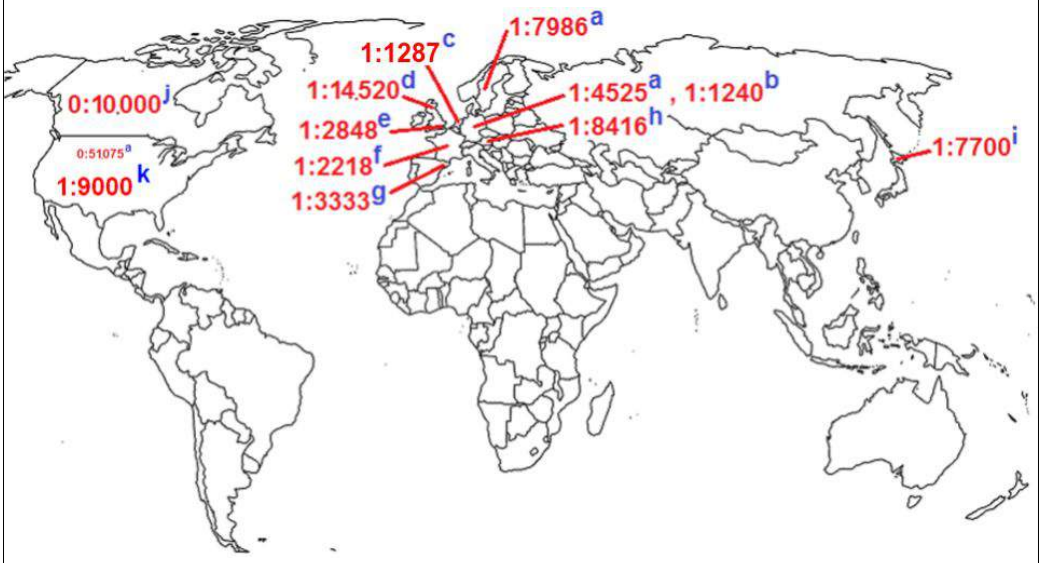
Monthly donorscreening for HEV RNA in NL

~2000 donations/month; in pools of 96; for SD-plasma production



overall: 57 / 73341 (1:1287) donorations HEV RNA+
last 12 months: 1:852 HEV RNA+

HEV RNA positive blood donors



a) Baylis,Vox 2012; b) Vollmer, JCM 2012; c) Sanquin, submitted 2015; d) Cleland, Vox 2013;
e) Hewitt, Lancet 2014; f) Gallian, EID 2014; g) Sauleda, Transfusion 2014; h) Fischer, PlosOne 2015;
i) Ikeda, ISS 2009; j) CBS Surveilance Report 2014; k) pers. communication J.S. Epstein.

Course of infection in 41 NL blood donors

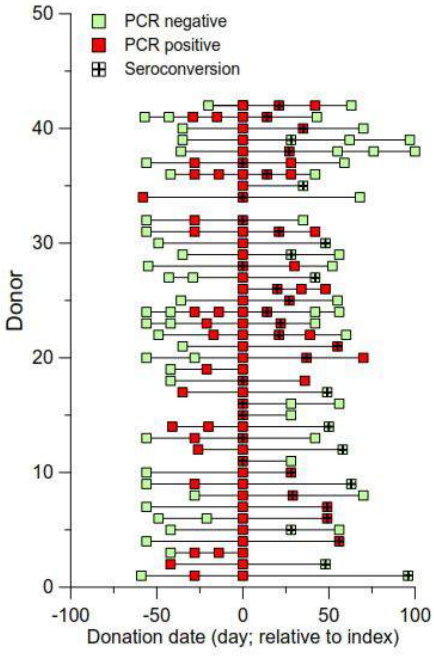
- all donors seroconvert

- index donations:
  2/3 seronegative
  HEV RNA range:
  pos < 20 - 2,3E6 IU/mL

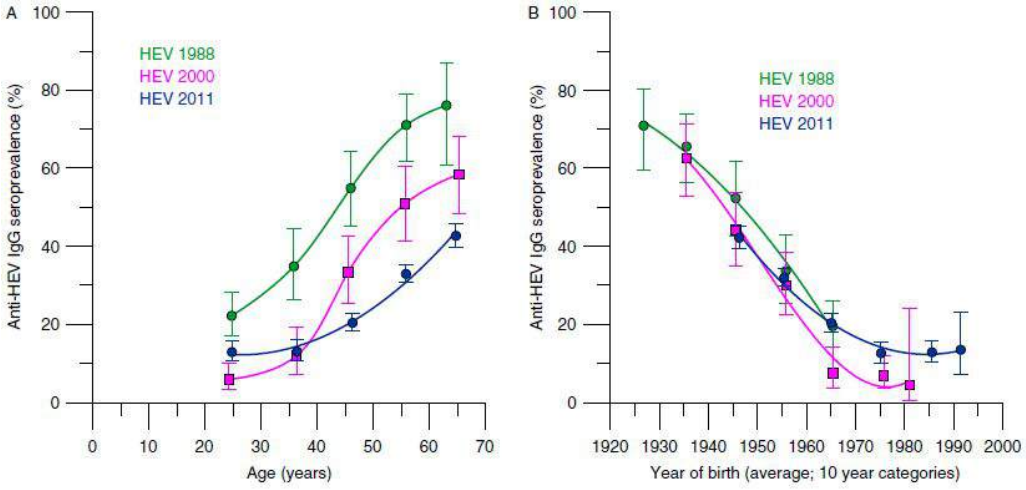
- avg. duration of viremia:
  68 days

- normal or slightly elevated ALT

(submitted)

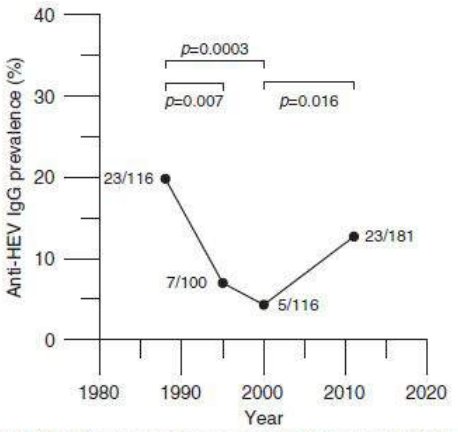


anti-HEV seroprevalence: age cohort effect



Hogema ea , Transfusion 2014

anti-HEV seroprevalence: recent increase among young donors

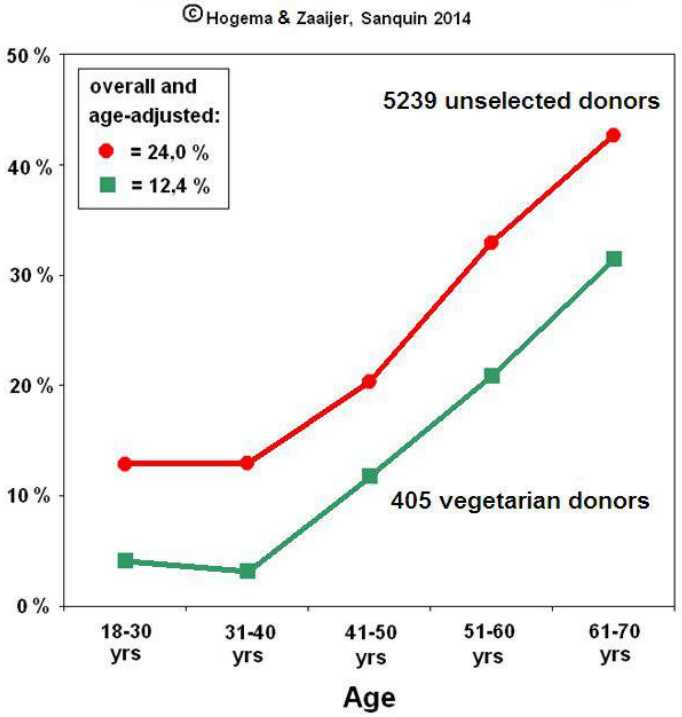


Anti-HEV IgG seroprevalence among donors aged 18 to 21 in 1988, 1995, 2000, and 2011.

Hogema ea , Transfusion 2014

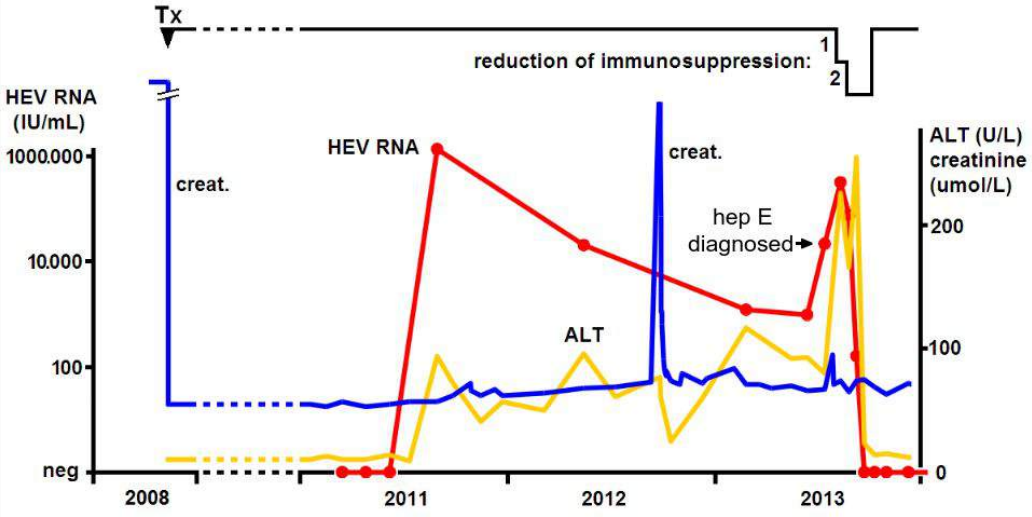
less HEV among vegetarian donors

HEV antibodies in Dutch donors (2011)



(AMC) boy A, 10 yrs

2006: severe pneumococcal infection → HUS → kidney Tx in 2008
2011-2013: chronic hepatitis eci, 'drug induced liver injury' (dili) ?



stap 1 = mycophenolate mofetil: 800 to 600 mg/m2/day
stap 2 = tacrolimus: 0.1 to 0.05 mg/kg/day
(prednisolone remained unmodified at 2 mg/m2/day)

A. Bouts, Pediatrics 2015, vol 135, nr 4

HEV: inactivation and removal

Sanquin's ad interim assessment of HEV and blood safety:

Effective removal or inactivation:
- Planova15N of Planova20N filtration
- Pasteurisation at 60 °C
- Immunoaffinity chromatography purification

Limited or no inactivation:
- SD treatment
- Low-pH treatment
- Alcohol fractionation
- Neutralisation by anti-HEV antibodies
  (due to a protective lipid layer covering HEV virions in blood:
  only neutralisation in serum or cell cultures after SD- or protease treatment)

See:
Summary of workshop presentations in Appendix to reflection paper, of the "EMA Workshop on viral safety of plasma-derived medicinal products with respect to hepatitis E virus" (London, Oct. 28th/29th, 2014); aimed to be released for public consultation in July 2015.

"Post-transfusion hep E" in NL ; policy

Cave pseudo transmission:

11 cases of "post-transfusion hep E" notified to Sanquin:

10 : all implicated donations HEV PCR negative.

1 : 1 implicated donor HEV RNA pos. (low viremia, aHEV-IgG +++).

> donorscreening only would have prevented 1/11 notified Dutch cases.

(NB several HEV transmissions via transfusion have been reported elsewhere)

Sanquin's point of view:

- Instead of (selective) donorscreening, transmission routes to donors and patients must be clarified and removed.

- June 12th 2015: For the time being this approach is supported by expert meeting at National Institute for Public Health.

- impact of policy elsewhere, eg. in UK?

HEV team at Sanquin:

Boris Hogema

Michel Molier

Ed Slot

Hidde Koot

Hans Zaaijer