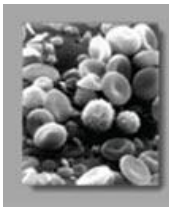

13th Annual Canadian Blood Services International Symposium

Blood-Borne Pathogens: Defend, Detect, and Destroy

Canadian Blood Services
it's in you to give

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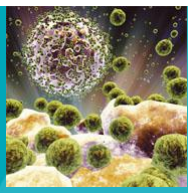

Economic and Health Outcome Implications of Introducing New Pathogen Testing and Inactivation Technologies

September 26, 2015

13th Annual Canadian Blood Services International Symposium
Blood Borne Pathogens: Defend, Detect, and Destroy

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Conflict of Interest Disclosures
Brian Custer

I have had, in the past 5 years, financial interest, arrangement or affiliation with the following organizations that could be perceived as a direct or indirect conflict of interest in the content of this presentation:

- Grant/Research Support:
  - Grifols/Hologic
  - Macopharma
  - TerumoBCT

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Outline

- Review health economics in the blood safety context
- Provide an update on available health economic analysis results for new testing and/or pathogen inactivation technologies
- Explain how the Risk-Based Decision-Making Framework for blood safety can contribute to the process

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Economics

Not a “gay science” I should say like some we have heard of; no, a dreary desolate and, indeed, quite abject and distressing one; by way of eminence, the dismal science.

Thomas Carlyle (1849)

Scarcity Choice Opportunity Cost

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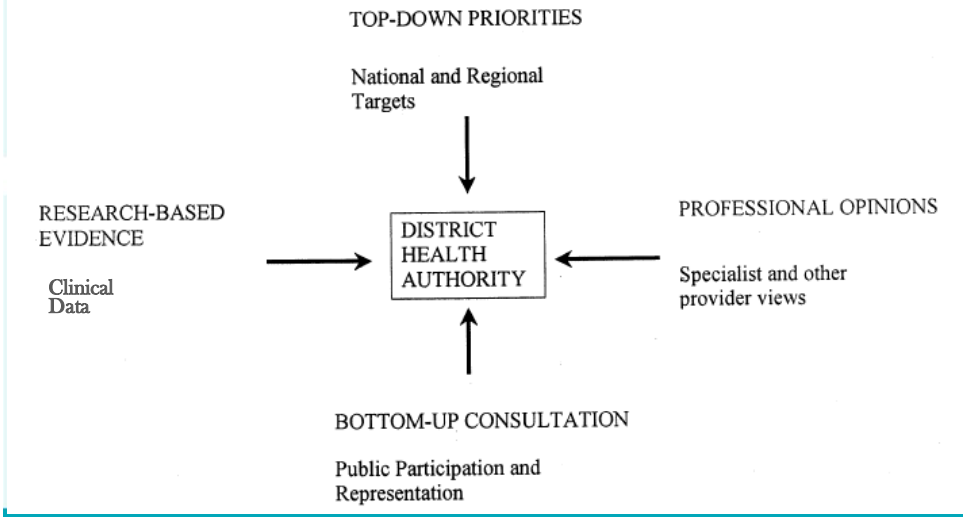
Determinants of Health Priorities



Robinson, Health Policy, 1999;49:13-26

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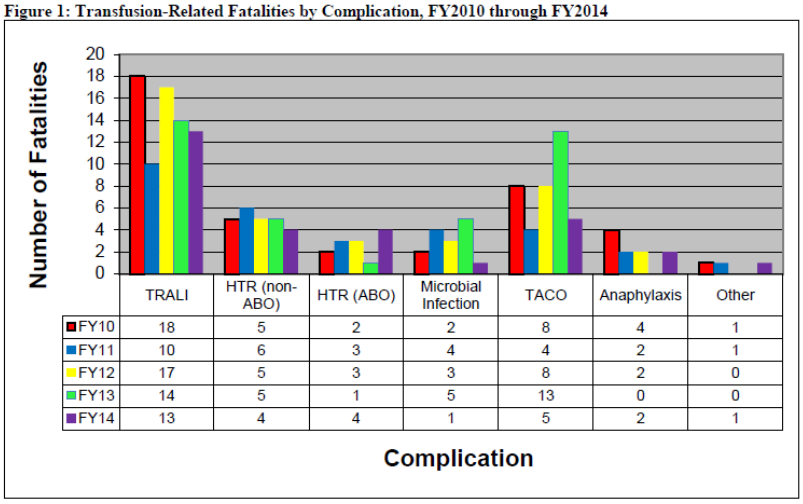
USA Fatalities – Reported to FDA

Figure 1: Transfusion-Related Fatalities by Complication, FY2010 through FY2014



	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY10	18	5	2	2	8	4	1
FY11	10	6	3	4	4	2	1
FY12	17	5	3	3	8	2	0
FY13	14	5	1	5	13	0	0
FY14	13	4	4	1	5	2	1

http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM459461.pdf

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Microbial Fatalities Reported to FDA

Table 3: Microbial Infection by Implicated Organism, FY2010 through FY2014

Organism	FY10	FY10	FY11	FY11	FY12	FY12	FY13	FY13	FY14	FY14	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Babesia microti	1	50%	1	25%	1	33%	1	20%	0	0%	4	27%
Staphylococcus aureus	0	0%	1	25%	1	33%	0	0%	0	0%	2	13%
Escherichia coli	1	50%	0	0%	0	0%	0	0%	0	0%	1	7%
Staphylococcus epidermidis	0	0%	0	0%	0	0%	1	20%	0	0%	1	7%
Morganella morganii	0	0%	1	25%	0	0%	0	0%	0	0%	1	7%
Streptococcus viridans	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Streptococcus pneumoniae	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Staphylococcus warneri	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Klebsiella pneumoniae	0	0	1	25%	0	0%	0	0%	0	0%	1	7%
Serratia marcescens	0	0	0	0	1	33%	0	0%	1	100%	2	13%
Pseudomonas fluorescens	0	0%	0	0%	0	0%	1	20	0	0%	1	7%
Acinetobacter sp.	0	0%	0	0%	0	0%	1	20	0	0%	1	7%
West Nile virus	0	0%	0	0%	0	0%	1	20	0	0%	1	7%
Total	2	100%	4	100%	3	100%	5	100%	1	100%	15	100%

http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM459461.pdf

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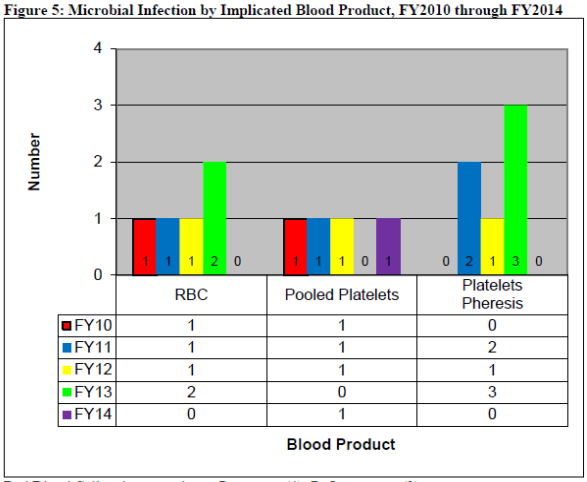
Fatalities by Product Type

Figure 5: Microbial Infection by Implicated Blood Product, FY2010 through FY2014



	RBC	Pooled Platelets	Platelets Pheresis
FY10	1	1	0
FY11	1	1	2
FY12	1	1	1
FY13	2	0	3
FY14	0	1	0

Blood Product

Red Blood Cells microorganisms: *B. microti (4), P. fluorescens (1)*
Pooled Platelets microorganisms: *S. aureus (1), E. coli (1), S. Marcescens (2)*
Platelets Pheresis microorganisms: *S. aureus (1), S. epidermidis (1), M. morganii (1), K. pneumoniae (1),* West Nile virus *(1), Acinetobacter sp. (1)*

http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM459461.pdf

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Framing Health Economics

- the Blood Supply is a Public Good
- Welfare economics:
  - Allocation of scarce resources in ways that maximize social welfare
- Systematic identification, enumeration and valuation of costs and benefits (or consequences) of alternate health care interventions or programs: 'value for money'
- Allocative efficiency
  - May not align with ethical considerations

Custer & Janssen, Transfusion 2015 Aug;55(8):2039-47

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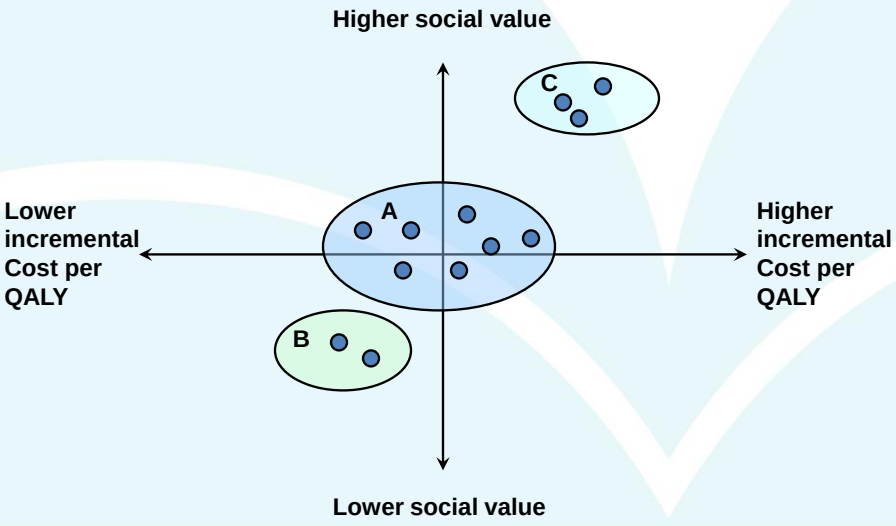
Social Value and Cost/QALY



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What are we trying to measure?

- Costs
  - Whose costs?
  - How are they measured?
- Consequences
  - What are the range of consequences?
  - Do they match our current understanding of risks and outcomes?
- Cost-effectiveness
  - Ratio of costs to certain aspects of consequences

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Economic Anlaysis Lifecycle

- In advance (*ex ante*)
  - Guides thinking and adoption decisions
  - Based on clinical trial or preliminary data and often requires significant modeling effort
  - Often high has high uncertainty
- Actual use (*post hoc*)
  - Equivalent to Phase IV studies
  - Observed system costs in use compared to costs saved from adverse event prevention
  - Based on actual event probabilities and costs

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Economic Evidence Grid

Pathogen or Technology	Budget Impact Analysis	Cost-Effectiveness/Utility
Chikungunya Virus	Not Available	Not Available
Dengue Virus	Not Available	Not Available
Hepatitis E Virus	Not Available	Not Available
Bacterial Culture Platelets	 Yes	 Yes
Pathogen Inactivation Methods - PIM Plasma Platelets Red Cells/Whole Blood	 Yes Yes ?	 Yes Yes Yes
Babesia	Yes	Yes

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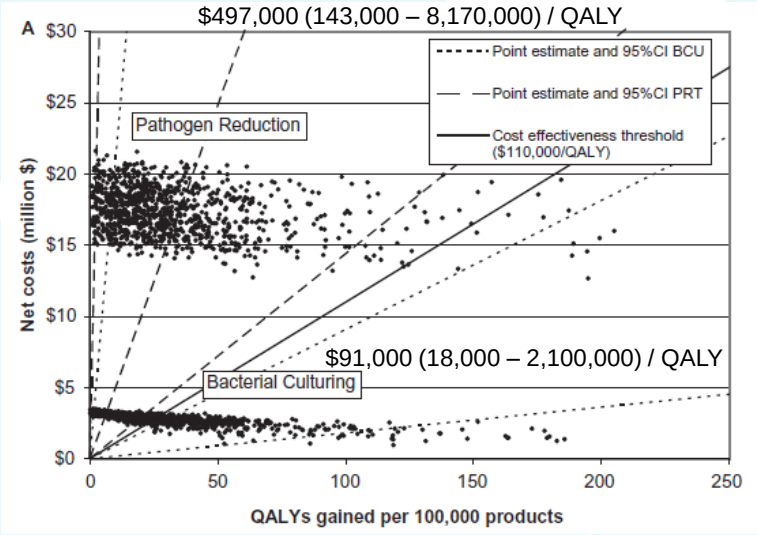
Bacterial Culture or PIM



Janssen et al. Transfusion 2006

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Increment of PIM Over Bacterial Culture

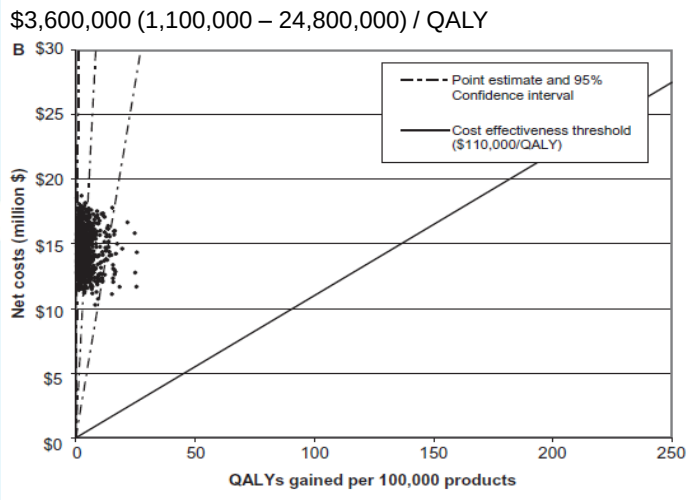

Fig. 2. (A) Relative CE of BCU and PRT versus "no additional treatment." (B) Relative CE of PRT versus BCU.

Janssen et al. Transfusion 2006

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Platelets and Plasma
Pathogen Inactivation Methods (PIM)

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SD Plasma

Multiple pathogen and adverse event models

– HIV, HBV, and HCV

CADTH Report

– Baseline result $933,400/QALY, including HAV and B-19 risks for FFP

Membe et al. CADTH 2011

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Intercept for Platelets US and Japan

Intervention	Pediatric Acute Lymphocytic Leukemia	Adult Hip Arthroplasty	Adult Coronary Artery Bypass Graft	Adult Non-Hodgkin's Lymphoma
Single Donor AP prepared with PIM compared to all current screens				
Without bacterial culture	$1.3mil/QALY	$2.3mil/QALY	$2.6mil/QALY	$4.5mil/QALY
With bacterial culture	$4.8mil/QALY	$10.7mil/QALY	$13.4mil/QALY	$23.0mil/QALY
Random Donor PP prepared with PI compared to all current screens				
Without bacterial culture	$460K/QALY	$880K/QALY	$1.1mil/QALY	$1.8mil/QALY
With bacterial culture	$1.0mil/QALY	$2.6mil/QALY	$3.4mil/QALY	$6.0mil/QALY

(1) Bell et al. Clinical Therapeutics 2003;25:2464-86

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Intercept for Platelets – Europe

Intervention	Pediatric Hematology-Oncology	Adult Breast Cancer	Adult Coronary Artery Bypass Graft	Adult Hematology-Oncology	Overall or for Average Patient
RD pooled platelets (buffy coat) prepared using PI compared to all other screens					
RDPP with Bact. Cult (1)	$339K/LYG		$616K/LYG	$889K/LYG	$725K/LYG
Bact. Cult. (2)	$276K/QALY	$3.0mil/QALY	$550K/QALY	$254K - 4.6mil/QALY	
RDPP prepared with bacterial testing or inactivation compared to all other screens					
Bact. Cult. (3)					$91K/QALY
PIM					$497K/QALY
PIM compared to Bact. Cult.					$3.6mil/QALY

(1) Postma et al. Transfusion Medicine 2005;15:379-87
(2) Moeremans et al. Transfusion Medicine 2006;16:17-30
(3) Janssen et al. Transfusion 2006;46:956-65

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Baseline results from PIM Analysis for Mirasol

PIM as an addition to current screens

Intervention (Comparator)	Cost per QALY
Whole Blood PI (current screens)	1,276,000
Platelets and Plasma PI (current screens)	1,423,000

Based on a model that included the following infections and non-infectious threats: HIV, HBV, HCV, HTLV, WNV, syphilis, CHIKV, *Trypanosoma cruzi*, Bacteria, GVHD, FNHTR, and TRIM, CMV for immunocompromised patients only

Most important pathogen: Analysis most sensitive to bacteria in platelets

Custer et al, Transfusion 2010;50:2461-2473.

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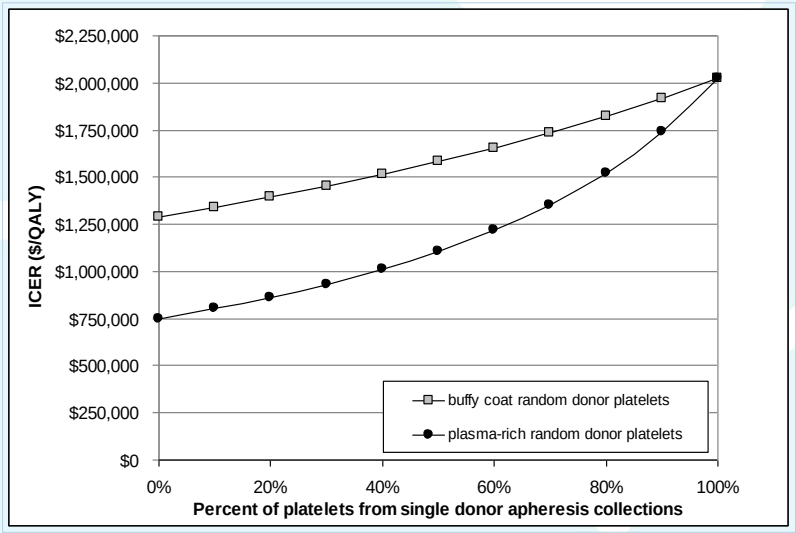
Impact of Platelet Preparation Method



Agapova & Custer ISBT Berlin 2010

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An Emerging Chronic HIV-like Agent

Intervention (Comparator)	Cost per QALY
Whole Blood PI (current screens)	Cost saving $257 per donation
Platelets and Plasma PI (current screens)	Cost saving $144 per donation

An Emerging Acute WNV-like Agent

Intervention (Comparator)	Cost per QALY
Whole Blood PI (current screens)	279,000
Platelets and Plasma PI (current screens)	165,000

Custer AABB Annual Meeting 2011

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Poland Cost Effectiveness Results

Strategy	Comparison	ICER ($/QALY)	Confidence Interval	
Plasma PIM	**Current Screens**	**1,521,000**	**1,058,000**	**2,160,000**
Platelets PIM	**Current Screens**	**864,000**	**580,000**	**1,238,000**
Platelets & Plasma PIM	**Current Screens**	**513,000**	**360,000**	**719,000**

- Most influential variables (reference case): cost of Plasma PI, quality of life post-transfusion, discount rate for effects, additional component use, variation in post-transfusion mortality and annual mortality thereafter, and bacteria related variables

Agapova et al. Transfusion Medicine and Hemotherapy 2015

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Potential Cost Savings of PIM?

- Replacement of bacterial culture
- Avoidance of irradiation
- Avoidance of separate CMV negative inventory
- Extended platelet storage period to 7 days
- Avoidance of some travel deferral for platelet donors

Murphy WG, Transfusion Clinique et Biologique 2011;18:4

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Cost Modifications

In the platelet and plasma PI-treated arm of the model the following costs were removed:

1. Bacterial culture of platelets
   ~$25 per platelet product
2. Assumed roughly 10% of donations are gamma-irradiated
   ~$5/donation*10%

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Results

Platelets and Plasma PI	ICER/QALY	Marginal Savings to the Healthcare System
All current screens	1,423,000	-
Remove bacterial culture	1,222,000	$201,000 (14.1%)
+ Remove gamma irradiation	1,215,000	$7,000 (14.6%)

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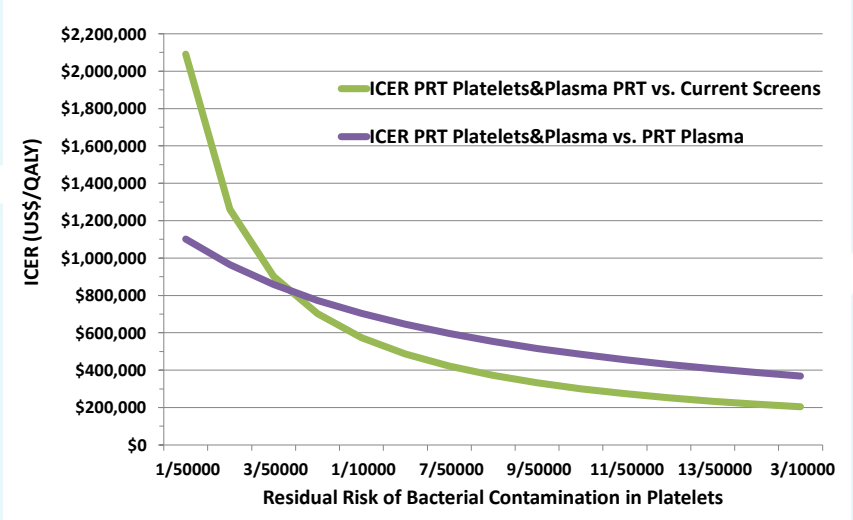
Redefined Residual Risk of Bacterial Contamination

1 per 3300 (~yield of bacterial culture)



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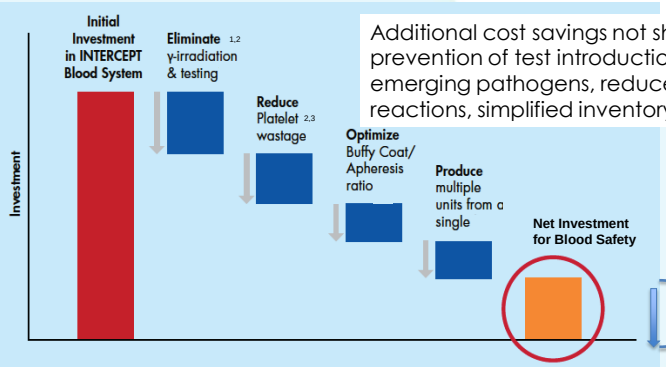
Operational Gains May Offset Investment Costs for PIM



Additional cost savings not shown: prevention of test introduction due to emerging pathogens, reduced transfusion reactions, simplified inventory management.

Cost neutrality may be attained depending on site practices

INTERCEPT offsets costs through streamlined operations, and provides significant clinical benefits via proactive reduction of transfusion-transmitted infections,[1,2] at a minimal investment.

**Varies depending on production practices*

(1) Berger K, et al. Onkologie 2013;36:53-59.
(2) Girona-Llobera, et al. Transfusion 2013; Epub ahead of print.
(3) Veihola M et al. Transfusion 2006;46(6):991-995.
(4) Cost analysis, Strasbourg / Nantes, France 2004.

Slide courtesy of Cerus; previously presented Custer ISBT Amsterdam 2013

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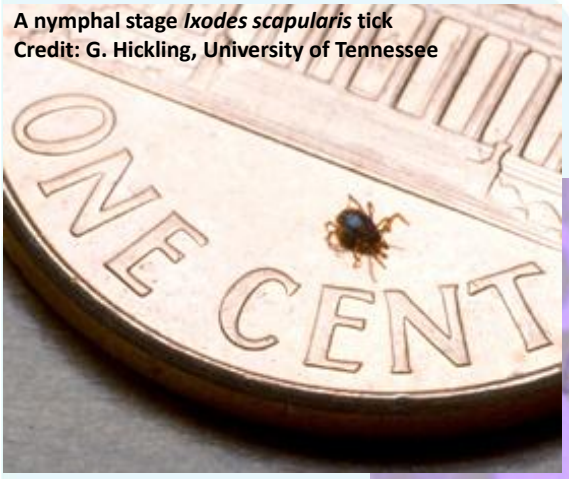
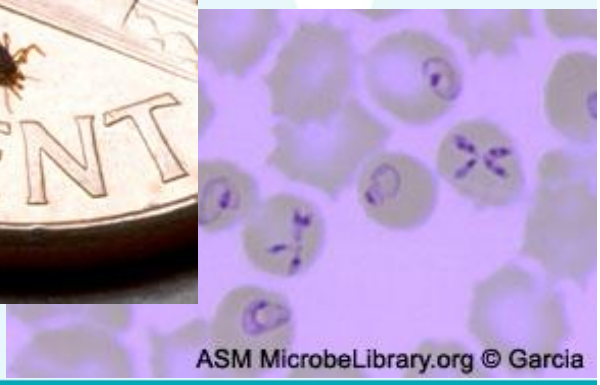
Babesia

A nymphal stage *Ixodes scapularis* tick
Credit: G. Hickling, University of Tennessee





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Babesia Testing - Consequences

(ELISA+PCR screening of donations)

Intervention	Endemic Region (4-state screening CT, MA, NY, RI)	Endemic Region (7-state screening CT ME, NY, RI, NJ, MN, WI)	20-state screening	Universal Screening
RBC transfusions	1,500,000	2,500,000	9,200,000	15,000,000
Babesia infected units	10,300	13,200	22,000	26,500
Averted TTB	99.0	126.8	213.8	255.9
Deaths prevented	0.8	1.0	1.7	2.0
Total Cost	$51,300,000	$82,700,000	$300,300,000	$484,000,000

Goodell et al. Transfusion 2014

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Babesia Testing - Consequences

(Ab+PCR screening of donations)

Intervention	Endemic Region (4-state screening) CT, MA, MN, WI)	Endemic Region (7-state screening CT, MA, MN, WI, NJ, NY, RI)
RBC transfusions	-	2,000,000
Babesia infected units		-
Averted TTB	32.75 per 100,000 transfusions	131.35
Deaths prevented	-	10.82
Total Cost		$50,709,761

Bish et al. Transfusion 2015

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Babesia Cost-Effectiveness/Utility

(compared to no intervention)

Intervention		Endemic Region (4-state screening) $/QALY	Endemic Region (7-state screening) $/QALY	20-state $/QALY	Universal $/QALY
Ab screening	(1)	51,000			
	(2)	760,000			
	(3)	2,615,000	3,231,000	6,685,000	8,921,000
PCR		(63,600)			
		5,006,000	6,394,000	14,185,000	19,122,000
Ab/PCR		251,000			
		8,778,000			
		5,210,000	6,582,000	14,228,000	19,177,000

(1) Bish et al. Transfusion 2015
(2) Simon et al. Transfusion 2014
(3) Goodell et al. Transfusion 2014

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Developing the Framework

The RBDM framework is intended to be embedded in an organisation's risk management program.
It has two distinct components:

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RBDM Framework

- What adherence to the framework could bring to HE and to blood safety decision making
  - Greater consistency in methods and results
  - Use of societal perspective
  - Greater consideration of externalities, including results of other assessments such as contextual issues (social concern & perception, equity, trust, legal & jurisdictional)

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RBDM Case Studies

Babesia – Risk Assessment Question

Assuming FDA licensure of a babesia donor screening assay (or assays) and assuming that FDA does not mandate its use, then what are the risks and benefits to blood recipients and donors as well as costs to blood operators and the health care system (including hospitals) of different potential donor screening policies?

Alliance of Blood Operators

Identify Preliminary Risk Management Options

Scenario	Babesia Risk Management Options
Status Quo	No babesia screening
Option A	Universal donor screening
Option B	Regional donor screening: screen all units collected in "endemic" regions
Option C	Regional and selective screening for selected at risk recipients in "endemic" regions (i.e. CMV model)
Option D	Regional donor screening based on hospital customer requests
Option E	Extended regional screening: all units collected in and transfused in endemic regions (including imports)

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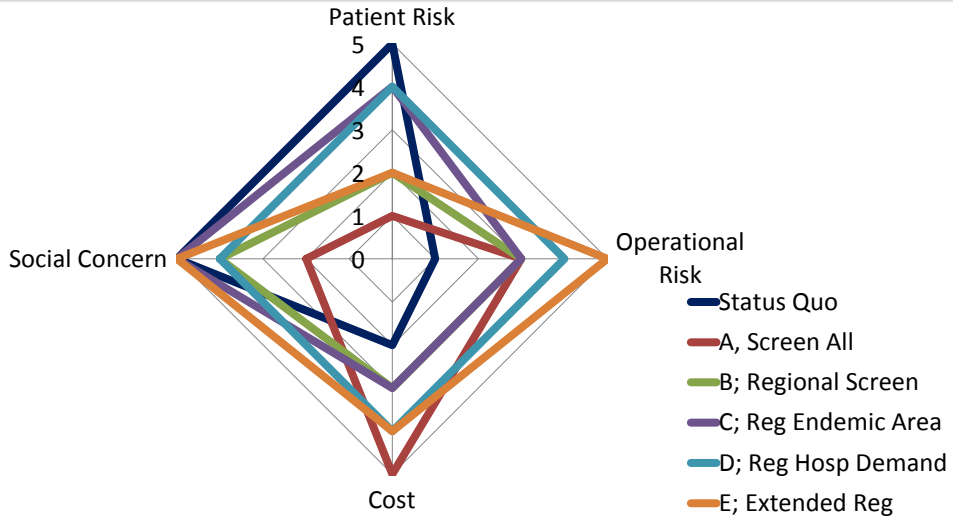
Babesia: Initial Screening Assessment

Level of Risk	Rating
None to Minimal	1
Between Minimal and Medium	2
Medium	3
Between Medium and High	4
High	5

Scenario	Status Quo	Option A	Option B	Option C	Option D	Option E
Patient Risk	5	1	2	4	4	2
Operational Risk	1	3	3	3	4	5
Cost	2	5	3	3	4	4
Social Concern	5	2	4	5	4	5
Risk Rating	***13***	***11***	***12***	***15***	***16***	***16***

Babesia: Initial Screening Assessment



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Cost Utility League Table of Blood Safety Interventions

Intervention (Comparator)	Cost per QALY	Year of Publicat.
HCV Ab (no screen)	Cost saving	1997
HIV Ab (no screen)	3,600	1988
Bacterial culture of platelets	91,000	2006
Mechanical barrier to prevent ABO-mismatch (none)	197,000	1996
Babesia microti Serology+PCR (no screen)	251,000 – 6,582,000	2014-2015
WNV NAT (no screen)	520,000 – 897,000 ↑	2005
Trypansoma cruzi Ab (no screen)	757,000 – 1,360,000 ↑	2010
PIM platelets (current screens)	458,000 – 1,816,000	2003
PIM platelets and plasma (current screens)	1,423,000	2010
Minipool HIV/HCV/HBV NAT (serology)	1,500,000 ↑	2004
Individual Donation HIV/HCV/HBV NAT (serology)	7,300,000	2004
HTLV	Not available	
Syphilis	Not available	
TRALI risk reduction	Not available	

Assessment and Evaluation of Results

- Adherence to best practices
- Completeness
- Do underlying assumptions align with available information

- Importance and role of uncertainty
  - Critically important

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Health Economic Conclusions

- We are truly in need of a core set of guiding principles for health economic and outcomes assessments of blood safety interventions
- The RBDM Framework and the recommendations therein are one proposed approach
- Blood safety interventions under consideration continue to fall outside of established thresholds for cost-effectiveness in other parts of health and medicine
  - Within the blood safety context new technologies are relatively cost-effective
  - Competing priorities and opportunity cost must be considered
- Implementation of broad spectrum interventions such as PIM are likely to require discontinuation of some current interventions
  - This is a strikingly different approach to blood safety implementation and decision making than in the past

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Thank you for your attention

bcuster@bloodsystems.org

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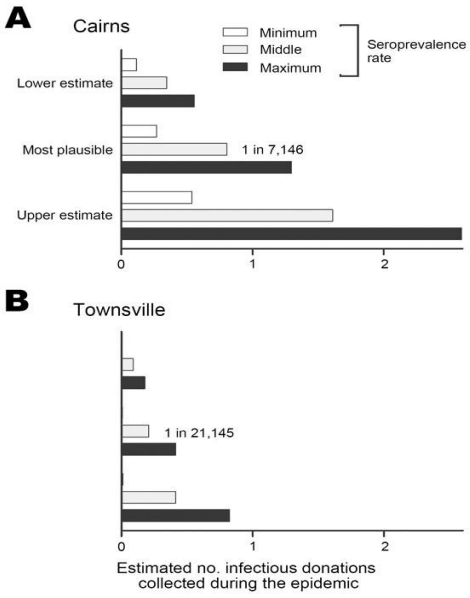
An example of the basis for a good cost-effectiveness analysis

Dengue Serology



Faddy et al. EID 2013

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