RISK-BASED DECISION-MAKING (RBDM) FRAMEWORK FOR BLOOD SAFETY

Application of RBDM to Current Risks, Case Studies

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IPFA/PEI 22nd International Workshop on
Surveillance and Screening of
Blood Borne Pathogens
Prague, Czech Republic 21 May 2015

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Problem Formulation

Purpose

- To generate a **contextual understanding** of the issue and its genesis, and assess which risk management principles are most relevant;
- To consider potential significant **impacts on key stakeholders**;
- To identify **potential risk management options** that should be considered by the assessments and compared in the evaluation stage;
- To develop a clear risk/benefit **assessment question**;
- To identify the **decision support** (information gathering) team and the decision-makers, and declare and resolve any conflicts of interest that could affect assessment, evaluation and decision

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FEASABILITY CASE STUDY
Problem Formulation

VIRUS X - THE ISSUE

- Pathogen Inactivation/Reduction has been approved in an adjacent jurisdiction.
- Virus X has emerged in that jurisdiction, but the extent of the virus within your donor population is unknown.
- 3 to 4 case reports of transfusion-transmission of Virus X.
- Persons who travel to other geographic regions may acquire the infection and may maintain the agent in their blood without any clinical symptoms for up to 28 days after their exposure and then donate during this period.
- Virus X is associated with a 1% mortality rate in otherwise well persons, and a 5-10% rate of hospitalization for an average of 4 days. The impact of infection during pregnancy or for immune-compromised patients is not well characterized.
- No specific antiviral therapy is available.

Development of Risk Management Options

Virus X Case Study Options:

Status Quo: Maintain status quo, while conducting a study to determine the prevalence of Virus X in blood donors in your own jurisdiction

Option A: Institute a deferral for travelers to regions where Virus X is now thought to be endemic while exploring testing options

Option B: Implement a Pathogen Reduction (PR) methodology without modification of existing safety procedures

Option C: Implement PR methodology with modification of:

a) existing criteria for some travel or behavioural based deferrals;
b) one or more donor screens (i.e., laboratory tests);
c) irradiation of blood components; or
d) some combination of options a-c

Option D: Implement PR for a subset of product inventory (PRT applied to general inventory and non PRT for a subset of inventory for use with targeted patient groups)

(New) Option E: Initiate a staggered implementation e.g. address Virus X now (by deferral) and implement PR over the next 12-18 months

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Assessment Question

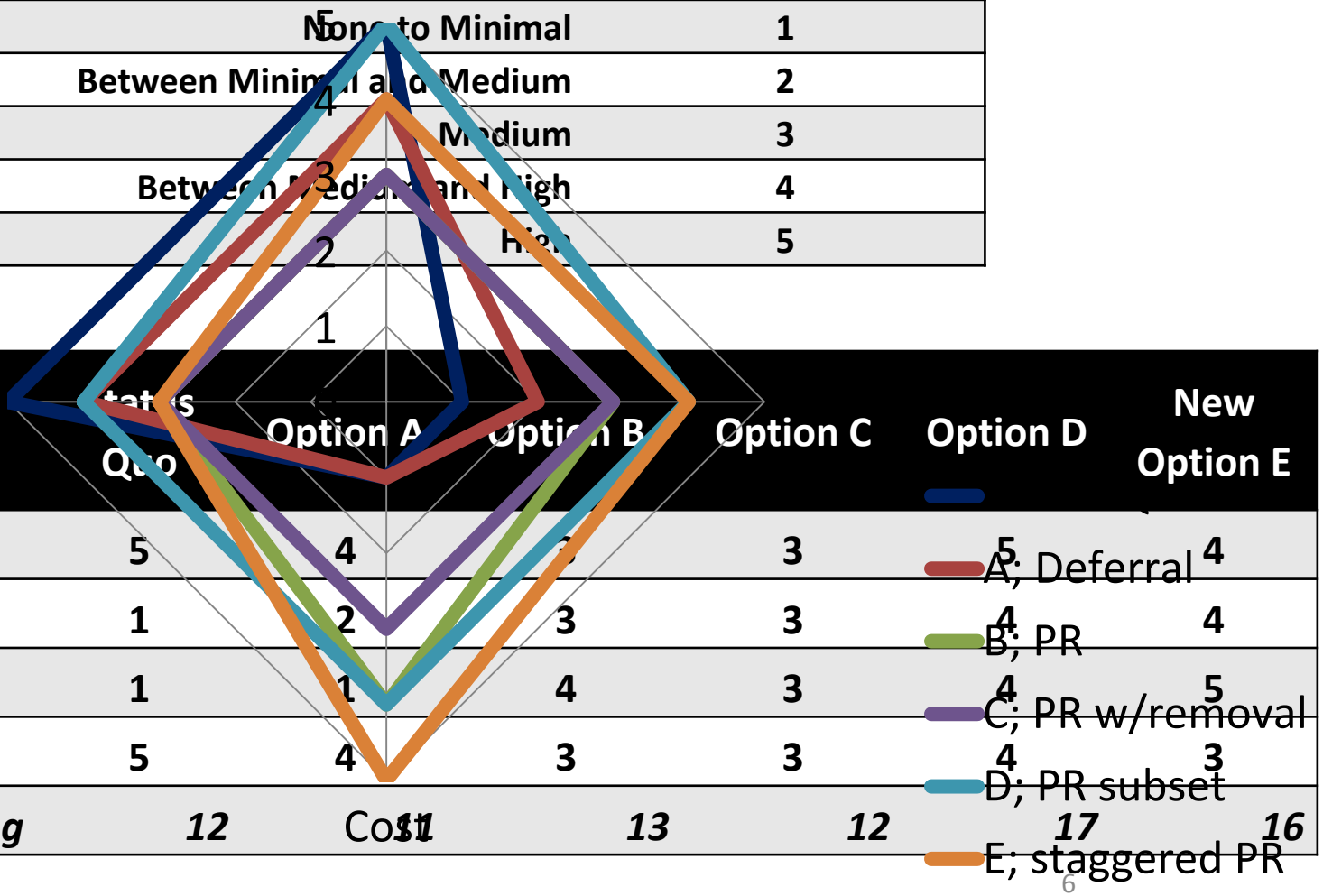
Virus X Case Study

"What is the effect, in terms of risks and benefits to blood recipients and donors as well as costs to the blood operator, of the proposed risk management strategies, particularly implementation of pathogen reduction with and without modification of existing blood safety procedures, to reduce the risk of Virus X?"

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	New Option E
Patient Risk	5	4	3	3	5	4
Operational Risk	1	2	3	3	4	4
Cost	1	1	4	3	4	5
Social Concern	5	4	3	3	4	3
Risk Rating	*12*	*11*	*13*	*12*	*17*	*16*



Assessments

Assessments

- Blood safety risk assessment
- Health economics and outcomes assessment— budget impact, cost effectiveness
- Stakeholder assessment— stakeholder impact
- Operational impact assessment
- Contextual assessment— legal, jurisdictional issues, trust, equity concerns, risk perception

Additional assessments

- Travel survey to assess percentage of donors that would be deferred, if this information is not already known
- New study regarding the prevalence of Virus X in our geographic region may be required
- The regulatory file indicates that several of the components have different in-vitro characteristics upon storage than do their non-PR treated counterparts, leading some scientists to question whether the PR components have equivalent quality. Consideration should be given to further assessing this through product quality assessments for each component type

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Blood Safety Risk Assessment

Option:	VIRUS X RISK: Autochthonous and travel-related risk estimates are as follows:	Other Risks: Some Virus X intervention options will modify non-Virus X risks
Status Quo	Autochthonous: Most likely estimate: chosen as 10th percentile of the distribution; 1.6 per 10,000 (16 per 100,000) Travel-related: Most likely estimate: 6.5 per 100,000 Total risk: Most likely estimate: sum of the most likely estimate for each risk component: 22.5 per 100,000	Data from previous publication on PR with the following modifications: • Adjust bacterial risk from platelets from 1 in 47,00 to 1 in 2,000 • Adjust bacterial risk from other components from 1 in 50,000 to 1 in 500,000 • Adjust HBV risk from 1 in 153,000 to 1 in 750,000 • Eliminate CMV, FNHTR, and TRIM from the model

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Blood Safety Risk Assessment

Option:	VIRUS X RISK: Autochthonous and travel-related risk estimates are as follows:	Other Risks: Some Virus X intervention options will modify non-Virus X risks
Option A: Deferral for travelers to regions where Virus X is thought to be endemic	100% effective for travel-related cases; no effect on autochthonous case risk	No effect on any of these variables
Option B: Pathogen reduction without modification of existing procedures	50-fold risk reduction for each risk component; i.e., risk is 2% of the baseline total risk	Retain risk reduction factors from previous anlaysis
Option C: Replacement of current safety interventions with pathogen reduction	50-fold risk reduction for each risk component; i.e., risk is 2% of the baseline total risk	Retain risk reduction factors from previous analysis
Option D: Implement PR for a subset of product inventory (for platelets only)	Not quantified due to the group's assessment that this option will be ruled out based on the operational risk and social/contextual assessment	Not quantified due to the group's assessment that this option will be ruled out based on the operational risk and social/contextual assessments

Virus X: Health Economics and Outcomes Assessment

Operating Cost	Cost of Patient Care	Total Cost	Cost Increase	Total QALY Loss	Cost Utility Ratio
Status Quo					
$125,000,000	$2,922,078	$127,922,078	—	-138.6	—
Option A: Deferral for travelers to regions where Virus X is thought to be endemic					
$126,750,000	$2,769,697	$129,519,697	$1,750,000	-133.0	$286,408/QALY
Option B: Pathogen reduction without modification of existing procedures					
$270,000,000	$61,319	$270,061,319	$145,000,000	-3.0	$1,048,491/QALY
Option C: PR with replacement of some current safety interventions					
$201,372,000	$67,451	$201,439,451	$76,372,000	-3.4	$543,523/QALY
Option D: Implement PR for a subset of product inventory (for platelets only)					
$129,750,000	$1,940,981	$131,690,981	$4,750,000	-74.0	$58,027/QALY

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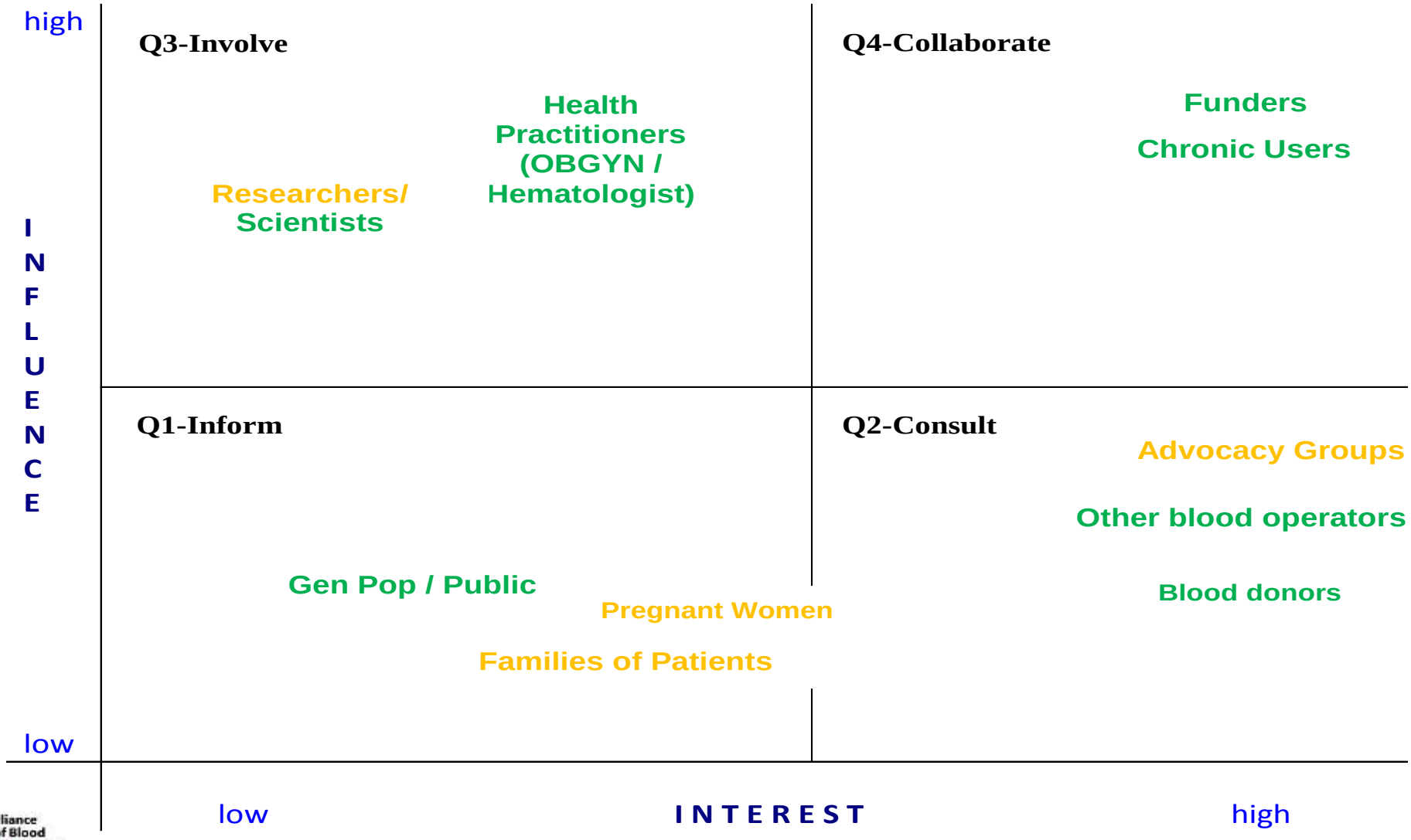
Stakeholder Engagement Plan and Assessment



Group	Interest (Int.) & Influence (Inf.)	Plan	Issues
General Populace/Public	Low int. / low inf.	Inform	-Adequacy and safety of supply -Perception that their jurisdiction is left vulnerable when technology exists to remove Virus X
Pregnant Women	Low int. / low inf.	Inform	Unknown long term effects on fetuses
Families of Patients	Low int. / low inf.	Inform	-Adequacy and safety of supply -Discriminatory when technology exists to remove Virus X.
Advocacy Groups	High int. / low inf.	Consult	-Long term side effects of PR and adequacy and safety of supply -Having access to treated vs. untreated products -Seeking meaningful interaction
Other Blood Operators	High int. / low inf.	Consult	
Blood Donors	High int. / low inf.	Consult	-Additional travel restrictions leading to deferral
Researchers & Scientists	Low int. / high inf.	Involve	-Access to information to be able to inform and advise their patients.
Clinicians (OBGYN & Hematologists)	Low int. / high inf.	Involve	-May be concerned with in-vitro characteristics -Long term effects on chronic users -Storage/shelf-life of pathogen reduced products -Social or economic impacts
Funders	High int. / high inf.	Collaborate	-Impact on budget
Chronic Users	High int. / high inf.	Collaborate	-Safety and security of supply -Long term side effects (toxicity) -Control risk through surveillance

Stakeholder Assessment - *Insights*

Status Quo
Option is ineffective. Blood products less safe and chronic users vulnerable to Virus X. Stakeholders could influence thought leaders, decision-makers and engage the media to make views public.
A: Deferral for travelers to regions where Virus X is thought to be endemic
Risk mitigation without new concerns such as unknown long term effects for chronic users and pregnant women. Concerns about adequacy of supply due to the loss of donors. Permanent donor loss if offended by the deferral. Persons from endemic areas may consider this a cultural judgment.
B: Pathogen reduction without modification of existing procedures
Pregnant women and chronic users fear the long term, unknown effects of PR. Some groups critical of costs. While others focused on safety. Stakeholder communication and consultation would be critical to determining the path forward.
C: PR with replacement of some current safety interventions
PR will increase stakeholder confidence. Withdrawal of tests may create angst. Stakeholders may view cost savings as more important than patient safety. Stakeholder communications, presentations and consultations will require educational component to deepen stakeholder understanding of all process change implications. Post implementation monitoring and communication.
D: Implement PR for a subset of product inventory (for platelets only)
Stakeholders question process to decide who receives treated or untreated product. Patients may view the treated product as better quality. Stakeholders will seek clarity on this option. Patients not receiving treated product will want to understand the lack of risk mitigation for their subset.

Operational Impact Assessment

Option A : Deferral for travelers to regions where Virus X is thought to be endemic

Issue	Risk	
Multiple factors must be considered in determining the deferral criteria including geographic locations where Virus X is endemic, length of time when a donor could be viremic yet asymptomatic, whether the likelihood of infection is greater for citizens vs. travelers to area.	Lack of information about Virus X may result in overly stringent deferral criteria, removing a higher than necessary proportion of blood donors. Blood supply may be negatively impacted or additional cost expended to ensure replacement donors are quickly located.	Risk Magnitude Medium Probability Unlikely Impact Moderate
Implementation of geography-based deferrals requires immediate update of criteria as the pathogen spreads. Blood operator must issue updates, ensure screening staff is trained on the changes, and ensure the new criteria are being applied - Requires nimble process.	Updates to the deferral criteria will not be implemented quickly enough and an at-risk donor will be accepted for donation	Risk Magnitude Medium Probability Unlikely Impact Major
	Information relating to the deferral updates will not be clear or specific enough and staff will interpret the criteria incorrectly, and an at-risk donor will be accepted for donation.	Risk Magnitude Medium Probability Unlikely Impact Major

VIRUS X CASE STUDY - SUMMARY OF ASSESSMENT RESULTS

Option	Blood Safety Risk	Health Economics	Operational	Stakeholder	Social Concern/Trust
Status Quo	16/100,000 (endemic) 22.5/100,000 (overall)	$127,922,078 138.6 QALY loss	No impact	Not acceptable	
Deferral	16/100,000 (endemic) 0/100,000 (travel)	$129,519,697 133.0 QALY loss	Medium risk	Acceptable	May not be considered sufficient protection
PR in addition to existing	50 fold risk reduction; risk is 2% of baseline total	$270,061,319 3.0 QALY loss	Medium to extreme	Acceptable, requires risk communication of PR on product	Positive
PR with replacement	50 fold risk reduction; risk is 2% of baseline total	$201,372,000 135.3 QALY gain	Low to medium	Acceptable, requires risk communication of PR on product	Positive but will require risk communication about technology/safety
PR partial	Not quantified	Not quantified	Low to medium	Confusing	Negative

Mock Decision

- Assessment team identified the advantages and disadvantages of each option and used an options rating scale to rate the safety risk of each.

- Debate and discussion. As the discussion progressed, some options were discarded and three options seemed the most feasible.

- The consensus was to recommend to the Executive:

  Modified Option C: Introduction of pathogen reduction, with a gated approach to replacement of some deferrals or tests.

- Prepare report and recommended actions for Executive consideration.

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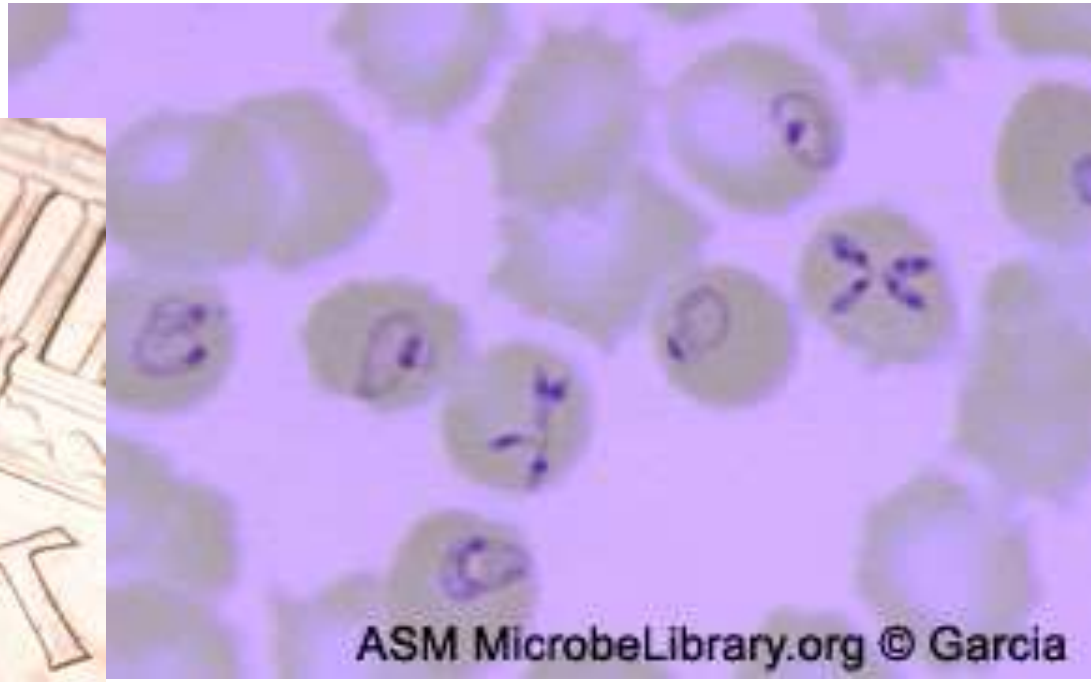
RBDM Case Studies

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



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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?

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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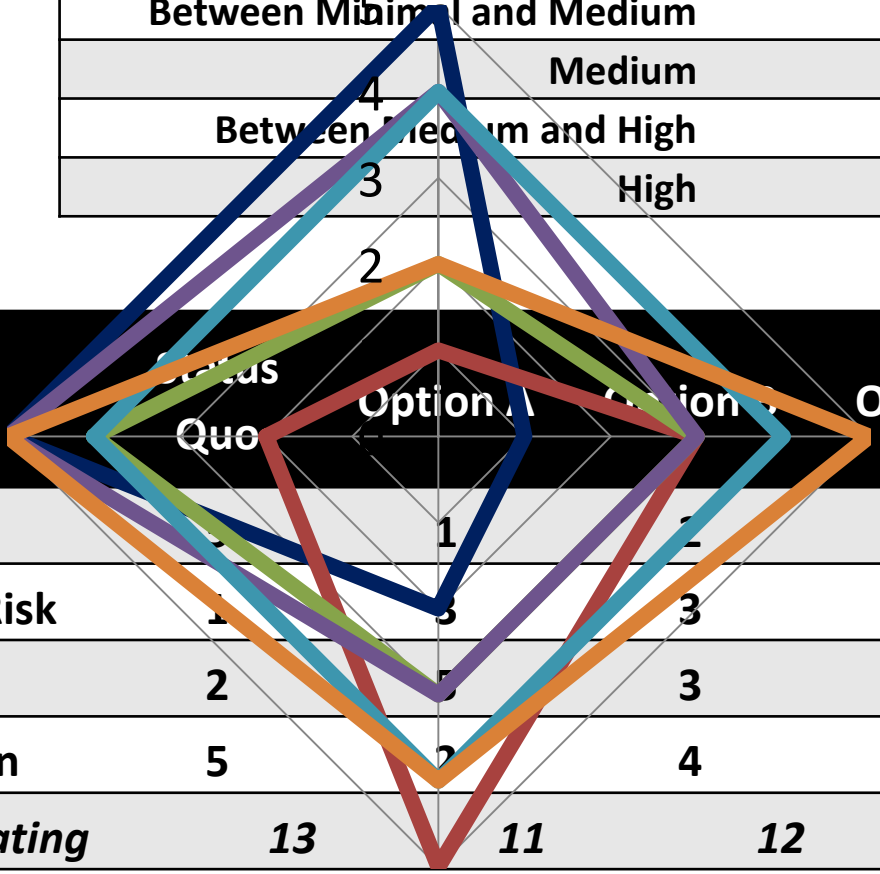
Babesia: Initial Screening Assessment

Level of Risk	Rating
Not Risk / 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*

AABB Recommendations

1. Year round regional testing of all donations of transfusable red cell products – specifically in the 9 states described above, with inclusion of additional states based on scientific data, or exclusion of specific areas within a state as described below. (Other Considerations, #3)
2. FDA should move expeditiously to review submissions of test applications for use with screening blood donors for *Babesia*.
3. As the agency develops current thinking around the use of *B. microti* testing it should consider the use of testing system(s) that have high positive predictive values/low rates of false positivity to conserve blood availability, and low rates of false negativity leading to optimal safety.
4. AABB encourages the development and approval of a supplemental test and/or reentry algorithms to allow for donor re-entry as expeditiously as possible. It is important that the number of donors who are not infected with *B. microti*, yet who are deferred due to false positive reactions, remains low.

Donors

Presented by
M. Allene Carr-Greer, Director, Regulatory Affairs

RBDM Developing Evaluations

Canadian Blood Services

- Pathogen Inactivation/Reduction technologies
- Chikungunya virus

Australian Red Cross Blood Service

- Dengue testing in donors

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Content courtesy of Judie Leach Bennett and Peter McDonald

RBDM Developing Evaluations

National Health Service Blood and Transplant - NHSBT (UK)

- Hepatitis E – screen all donors, donors for high risk immunosuppressed blood recipients only, or neither?
- Bacterial contamination of platelets – continue bacterial screening or switch to pathogen inactivation?
- HTLV screening of blood donors – test all donors every time, or switch to new donors only?

Content courtesy of Lorna Williamson

RBDM Summary

- Available case studies are currently limited
  - Even so, the limited case studies show the Framework can identify key considerations
- Framework has a range of tools that assist in defining approaches to broadly different risks blood operators may face
  - Problem Formulation
  - Risk Management/Mitigation Options
  - Specific Assessment Tools (RA, HEO, Stakeholder, Operational Impact, Contextual)
- Use of each tool may not be relevant for each risk
- Online framework will help to lower barriers to use
- Planned use by large organizations will demonstrate the ability of the tool to assist decision-making

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Thank You

Acknowledgements

Sam Bagnato, ARCBS

Mary Beth Bassett, Blood Systems Inc.

Brian Custer, Blood Systems Research Institute

Michel T. Giroux, Institut de consultation et de recherche en éthique et en droit

Smaranda Ghibu, Héma-Québec

Matt Granato, America's Blood Centers

Mart Janssen, Sanquin Blood Supply

Louis Katz, America's Blood Centers

Andy Kelly, Irish Blood Service

Stephanie Kelly, Canadian Blood Services

Steven Kleinman, Kleinman Biomedical Research

Lorna Lemay, LL Concord Consultation & Mediation Services

Peter McDonald, Australian Red Cross Blood Service

Jay Menitove, AABB

Greg Paoli, Risk Sciences International

Mark Skinner, World Federation of Hemophilia

Peter Tomasulo, Blood Systems Inc.

Sheila Ward, Canadian Blood Services

Anne Wiles, Risk Sciences International

Lorna Williamson, NHS Blood & Transplant

Ralph Vassallo, Blood Systems, Inc.

Tina Viner, Canadian Blood Services

Judie Leach Bennett, Canadian Blood Services

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Framework Highlights

- Builds in the ability to gauge both quantitative and qualitative risk, as well as overall **risk acceptability or tolerability** in the context of patient and donor safety.
- Provides guidance regarding the **use of health economics and outcomes assessments** necessary for the evaluation of the cost utility of mitigation options.
- Includes guidelines to enable **stakeholder engagement** on considerations such as risks, opportunities, alternate solutions, unintended consequences, resources, and implementation implications with the ultimate goal of transparency and optimal input.
- Integrates these dimensions into an **overall risk profile** in order to inform the decision-making process.

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Babesia: Identifying Risk Management Options

Scenario	Risk Management Option	Patient Risk	Operational Risk	Cost Utility	Contextual Factors
Status Quo	No babesia screening	Major risk to recipients	n.a.	-No implementation costs -Costs associated with transfusion-transmitted infection	-Breach of ethical principles as current risk level appears to exceed a risk tolerability threshold -Erosion of trust – patients and other stakeholders
	Risk Rating: 13	5	1	2	5
Option A	Universal donor screening	Substantially lowers patient risk	- New testing system and new vendor; more operationally complex -Universal testing is the simplest -Unnecessary donor deferral - false positives	-Reduced cost utility; implementation in regions where not warranted by risk	-Failure to move beyond a "precaution at all costs" paradigm
	Risk Rating: 11	1	3	5	2
Option B	Regional donor screening: screen all units collected in "endemic" regions	Substantially lowers patient risk but not as much as universal screening	- New testing system and new vendor; more operationally complex - Difficult to define endemic and "regions" -Require ongoing monitoring leading to changes in definition -This confounds patient risk and cost utility assessments	-Improved cost utility due to closer proportionality between the mitigation measure and the risk magnitude and patient outcomes achieved	-Significant safety, feasibility, and economic implications by "imposing" definitions -Reduced competitiveness of blood components produced in endemic areas