Safety and Security of Supply in Blood Transfusion

Dr. Graham Sher, O.C.
CEO
August 24, 2022

Canadian Blood Services
BLOOD
PLASMA
STEM CELLS
ORGANS
& TISSUES

Using risk-based decision-making to inform our choices and guide our actions.

“The public response to the possibility that AIDS might be transmitted by blood transfusion contains an element of hysteria, fueled by an over-reacting press and a paucity of information about suspected transfusion related cases.”

A U.S. blood bank medical director,
testifying before Congress, August 1983
when 20 cases of AIDS related to transfusion had already been reported to the CDC

Background

- Since the 1980s, numerous measures aimed at *maximizing* blood safety have been implemented based on:
  - Varying interpretations of the precautionary principle.
  - An unsustainable pursuit of “zero risk”.
  - A lack of evident consideration of cost-effectiveness and opportunity cost.

Background

- Pursuit of “freedom from transmissible harmful agents” has been both:
  - Spectacularly successful.
  - Increasingly expensive, controversial and impactful on supply.
- Early risk interventions (e.g. HIV Ab, HCV Ab testing) unanimously adopted, with demonstrable increments in safety.
- Remote and recent interventions (e.g. MSM policies, vCJD deferral, universal pre-storage leukoreduction, pathogen inactivation technology, ZIKA virus, etc.) marked by dissention and disagreement.

Alliance of Blood Operators International Consensus Conference

- Risk is inherent from vein to vein.
- Zero risk is unattainable.
- Well-being of transfusion recipients must be central to blood safety decision-making.
- An integrated risk framework must be developed to:
  - Enhance decision-making.
  - Facilitate proportional responses to risk.
  - Ensure decisions are evidence-based.
  - Increase trust in investment decisions.
  - Allow for redirection of resources to improve effectiveness.

Changing the decision-making paradigm

From	To
Pursuit of zero-risk regardless of cost	Determination of acceptable risk based on societal considerations
Siloed decision-making: mainly blood operator and/or regulator input	Integrated decision-making: multiple sectors included in process
Industry-driven approach	Evidence-based, with robust risk assessment tool
Inconsistent, issue-by-issue decisions	Consistent, standardized approach
Blood industry focus	Health sector focus

Alliance of Blood Operators framework for risk-based decision-making (RBDM)

Alliance of Blood Operators

Risk-Based Decision-Making Framework for Blood Safety
https://riskframework.allianceofbloodoperators.org

RBDM framework

- Intended to be embedded in an organization's risk management program.
- Has two distinct components:
  - Policy foundations.
  - Decision-making process.
- Can be scaled for large or small decisions.
- Appropriate in multiple different contexts.

Policy foundations (i)

Risk management principles:

- Govern the process and actions that flow from decisions
- Include:
  - beneficence
  - transparency
  - evidence and judgement
  - vigilance
  - fairness
  - consultation
  - proportionality
  - continuous improvement

Risk communication and stakeholder participation:

- Essential to involve all relevant stakeholders in the process
- Does not mean the organization gives up authority to make decisions
- Improves quality of decision-making
- Creates a shared understanding of risk-management actions
- Lays foundation of trust

Policy foundations (ii)

Assessment principles:

- Proportionality
- Timeliness
- Judicious use of evidence
- Characterization of uncertainty
- Variability, integration with related analyses
- Transparency and confidentiality

Risk tolerability:

- The judgement that a risk is reasonable given the expected benefits of an activity and resources required to manage risk
- Made by the blood operator, with consideration of stakeholder and public concerns
- Viewed through the lens of ALARA "As Low As Reasonably Achievable"

Sample RBDM case studies

Risk consideration	Country	
Babesia microti	Canada, U.S. (AABB)	
HTLV	Australia	
Rh (D)	Australia	
Pathogen inactivation	United Kingdom, Australia	
HTLV	Republic of Ireland	
CMV (testing elimination)	Canada	√
Acupuncture and other donor deferral policies	United Kingdom	
Plasma and immunoglobulin security of supply	Canada	√

Stage one

Preparation

Before starting the process, it is important to review the foundational elements of risk management so that each stage can be carried out efficiently and effectively.

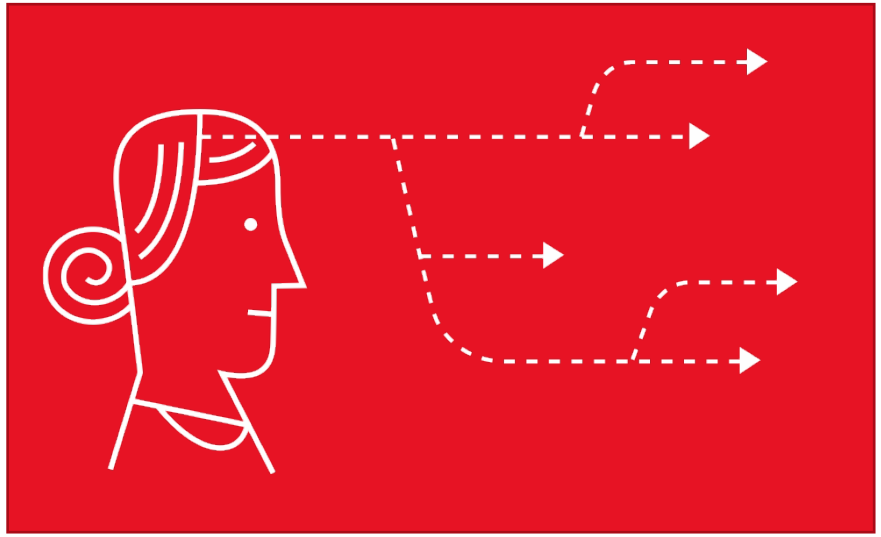
Launching a RBDM analysis

- Review of pertinent literature and existing expert advisory committee recommendations.
- Risk assessment team assembled, with range of expertise as needed: e.g. medical microbiology, epidemiology, transfusion medicine, health economics, stakeholder engagement, communications and risk management.
- Review of policy foundations and decision-making process of the RBDM framework.
- A readiness checklist can be useful.

Stage two

Problem formulation

The purpose of this stage is to define and characterize the problem in order to identify the overall assessment question, the decision drivers and the risk management options to evaluate.



Risk characterization

- CMV is a common herpes virus infection, frequently asymptomatic or causes mild disease.
- Virus replicates in mononuclear white blood cells where the virus becomes latent.
- CMV can be transfusion-transmitted, but the vast majority of blood products from CMV-positive donors will not transmit an infection.
- TT-CMV infection poses a risk to immunocompromised patients and high-risk groups.
- CBS employs two strategies to reduce risk: pre-storage leukoreduction for all donations; and CMV antibody-negative inventory available upon request.

Decision drivers and risk assessment questions

- Is the current CMV risk mitigation undertaken by Canadian Blood Services proportional to the risk associated with transfusion transmission of CMV?
- If not, what alternative strategies for CMV testing could be implemented, taking into account safety and operational impacts?

Risk management options

A. Status quo: Meet all orders for CMV-negative product using antibody testing.

B. Stop providing CMV-negative product entirely and rely on leukoreduction to reduce transmission risk.

C. Provide CMV antibody-negative product for intrauterine transfusion (IUT), neonates under 28 days of age, and in elective transfusion of CMV-seronegative pregnant women **OR** provide CMV antibody-negative product for intrauterine transfusion.

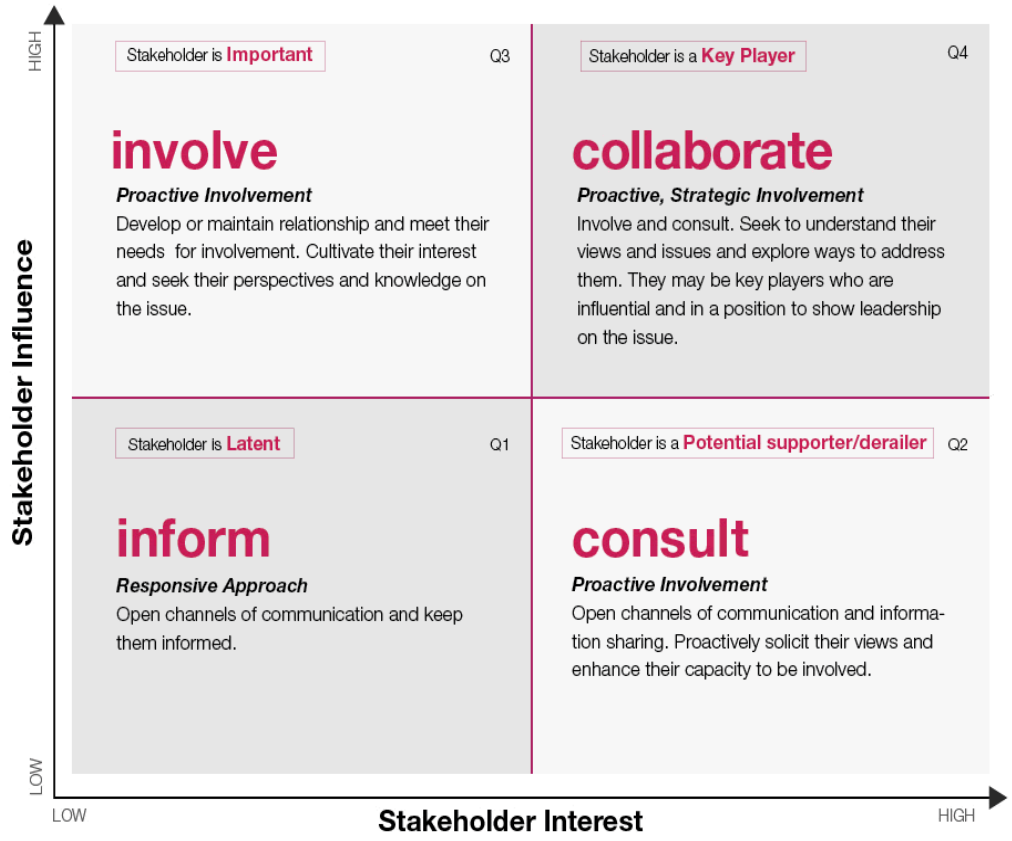
D. Use nucleic acid testing (NAT) to identify CMV-negative product for target risk groups listed in Option C.

E. Introduce pathogen reduction technology.

Stage three

Participation strategy

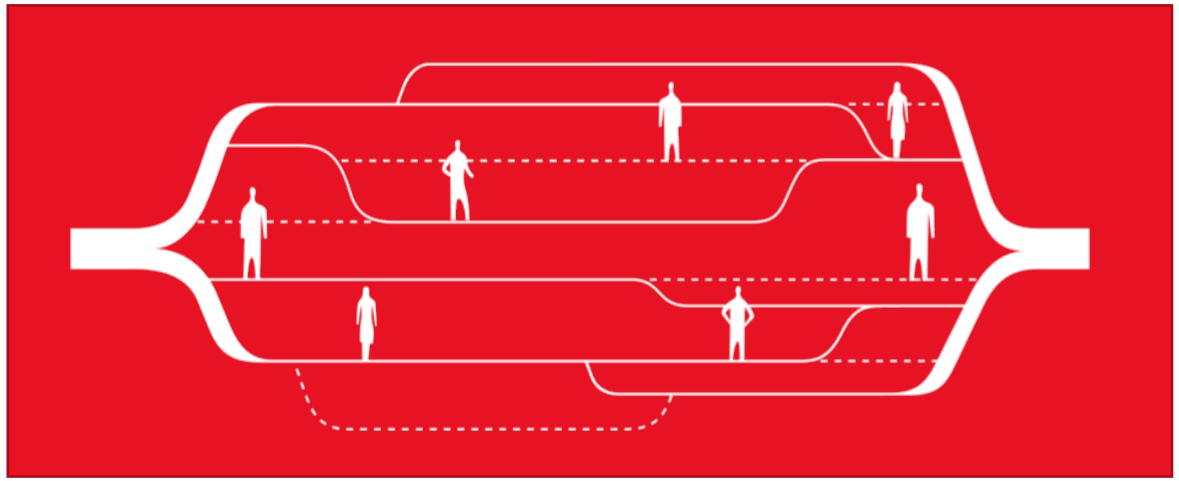
The purpose of this stage is to define the need for risk communication and stakeholder involvement, identify relevant stakeholders and develop a participation plan.



Stage four

Assessments

The purpose of this stage is to accumulate the data necessary to analyze the risk management options effectively, by performing a series of quantitative and qualitative assessments.



Assessment findings

- Blood safety risk assessment: Residual risk of CMV in leukoreduced products shown to be very low.
- Budget impact assessment: Canadian Blood Services was testing approximately 47 per cent of all blood donations for CMV; in a selective inventory approach, the cost of testing would be substantially lowered based on estimated demand.

Assessment findings continued

- Operational impact assessment: Main operational risks of introducing a new testing algorithm were associated with managing a “boutique” product distribution; the risks of a leukoreduction filter failure or of the wrong unit being sent to hospital was rated “rare”.
- Contextual assessment: Recommendations from National Advisory Committee on Blood and Blood Products, SaBTO, etc.

Stage five

Evaluation

In the evaluation stage, assessment results, stakeholder feedback and risk tolerability analysis are used to compare the risk management options.

Evaluation

CMV testing in Canada

Risks	Risk Management Option				
	Option A	Option B	Option C	Option D	Option E
Saftey Risks	1/3	1/3	1/3	1/3	2/3
Infrastructure & Resources Required	2/3	1/3	1/3	1/3	3/3
Other concerns (ethics, trust, strakeholder tolerability)	1/3	2/3	1.5/3	1.5/3	2/3
Total	4	4	**3.5**	3.5	7
Rank	3	2	1	2	3

Risk		Rank	
Low	1	Best option	1
Medium	2	Acceptable	2
Hight	3	Unacceptable	3

Stage six

Decision

Once all these factors have been considered, a risk management option is selected, and implementation and monitoring plans are defined. An important final step is to communicate the decision to stakeholders.

Responses to risk assessment questions

Is the current CMV risk mitigation undertaken by Canadian Blood Services proportional to the risk associated with the transfusion transmission of CMV?

The risk assessment suggests that:

- Current CMV “belt and suspenders” approach is not clinically required to provide CMV-safe product.
- A more restricted inventory of CMV-negative product is reasonable.

If not, what alternative strategy for CMV testing could be implemented, taking into account safety and operational impacts?

- Both options C1 and C2 would be acceptable strategies.

Recommendations/decision

It was recommended that:

- An antibody testing approach be implemented.
- Communication plans and physician education opportunities on TT-CMV risk be developed.
- The cost-effectiveness of NAT CMV testing based on outcome and cost data be determined and assessed whether to add a NAT platform to the existing antibody testing.

Using Risk-Based Decision-Making for a security of supply risk

2021–2022 RBDM analysis on Canada's plasma sufficiency for immunoglobulin

- Exploring plasma and immunoglobulin security of supply, including risks across both collection and fractionation capacity.
- RBDM process intended to project the risk scenarios over the next five years.
- Canada has insufficient source plasma for further manufacture into immunoglobulin.
- Global shortages of plasma pre-dated the pandemic, made much worse by it.
- Product scarcity, rising costs all impact patient care. This is a global risk, not unique to our context.
- Emerging competition from the for-profit, paid plasma sector in Canada.

RBDM decision drivers

- **Patient need**: Ensure secure domestic supply of immunoglobulin (Ig) for patients with essential need
- **System costs**: Deliver affordable Ig supply for Canadian healthcare system
- **Sustainability of national blood/plasma system**: Maintain donor engagement and sustained supply of blood/plasma to serve patients' needs; maintain donor well-being and trust and value proposition for workforce

Evidence-based analysis

Stakeholder engagements

1. Patient, clinician, and health organizations
2. Donors and public

Expert assessments

1. Canadian immunoglobulin utilization
2. Horizon scan: New FcRn drugs as alternatives
3. Security of supply for plasma and Ig
4. Global jurisdictional scan
5. Health economics and outcomes
6. Contextual factors

Risk mitigation options

1. Increase Canadian Blood Services' plasma collection capacity.
2. Purchase additional plasma, if available, collected within Canada or elsewhere.
3. Purchase additional finished Ig fractionated within Canada or elsewhere.
4. Develop domestic immunoglobulin supply chain from collection to fractionation, through commercial contracts.
5. Partner with provincial and territorial governments to optimize utilization
    a) Best practices in utilization of Ig
    b) Gatekeeping the use of Ig

Evaluation

Evidence used to evaluate risk management options on:

- ✓ Effectiveness in **risk reduction**
- ✓ Additional **benefits** they may provide
- ✓ Ability to manage **stakeholder concerns**
- ✓ **Operational feasibility** of the options
- ✓ **Risk tolerability** (i.e., reasonability to accept a risk given its expected benefits and resources required to manage the risk)

Evaluation outcomes

- While all options offer some benefit:
  - Option one (Canadian Blood Services increases its collection capacity) and
  - Option four (develop domestic Ig supply chain from collection through to fractionation via commercial contracts) in combination provide better risk reduction, in a reasonably timely and cost-effective manner.
- Supporting Ig utilization management (option 5a) remains important, but only a supportive measure.
- Options two (purchase additional plasma) and three (purchase additional Ig) not viable as stand-alone strategies and don't adequately mitigate risk.

Blood safety is multi-layered, complex, dynamic and context specific

Multi-layered approaches to blood safety

	Strategy	Examples
External	Surveillance Vigilance	Donor studies and risk assessment, emerging pathogen matrices, seroprevalence studies etc.
Organizational	Quality management and quality processes	Standardization, training, documentation, traceability
Individual	Donor screening and education	Donor questionnaires, health assessments
Product	Lab testing Manufacturing processes	Testing for various pathogens Pathogen inactivation technology, universal pre-storage leuko-reduction

Level of risk in Canada

Residual risk of HIV, HCV and HBV remains very low but other risks are emerging

Donor status	Number of donations	Percentage of donations	HIV		HCV		HBV	
			#	Rate	#	Rate	#	Rate
First time	66, 297	8.3	2	3.0	45	67.9	38	57.3
Repeat	731,193	91.7	1	0.1	12	1.6	1	0.1
			Residual risk					
			1 in 12.9 million donations		1 in 27.1 million donations		1 in 2.0 million donations	

# = number of confirmed positive donations
Rate = prevalence rate per 100,000 allogeneic donors
Note: Numbers and figures on this table are based on the 2021 calendar year

Pathogen inactivation technology — a game changer?

- Pathogen inactivation technologies provide the opportunity to increase the safety of the blood supply from infectious agents (even though the current system is exceedingly safe).
- Enhances preparedness should a new pathogen emerge that threatens blood safety, for which a test may not be (readily) available.
- The era of emerging pathogens is pretty active: WNV, SARS-CoV2, monkeypox, Zika.
- Implementation should aim to minimize product quality loss, optimize customer uptake and maximize cost-effectiveness.

Pathogen reduction at Canadian Blood Services

By 2024 all platelets and plasma for transfusion will be pathogen reduced

Platelets

- Pathogen reduced buffy-coat platelets implemented in one region in Jan. 2022 (~10 per cent of pooled platelet supply).
- Buffy-coat and apheresis pathogen reduced platelets will be rolled out nationally over the next 18 months. (120,000 platelet units per year).

Pathogen reduction at Canadian Blood Services

Plasma

- The most timely and cost-effective path to a pathogen reduced plasma supply is through solvent detergent (SD) plasma, which is currently available for limited clinical situations.
- Transition to SD plasma to occur in early 2023.
- Introduction of in-house pathogen reduced plasma is planned for 2024 (to be made available alongside SD plasma).

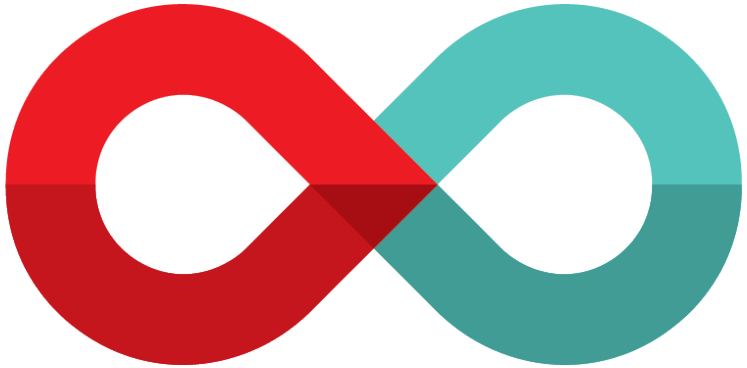
Concluding thoughts

Risk-based decision-making

- A framework that helps a blood operator identify, assess, act on and communicate risk in a manner suited to each situation. Allows an entity to:
  - Optimize the safety of the blood supply within reasonable standards.
  - Allocate resources in proportion to the risk and potential opportunity cost.
  - Use the framework when facing a new decision about blood safety.
  - Ensure it is flexible enough and suitable to the regulatory structures, local conditions and needs.
  - The framework consists of six sequential stages, each with a specific purpose and outcome.

Risk-based decision-making

- The tool developed by the Alliance of Blood Operators is scalable, flexible, context specific and validated
- For more information: Risk-Based Decision-Making Framework for Blood Safety
- **https://riskframework.allianceofbloodoperators.org**



Canadian Blood Services

BLOOD
PLASMA
STEM CELLS
ORGANS
& TISSUES