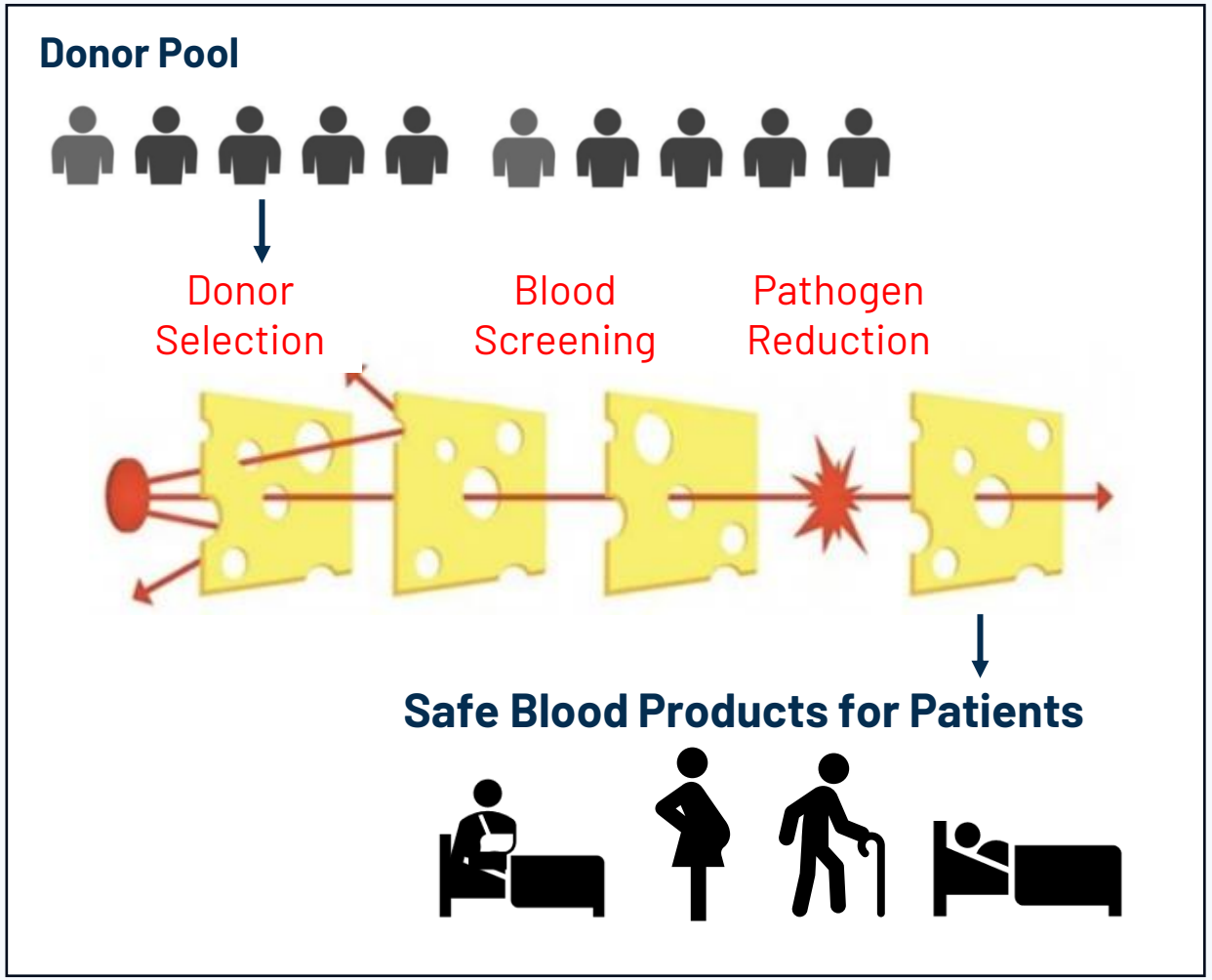
Current Blood Safety Mitigation Strategies: Limits, Redundancy, or Added Benefit?

Creative Testing Solutions

Marion LANTERI, PhD
Vice President of Scientific Affairs



Blood Safety Relies on the Redundancy of Mitigation Strategies



- **Benefits**
- **Limits**
- **Redundancy**
- **Added Benefits:**
  - Blood Safety
  - Blood Availability
  - *Cost Considerations*

Donor Selection

Benefits

Eligibility process

Selects for ***healthy*** donors

- Physical examination
  - Temperature, Blood Pressure, Hematocrit, Pulse, Weight
- Donor health questionnaire (DHQ)
  - Symptoms, Risk behaviors, Infectious diseases, Immunizations, Medication, Travel history…
    - Recipient safety (TTI risk mitigation)
- Eligible or deferred

Limitations

1. Deferrals negatively impact blood availability
   - Social pain
   - Missed donations
   - Lower return rates
2. TTI prevention relies on
   - DHQ response accuracy
     - Non-disclosure
   - Pre-symptomatic donors
   - Asymptomatic infections
   - Complexity of travel deferrals

Mitigation

- Donor recruitment efforts
  - Repeat, first time, deferred
  - Incentive programs
- Relaxing deferrals
- Post-Donation information

➢ Rely on blood screening and pathogen reduction

Donation Screening

Benefits

- Complex testing algorithms
  - Sensitive screening + Confirmatory assays
- If reactive, products are discarded
- Donor is deferred
- Donor counselling
  →Referral/treatment
  - Re-entry

✓ Advances in blood screening tests progressively reduced the risk of TTI

Limitations

- Risk of false positives
  - Screening ≠ Diagnostic
  - Remain Ab+ after resolving infection
- Discarded products
- Deferred donors
  - Social stigma, lower return rates, re-entry testing with risk of being deferred again
- Limit of detection
  - Window period
  - Suppressed viral loads } ARV
  - Seroreversion
- EID:
  - Availability of assays?
  - Development timeline
  - Delayed implementation
- Cost *vs.* risk

Mitigation

- Decrease cost
  - Multiplexing for gain of efficiency
  - Increase availability by removing deferrals
- DHQ adjustments
  - Drug intake, list of medication
  - Behaviors and infection status
  - Motivation studies
- Accelerate development timeline
  - Preparedness efforts:
    - Horizon scanning
    - Molecular/Sero surveillance
    - Epidemiology studies
- Increase safety
  ➢ Add pathogen reduction

Pathogen Reduction – Blood Components

Benefits

1. Depends on inactivation levels
   - Viruses
   - Bacteria
   - Parasites
   - Leukocytes
2. Replace some deferrals/testing
   - Bacteria, Babesia, Malaria, ZIKV
3. Replace procedures (LR, irradiation)
4. Increased blood availability
   - Treated components not discarded
   - Earlier release
   - Longer shelf-life
5. Preparedness
   - Vector-borne
   - EID

Limitations

1. No universal PRT
   - Only available for plasma and platelets
   - Some pathogens are not inactivated
2. Is component quality impacted?
   - Contradicting results in various publications
   - Heterogeneity of production methods
     - ✓ Blood utilization
     - ✓ Clinical efficacy
3. Cost *vs.* risk

Mitigation

Current cost saving opportunities (before universal PRT):

- Increase blood availability
  - Relax deferrals
  - Replacement of look back for PDI
  - Remove some tests as approved for decreased testing cost and discard
- Change platelet production
  - WB derived *vs.* apheresis for decreased costs, increased quality and decreased utilization
  - Pooling to recover more plasma
  - Outdated platelet lysates safety
- Cost of PRT *vs.* cost of TTI

Pathogen Reduction – Plasma Fractionation

- Donor screening
- Testing (WP/LOD)
- Quarantine
- Fractionation

Viral inactivation steps (>4 log):

  - S/D treat (lipid membrane enveloped viruses)
  - Pasteurization/heat (non-enveloped viruses)
  - Filtration (larger viruses)

- Overall inactivation + margin

"An appropriate margin of safety is achieved when the overall virus reduction factor exceeds the maximum amount of virus potentially entering the manufacturing pool"

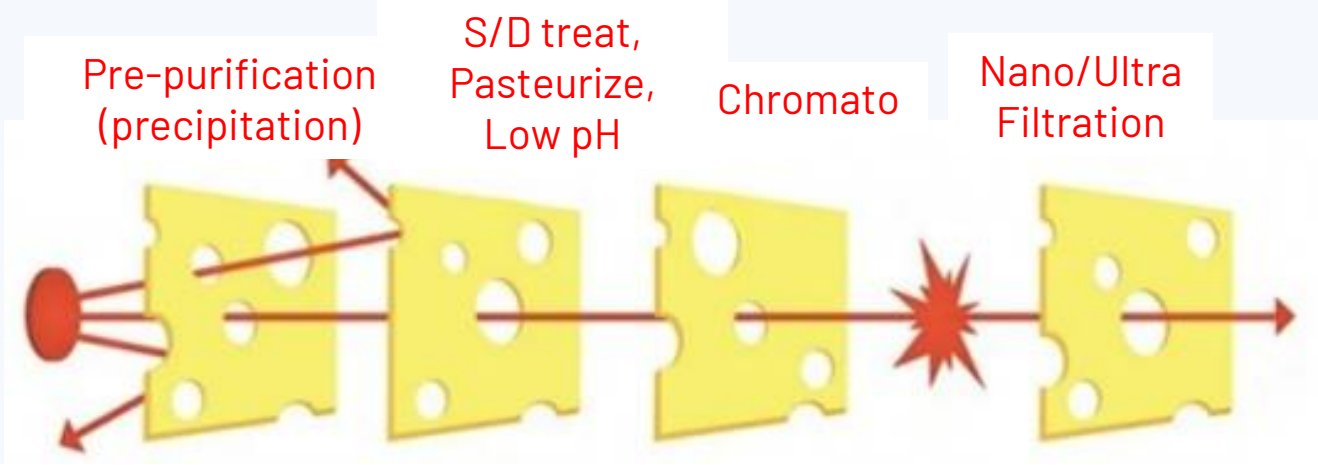


TABLE 2. Virus reduction factors (log) for relevant viruses reported for individual process steps*

	Virus reduction factors (log)									
	Enveloped viruses				Non-enveloped viruses					
	HIV,	HCV model,	HBV model		HAV and model		B19V and model			
Process step evaluated	HIV-1	BVDV	BHV	PRV	HAV	POL	B19V	PPV	CPV	MMV
Lyophilization[17,45]	1.2	1.7	1.3	–	2.1	3.4		–	<1.0	–
Precipitation										
Cryoprecipitation[32]	–	–	–	1.6	1.5	–		–	1.5	–
3.5% PEG precipitation[17]	<1.0	<1.0	<1.0	–	–	3.3		–	1.2	–
$Al(OH)_3$ adsorption/glycine precipitation/NaCl precipitation[32]	3.6	2.4	–	3.7	2.4	–		–	3.4	–
S/D[17,46]	≥11.1	≥4.5	≥8.0	≥8.5	NA	NA		NA	NA	NA
Dry heat[17,45,46]	5.2†	≥4.9‡	2.1‡	4.9§	≥5.8‡	≥2.5‡		4.1§	4.1‡	–
Pasteurization‖[32]	≥6.4	≥8.9	–	4.6	4.2	–	≥3.9		1.1	–
Chromatography[17]	≥2.0	<1.0	7.6	–	–	<1.0		–	<1.0	–
Virus filtration[19,47]	>6.4¶	6.6**	–	>6.0¶	6.8**	–		–	–	≤1.0¶
Vapor heat[19,48]	>6.8	>7.1	–	>7.4	>4.5	–	≥3.5††		–	≤1.0

Klamroth et al. Transfusion 2014

U.S. Donation Screening (per CTS)

Blood Screening

Marker	Test	Vendor	System
Classic Agents	**HIV/HCV/HBV NAT**	Grifols	Panther
	Anti-HIV-1/2 Combo	Abbott	Alinity s
	Anti-HCV	Abbott	Alinity s
	Anti-HBc	Abbott	Alinity s
	HBsAg	Abbott	Alinity s
	Anti-HTLV-I/II	Abbott	Alinity s
	CMV	Fujirebio	PK7400
	Syphilis	New Market Bio.	PK7400
	Syphilis RPR	Arlington	ASI
Vector-Borne Agents	**WNV NAT**	Grifols	Panther
	***Babesia* species NAT**	Grifols	Panther
	Anti-*T. cruzi*	Abbott	Alinity s
Blood Typing	**ABO/Rh**	Diagast	PK7400
	HLA Class I and II	Immucor GTI	Gemini
	RBC Antibody Screen	Immucor	Neo Iris
	Antibody Identification	QuidelOrtho	Vision
Donor Health	**Triglyceride**	Beckman Coulter	AU680
	A1C	Abbott	Alinity c
	Ferritin	Beckman Coulter	AU680

Plasma Screening Assays

Marker	Test	Vendor	System
Classic Agents	**HIV/HCV/HBV NAT**	Grifols	Panther
	Anti-HIV-1/2 Combo	Abbott	Alinity s
	Anti-HCV	Abbott	Alinity s
	HBsAg	Abbott	Alinity s
	Syphilis RPR	Arlington	ASI
	HAV/B19 NAT	Grifols	Panther
	HAV/B19 NAT (recovered)	Roche	c6800
Donor Health	***Serum Protein***	*Sebia*	*Capillarys*
	ALT		

Of Note:

- Regional Babesia screening (14 U.S. states +D.C.)
- HIV/HBV/HCV NAT performed in MP-16
- *T. cruzi* only for first time donors
- Plasma: Quantitative HAV and B19 to limit the amount of virus entering the pool not to exceed the viral inactivation capacity

Safety of Blood Components versus PDMPs



pathogens

Pathogens 2023, 12, 318.

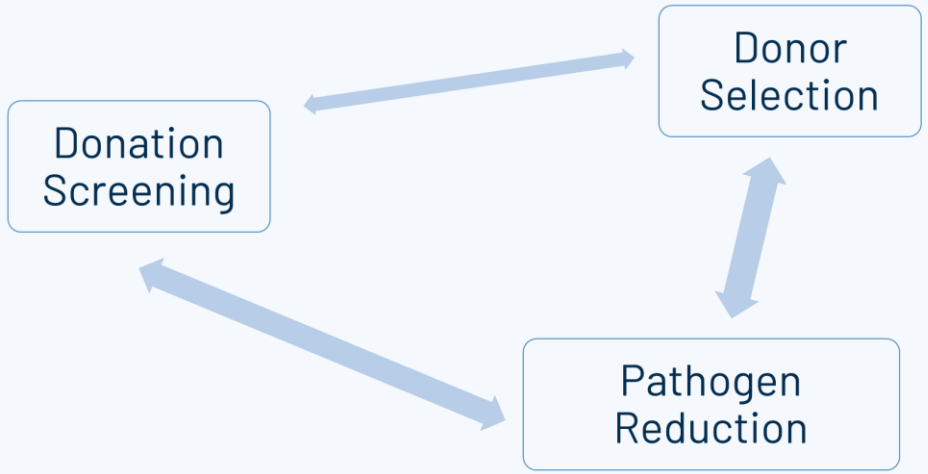
MDPI

Review

The Evolution of the Safety of Plasma Products from Pathogen Transmission—A Continuing Narrative

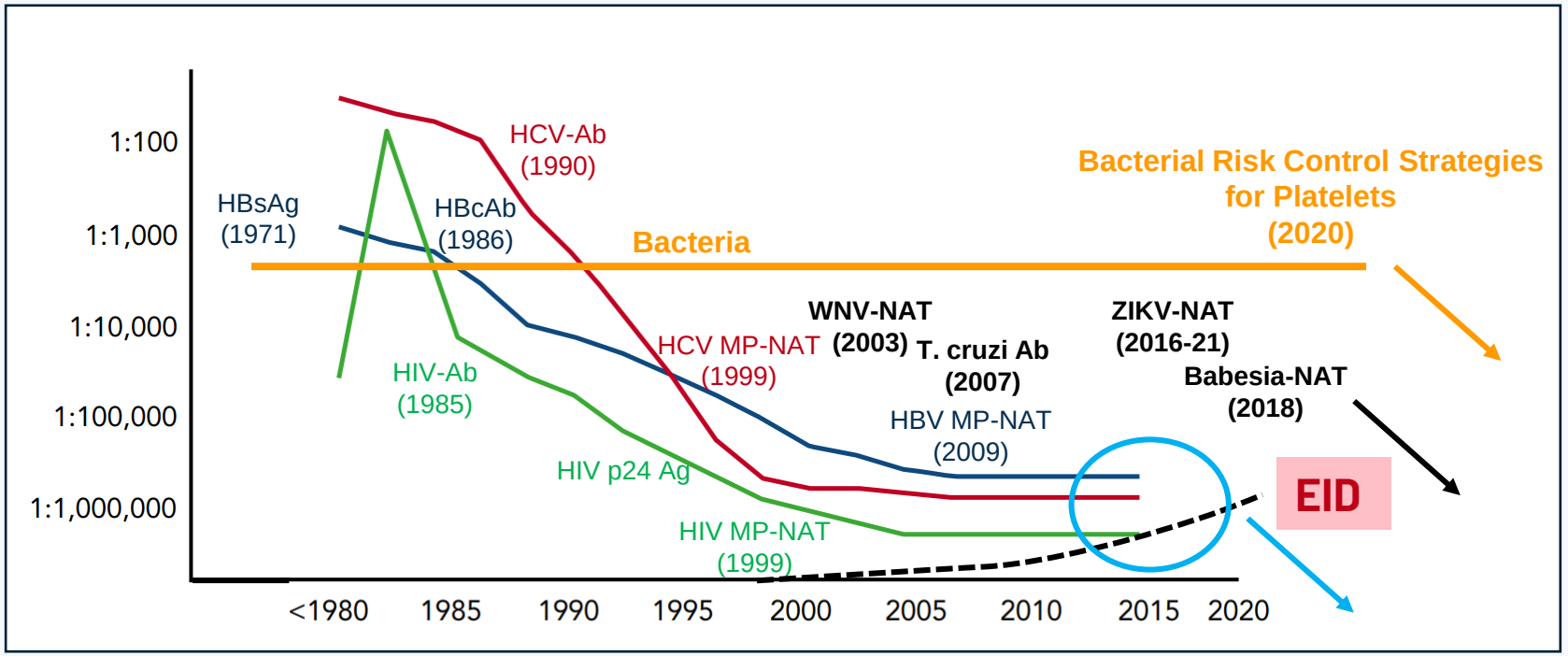
Albert Farrugia

UWA Medical School, Surgery The University of Western Australia, 35 Stirling Highway, Perth 6009, Australia; albert.farrugia@uwa.edu.au



- "In **the concept of "Tripod" of safety measures** – **1) donor selection, 2) donation testing and 3) pathogen reduction**—it is the systematic inclusion of robust pathogen inactivation/removal steps in the manufacturing process which have brought the safety of plasma derivatives to its current status [Turecek 2022].
- In the case of fresh blood components, this fundamental element of the "tripod" is still lacking in most transfusion practices.
- PR uptake has been limited to specific countries, frequently during topical, restricted outbreaks of infectious agents.

Advances in Blood Safety Have Progressively Reduced the Risk of Transfusion-Transmitted Infections

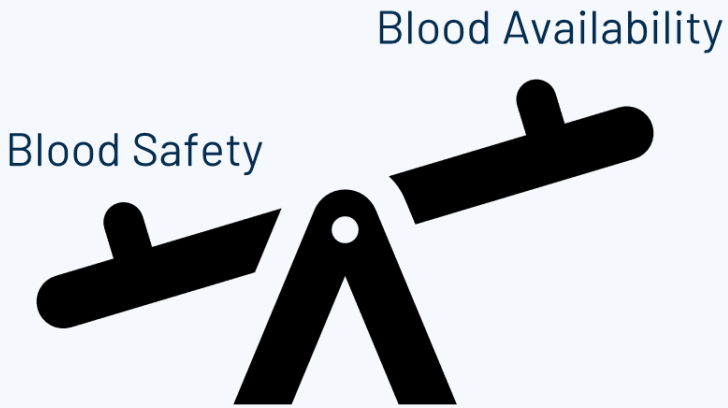


Adapted from Busch Blood 2018

- Blood safety heavily relies on blood screening
- Pathogen Reduction is now part of the tools available
- ✓ Both can be used to ensure blood safety and ***availability***

Redundancy Of Mitigation Strategies

Challenges



Tools



As needed:

- + Add Tests
- + Add PRT

A balancing Act

- Increasing blood availability while maintaining blood safety



- Cost – Benefits - Risk

Increasing Donor Inclusion and Blood Availability While Maintaining Safety

Relaxing/Replacing Sexual Risk Deferrals

Received: 20 February 2024 | Revised: 23 July 2024 | Accepted: 24 July 2024
DOI: 10.1111/trf.17981

TRANSFUSION

ORIGINAL RESEARCH
Donor Infectious Disease Testing

Implementing pathogen reduction technology while discontinuing blood donor deferral criteria for sexual risk behaviors: A simulation study

Marie-Pier Domingue[1,2] | Sheila F. O'Brien[3,4] | Yves Grégoire[1] | Marion C. Lanteri[5,6] | Susan L. Stramer[7] | Félix Camirand Lemyre[2] | Antoine Lewin[1,8]

Abstract

Background: Combining pathogen reduction technology (PRT) with blood screening may alleviate concerns over the risk of transfusion-transmitted infections (TTI) and support changes in blood donor selection to potentially increase blood availability. This study aimed to estimate the residual risk of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) transfusion-transmission in Canada after implementing PRT, while eliminating deferrals for sexual risk behaviors.

Study Design and Methods: A probabilistic approach that combined Bayesian networks with Monte Carlo simulations was used to estimate the risk of transfusing HIV-, HBV-, or HCV-contaminated blood components. Different scenarios were considered to compare the current residual risk after PRT implementation, with and without donor deferral criteria for sexual risk behaviors. Donor profiles and blood component outcomes were simulated based on a literature review including the prevalence and incidence of HIV, HBV, and HCV in the Canadian blood donor population; the use of current blood screening assays; and HIV, HBV, and HCV blood donor viral loads.

Conclusions: This risk model suggests that PRT for platelets and plasma (and eventually for RBCs when available) significantly reduces the residual risks of HIV, HBV and HCV transfusion-transmission and could enable the removal of blood donor deferral criteria for sexual risk behaviors.

Context:

- From MSM deferral to gender neutral selection:
  - <2013 indefinite MSM deferrals
  - 2013-2016: 5 years
  - 2016-2019: 12 months
  - 2019-2022: 3 months
  - >2022: Gender neutral (3 months if anal sex with new multiple partners)
- Canada implemented INTERCEPT™ Blood Systems for Platelets
- Removal of sexual risk questions?

Increased risk of HIV TTI?

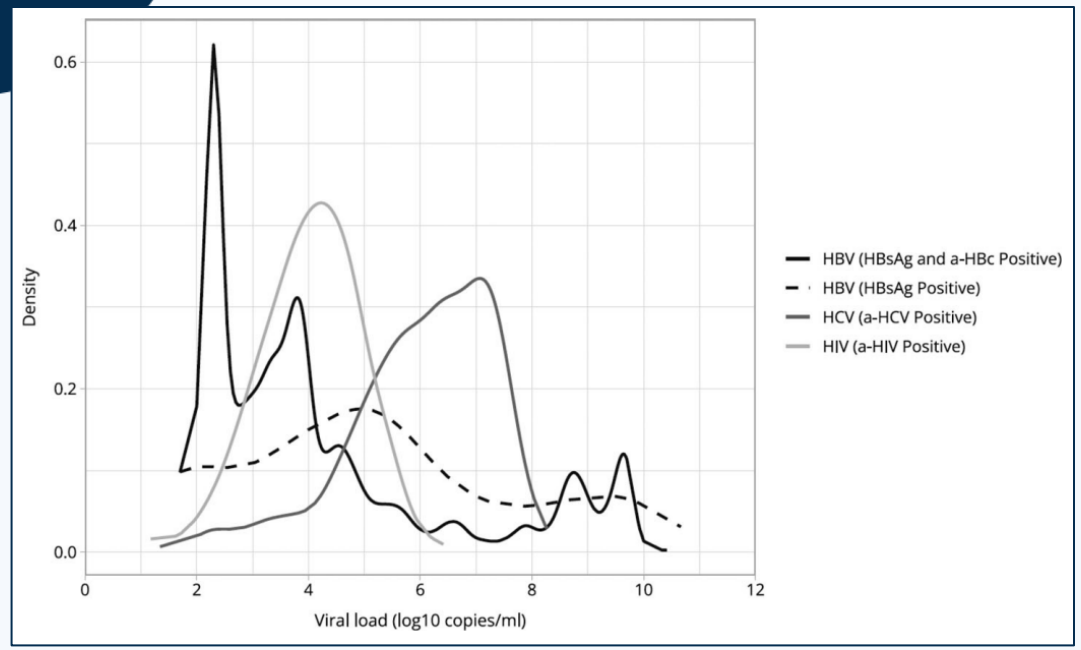
Embarrassing?

Covered by PR?

Retain donors

➢ PRT – An added benefit to eliminate sexual risk behavior questions?
- Probabilistic Risk Model

Risk under [Deferrals + Tests] *vs.* [Tests + Partial PR] *vs.* [Tests + Universal PR]



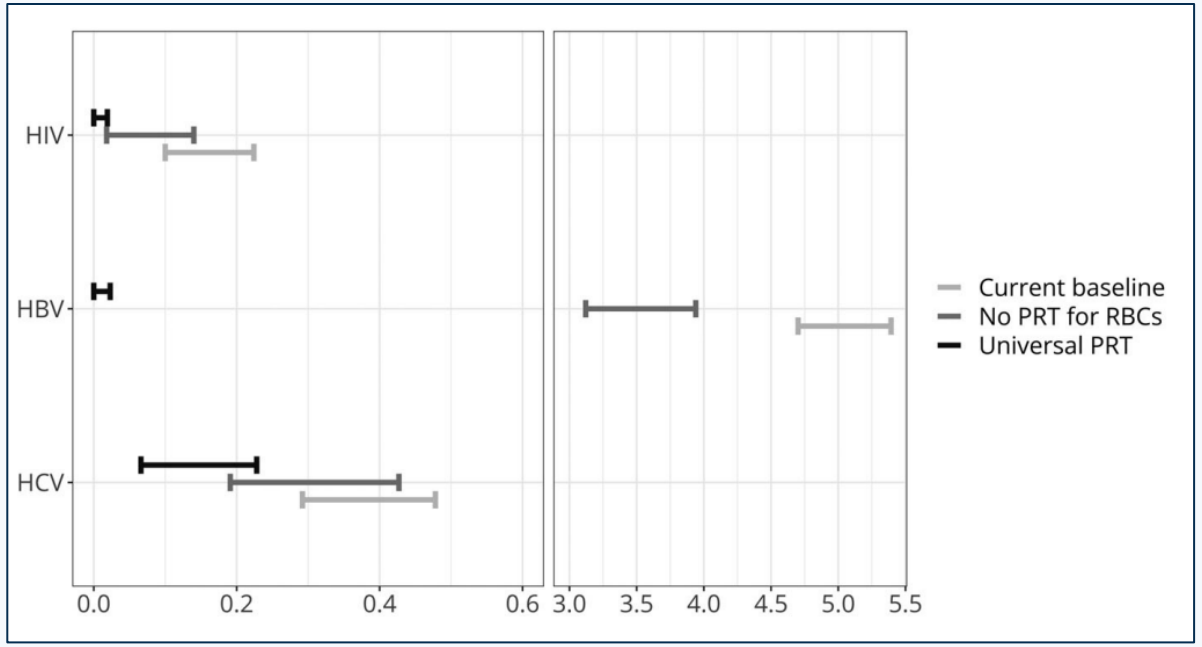


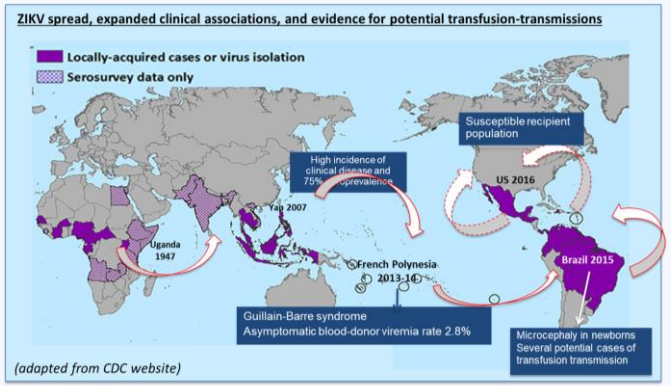
TABLE 5 Risk estimates per million components (95% CI).

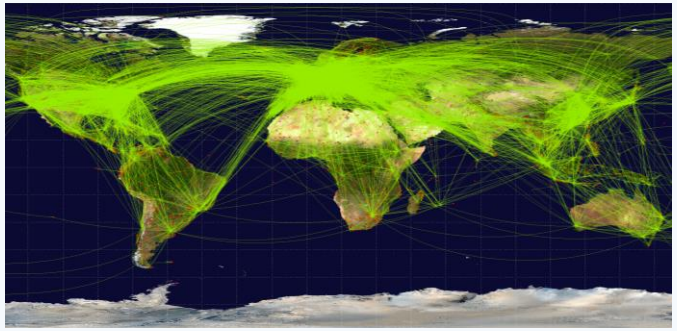
Scenario	Deferral	PRT	HIV	HBV	HCV
Baseline	Yes	No	[0.100; 0.224]	[4.701; 5.393]	[0.292; 0.478]
Universal PRT	No	Yes for plasma, platelets, and RBCs	[0.000; 0.019]	[0.000; 0.023]	[0.066; 0.228]
No PRT for RBCs	No	Yes for plasma and platelets	[0.018; 0.140]	[3.121; 3.940]	[0.191; 0.427]

- PRT – An added benefit to eliminate donor deferrals for sexual risk behavior

The Risk With Mosquito-Borne-Agents

ZIKV Emergence



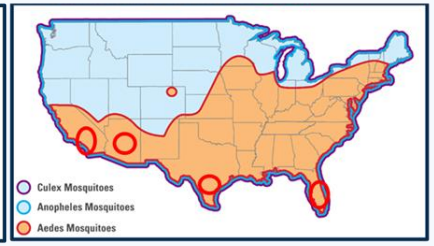


- Outbreaks are unpredictable
- Most probable in vector-endemic areas
  - ✓ Use multiplexed blood screening assays
  - ✓ Use PR for preparedness

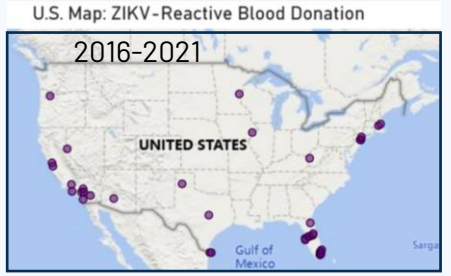
Culex mosquitoes (WNV)



Autochthonous cases of DENV

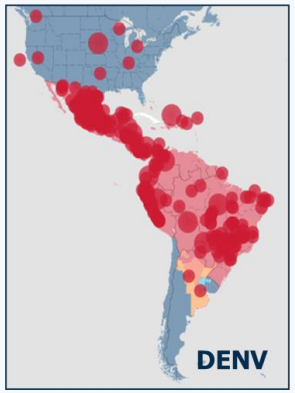


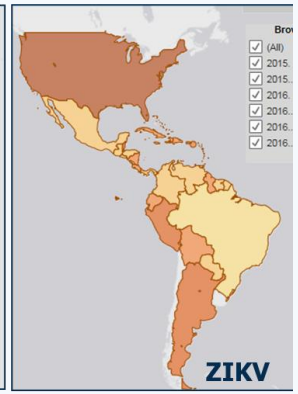
U.S. Map: ZIKV-Reactive Blood Donation

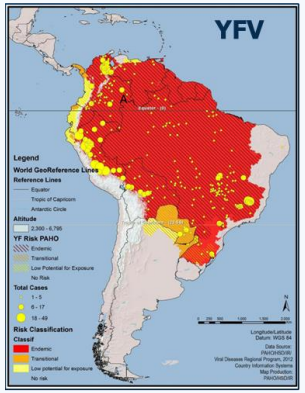


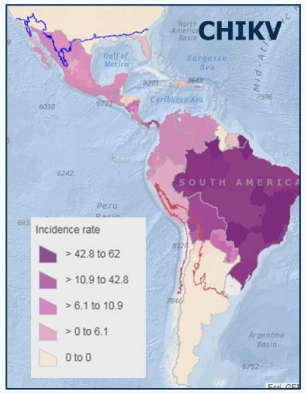
Autochthonous cases of Malaria

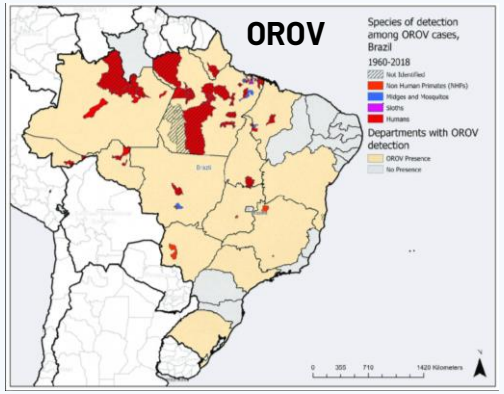


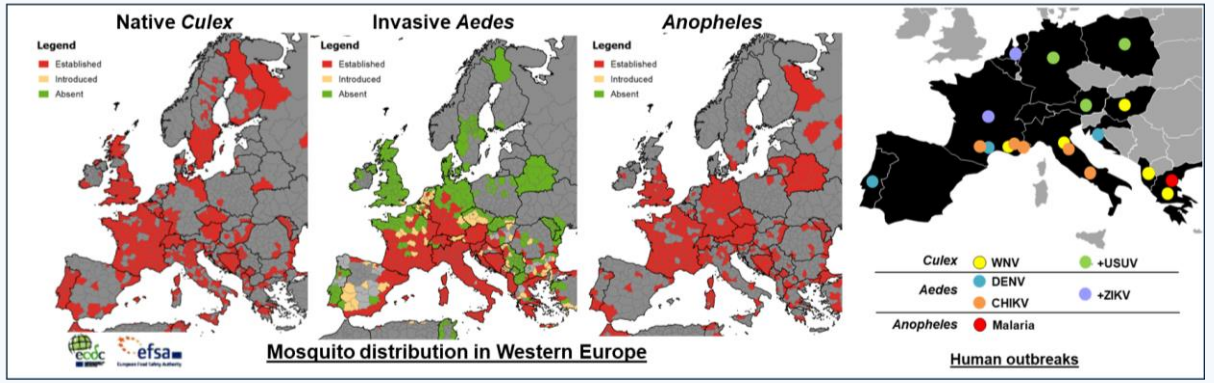












Recommendations to Reduce the Risk of Transfusion-Transmitted Malaria

Draft Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
January 2025

A Balancing Act

Autochthonous outbreaks
Travel to endemic areas:
- Mosquito-borne agents (Malaria, others)

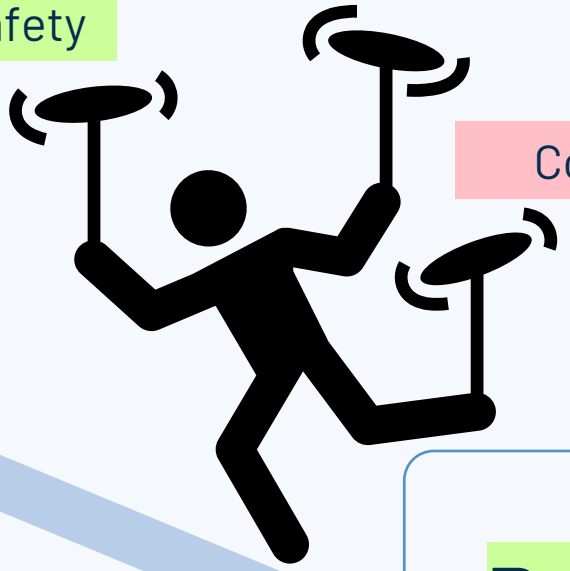
Deferred Donors

Availability

Safety

Cost

Add Tests (Universal)
Add PRT



Remove Deferrals

Cost of Blood

Life Saving Products

- Donor recruitment efforts
- Volunteering or paid donors
- Donor selection process
  - Sexual risk
  - Geography (country of origin, travels)
  - Clinical
- Donation screening (based on TTI risk)
  - Bacteria
  - Viruses
  - Parasites
- Processing/Manufacturing
  - Leukoreduction
  - Irradiation
  - PR
  - Fractionation
- Distribution , shelf-life and inventory

Added Cost

New challenges → New mitigations

- Bacterial risk
  - Culture based screening *vs.* PR
- Undisclosed sexual risk, HIV status, drug intake
  - Undetectable by NAT/Seroreversion
  - + PR
- Climate change and vector distribution
  - Vector-borne agents risk deferrals
  - Multiplexed NAT
  - +New assays *vs.* PR
- EID preparedness
  - Horizon scanning
  - Cost of development
  - Regulatory timeline

Added Benefits

- Add screening assays:
  - Remove some deferrals (Malaria, WNV EU, Babesia)
  - Tests allow for surveillance (multiplexed)
- Add PR
  - Remove donor deferrals (Babesia, Malaria, ZIKV, HIV/HBV/HCV risk)
  - Remove testing (bacteria, Babesia, Malaria, ZIKV)
  - Remove serology testing?
    - NAT+PR?
  - PR covers the risk with EID
- Cost-benefit analysis models
  - Relative cost of blood in the overall treatment protocol (cell therapy patients)
  - Legal implications of TTIs

Risk and Cost-Benefit Analysis Models

Risk estimate

Lancet Planet Health 2025; 9: e304–13

Blood under pressure: how climate change threatens blood safety and supply chains

Elvina Viennet, Melinda M Dean, Jorga Kircher, Karin Leder, Yuming Guo, Phoebe Jones, Helen M Faddy

Climate change substantially threatens public health, including the blood supply chain, which is crucial for medical treatments such as surgeries, trauma care, and chronic disease management. Extreme weather events, vector-borne disease shifts, and temperature fluctuations can disrupt blood collection, testing, transport, and storage, threatening both the safety and sufficiency of blood products. Although studies have highlighted some connections between climate change, transfusion-transmissible infections, and blood safety, there remains a lack of comprehensive understanding of the climate effects on each supply chain stage. In this Personal View, we address the potential climate-driven challenges across the blood supply chain, from donor health to blood component stability, emphasising the importance of proactive measures. To protect the availability and safety of blood supplies in an evolving climate, further research and adaptive strategies are needed to build a resilient blood supply system that can withstand emerging climate-related disruptions.

ELSEVIER

Curr Opin Virol. 2023;63:101377

The natural virome and pandemic potential: Disease X

Philip Lawrence[1,2], Michelle Heung[3], Julia Nave[3], Christoph Henkel[3] and Beatriz Escudero-Pérez[3,4]

Over the last decade, the emergence of several zoonotic viruses has demonstrated that previously unknown or neglected pathogens have the potential to cause epidemics and therefore to pose a threat to global public health. Even more concerning are the estimated 1.7 million still-undiscovered viruses present in the natural environment or 'global virome', with many of these as-yet uncharacterized viruses predicted to be pathogenic for humans. Thus, in order to mitigate disease emergence and prevent future pandemics, it is crucial to identify the global extent of viral threats to which humans may become exposed. This requires cataloguing the viruses that exist in the environment within their various and diverse host species, and also understanding the viral, host, and environmental factors that dictate the circumstances that result in viral spillover into humans. We also address here which strategies can be implemented as countermeasure initiatives to reduce the risk of emergence of new diseases.

Implementing New Tests

Annals of Internal Medicine — ORIGINAL RESEARCH

Screening the Blood Supply for Zika Virus in the 50 U.S. States and Puerto Rico

A Cost-Effectiveness Analysis

W. Alton Russell, MS; Susan L. Stramer, PhD; Michael P. Busch, MD, PhD; and Brian Custer, PhD

Background: In 2016, universal individual donation nucleic acid testing (ID-NAT) of donated blood for Zika virus began in U.S. states and territories.

Objective: To assess the cost-effectiveness of universal ID-NAT in the first year of screening compared with alternatives for the 50 states and separately for Puerto Rico.

Design: Microsimulation that captured Zika-related harms to transfusion recipients, sexual partners, and their infants.

Data Sources: National testing results compiled by AABB and costs, utilities, and outcome probabilities estimated from the literature.

Target Population: Transfusion recipients.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: Universal ID-NAT, universal mini-pool NAT (MP-NAT), and ID-NAT exclusively for components transfused to women of childbearing age. Seasonally targeted strategies in Puerto Rico and geographically targeted strategies in the 50 states were also considered.

Outcome Measures: Costs, quality-adjusted life-years (QALYs), and outcomes.

Results of Base-Case Analysis: In Puerto Rico, MP-NAT exclusively during high mosquito season was cost-effective at $81 123 per QALY (95% CI, −$49 138 to $978 242 per QALY). No screening policy was cost-effective in the 50 states. Universal ID-NAT cost $341 million per QALY (CI, $125 million to $2.90 billion per QALY) compared with no screening in the 50 states.

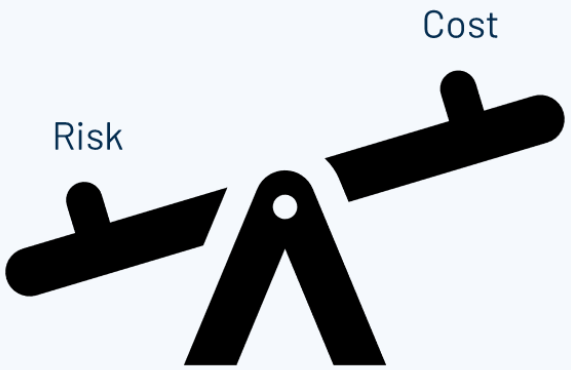
Results of Sensitivity Analysis: In Puerto Rico, MP-NAT only during the season of high mosquito activity was most cost-effective in 64% of probabilistic sensitivity analysis iterations. In the 50 states, no intervention was cost-effective in 99.99% of iterations. Cost-effectiveness was highly dependent on the rate of assumed infectious donations.

Limitation: Data were limited on the component-specific transmissibility of Zika and long-term sequelae of infection.

Conclusion: Screening was cost-effective only in the high mosquito season in Puerto Rico, and no evaluated screening policy was cost-effective in the 50 states. During periods with lower rates of Zika-infectious donations, the cost-effectiveness of screening will be even less favorable.

Primary Funding Source: None.

Ann Intern Med. doi:10.7326/M18-2238 Annals.org
For author affiliations, see end of text.
This article was published at Annals.org on 8 January 2019.



Implementing/Capitalizing on PRT

TRANSFUSION PRACTICE

Cost implications of implementation of pathogen-inactivated platelets

Jeffrey McCullough,[1] Dennis Goldfinger,[2] Jed Gorlin,[3] William J. Riley,[4] Harpreet Sandhu,[5] Christopher Stowell,[6] Dawn Ward,[2] Mary Clay,[1] Shelley Pulkrabek,[1] Vera Chrebtow,[7] and Adonis Stassinopoulos[7]

Received: 16 December 2019 | Revised: 27 April 2020 | Accepted: 15 May 2020
DOI: 10.1111/trf.15926

Check for updates

ORIGINAL RESEARCH — TRANSFUSION

Pathogen reduction of double-dose platelet concentrates from pools of eight buffy coats: Product quality, safety, and economic aspects

Konrad Rosskopf | Wolfgang Helmberg | Peter Schlenke

Received: 16 July 2024 | Revised: 30 August 2024 | Accepted: 9 September 2024
DOI: 10.1111/vox.13740

ORIGINAL ARTICLE — Vox Sanguinis ISBT

Introduction of 7-day amotosalen/ultraviolet A light pathogen-reduced platelets in Honduras: Impact on platelet availability in a lower middle-income country

Marcelo Pedraza[1] | Julio Mejia[1] | John P. Pitman[2] | Glenda Arriaga[1]

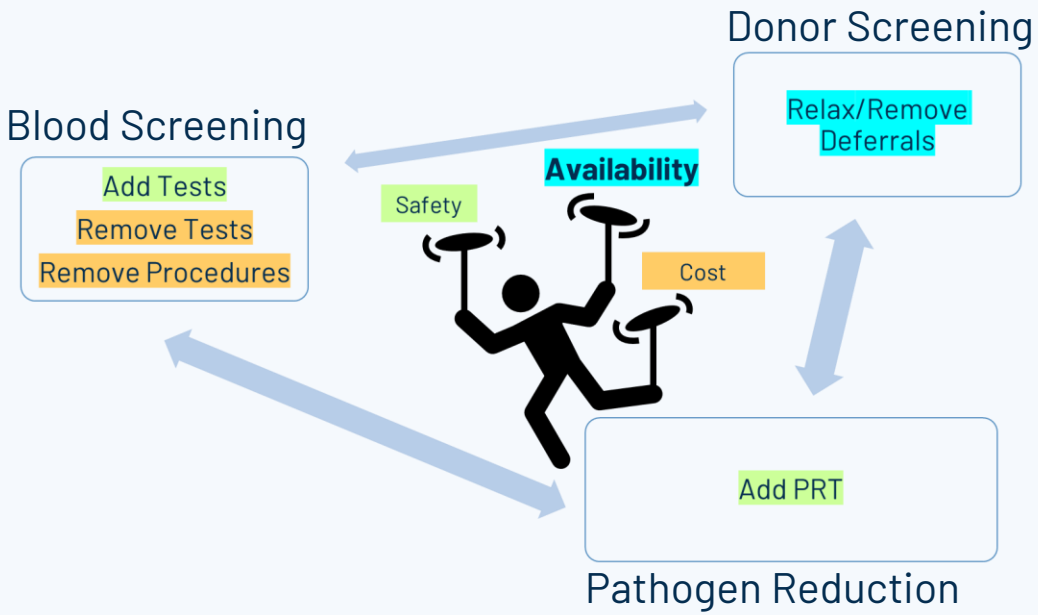
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ORIGINAL RESEARCH — TRANSFUSION
Donor Infectious Disease Testing

Quantifying the impact of a novel virus on the economic value of pathogen reduction technology for platelets

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A Balancing Act



- Blood Safety tripod
- To manage blood safety, availability, and sustainability
- Using the redundancy of measures
- To mitigate the risk under specific operations, geographies
- In resource constraints environment
- Cost considerations → cost benefit analysis models
- Select complementing mitigation strategies
- For maximum cumulative benefits