

Managing Emerging Threats and Unforeseeable Risks to Blood Safety

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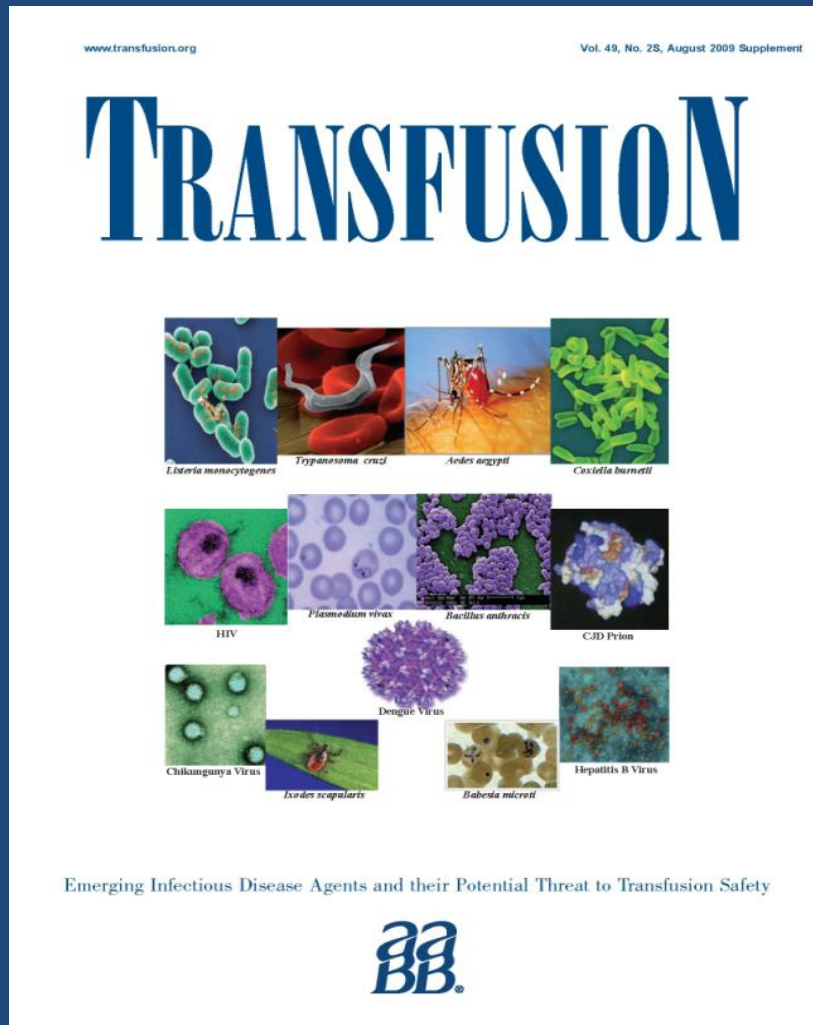
Managing Emerging Threats and Unforeseeable Risks to Blood Safety

- The nature of threats from Emerging Infectious Diseases (EIDs)
- General approach to control of EIDs
- Our safeguards and how well they work
 - Epidemiologically based donor deferrals
 - Donation testing by serology and NAT
 - Product quarantines
 - Steps in collection and processing
- Summary

EID Threats to Blood Safety are Multifactorial in Origin

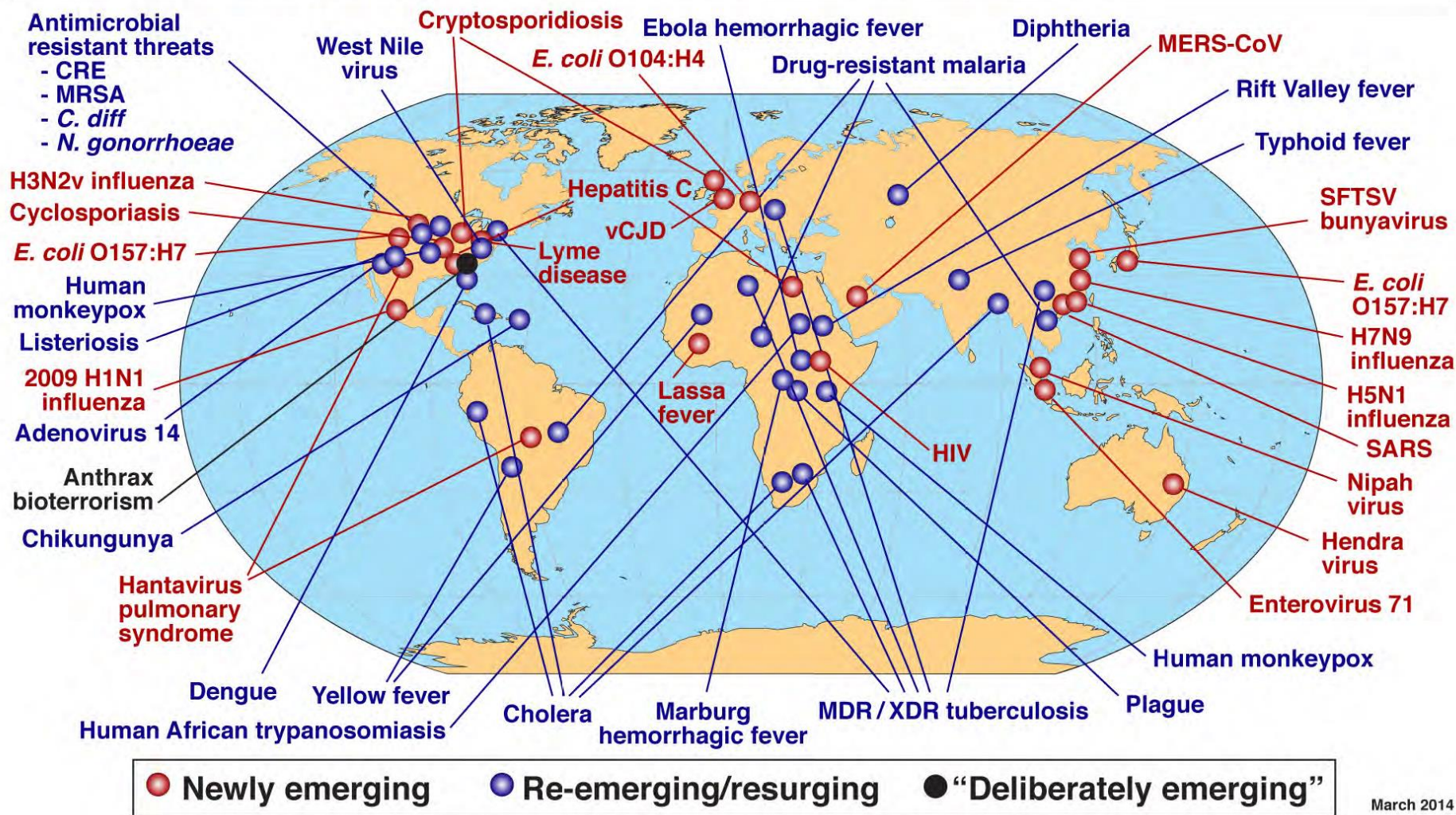
- AABB has identified ~70 blood borne infectious agents that may threaten transfusion safety (See: Transfusion 2009;49:1S-29S.)
- Recent EIDs have been zoonotic in origin, with epidemiology reflecting evolving environmental changes
 - Food exposure: vCJD, HEV
 - Blood exposure to primates: HIV
 - Vector exposure: WNV, T. cruzi, chikungunya virus (CHIKV), Dengue viruses (DV), babesiosis
 - Aerosol exposure: Q fever
- We must address diseases in search of agents (e.g., AIDS; non-A, non-B hepatitis) and blood transmitted agents in search of diseases (e.g., TT virus and other annelloviruses)
 - Newer technologies (e.g. Next Generation Sequencing) challenge us to determine the importance of newly demonstrated agents in blood

Special Issue: Emerging Infectious Disease Agents and their Potential Threat to Transfusion Safety



- BACTERIAL AGENTS
 - 10
- PARASITIC Agents (PROTOZOAN & NEMATODE)
 - 7
- PRION AGENTS
 - 4
- RICKETTSIAL AGENTS
 - 6
- VIRAL AGENTS
 - 42 listed (12 arboviruses)

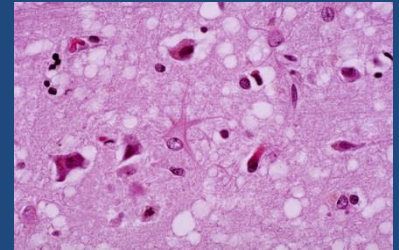
Global Examples of Emerging and Re-Emerging Infectious Diseases



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General Approach to Control of Emerging Infectious Diseases (EIDs) - I

- Types of EID
 - New agents
 - HIV, vCJD
 - Variants of known agents
 - HIV-2, HIV-1 Group O, HIV CRFs
 - Known agents with new epidemiology
 - WNV, CHIKV, DV, C. burnetti (Q Fever)
 - Previously unrecognized agents
 - HEV, HTLV
- Sources of risk
 - Geographical (environmental exposures)
 - Behavioral (MSM, CSW, IDU)
 - Medical (HCV from endoscopy, xenotransplantation)
 - Process related (bacterial contamination)



General Approach to Control of Emerging Infectious Diseases (EIDs) - II

Infrastructures needed to address EIDs

- Surveillance system
- Sentinel monitoring (includes “horizon scanning”)
- Laboratory infrastructure
- Capacity for epidemiological investigations
 - Access to donor blood samples
 - Donor and recipient sample repositories
 - Cohort controlled studies of highly transfused patients
- Risk assessment modeling tools
- Control authorities and mechanisms
- Risk communication skills and venues

General Approach to Control of Emerging Infectious Diseases (EIDs) - III

- Stages of the EID response
 - Epidemiological characterization of the disease and its transmissibility
 - Laboratory characterization of the disease agent
 - Development of options for intervention based on scientific assessments
 - Includes use of formal assessment tools
 - Benefit:Risk is considered in a societal context
 - Implementation of control strategies and risk communication
 - Assessment of impacts and outcomes
 - Policy reexamination and adjustment

Safeguards Against Transfusion Transmitted Infections

- Donor screening and deferral based on donor health and geographical, behavioral and medical risk factors (donor education, self deferral, donor interview)
- Laboratory testing of donations and related donor deferrals
- Use of deferral registries to prevent collection and release of blood from deferred donors
- Aseptic blood collection
- Quarantine controls to prevent release of unsuitable units
- Pathogen reduction in manufacturing
- Good Manufacturing Practices including investigation and correction of deviations

Basic Questions in Assessing Transfusion Safety for an EID

- Is the agent blood borne?
- Is there an asymptomatic period of infectivity?
- Is there a significant prevalence in donors?
- Does the agent survive product processing and storage?
- Can the agent/disease be transmitted by transfusion or transplantation?
- What is the disease attack rate and clinical impact on recipients?

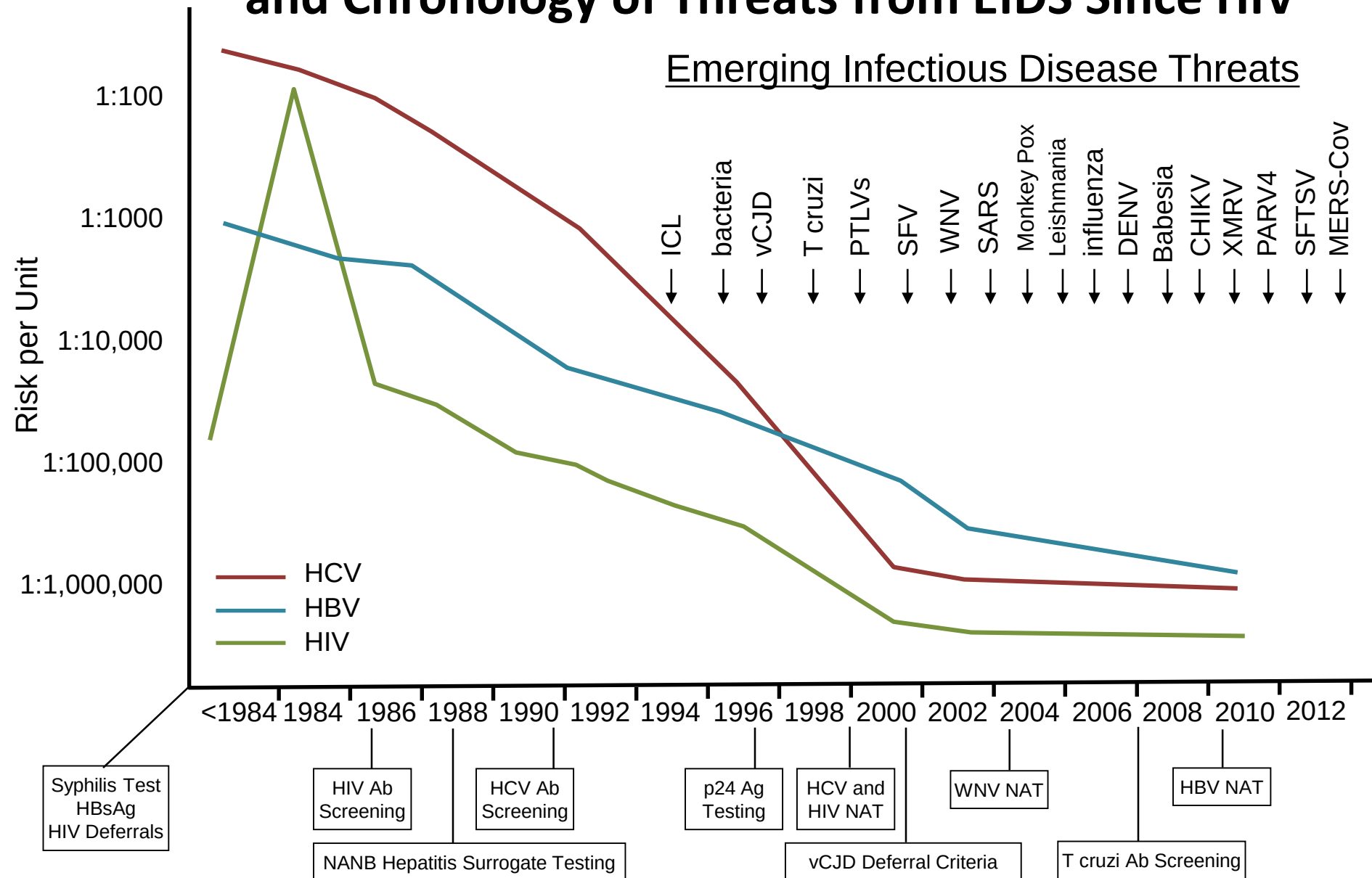
There is a responsibility recognized in many countries to take prudent measures in the face of scientific uncertainties.

Basic Questions Relevant to Potential Safety Interventions for an EID

- Can we screen donors for risk factors?
- Can we test donors for evidence of the infection?
- Are the available tests sufficiently sensitive to provide a meaningful safety benefit?
- Are the available tests sufficiently specific to avoid compromising product availability?
- What will be the medical impact on blood donors?
- Can the system bear the economic and logistic burdens of screening and testing?
- Are there suitable alternative safety strategies?

Decision making needs to be national and/or regional based on differences in epidemiology and consideration of societal factors (e.g. risk acceptance, prioritization and affordability, etc.)

Control of HIV, HBV and HCV Risks in the US Blood Supply and Chronology of Threats from EIDS Since HIV



Effectiveness of Blood Safeguards: Donor Screening and Deferral

Donor screening and deferral have variable effectiveness

- Deferral for HIV behavioral risks reduced AIDS risk ~ 90% before screening and now helps to control window period infections
- Geographic deferrals for BSE exposure reduce vCJD risk by ~80% (unpublished FDA estimate)
- Geographic deferrals for malaria are effective, but can cause large donor losses

Precautionary deferrals of uncertain effectiveness are common

- The reliability of donor questionnaires is not well characterized
- Deferral for fever and headache failed to address risk of WNV
- Risk factors screening for Chagas Disease was shown ineffective
- Traveler and case-contact deferrals have been widely adopted based on theoretical considerations

Effectiveness of Blood Safeguards: Serologic Testing

- Limitations of Serologic Testing
 - Serologic testing is unhelpful in acute infections where infectivity resolves rapidly after seroconversion (WNV, human parvovirus B19), but plays a major role in chronic infections
 - Surrogate testing is a consideration for unknown agents
 - Surrogate testing for non-A, non-B hepatitis by anti-HBc and ALT was ~40% sensitive, but caused large donor losses
 - Specific donation testing for HIV, HCV, and HBV is highly sensitive but clinically significant window period risks exist
 - Syphilis testing has uncertain specific value except for fresh blood, but has potential value as a surrogate for other STDs
 - Tests for HTLV and Chagas Disease are sensitive and specific, but the risks of disease transmission are low
 - Serologic testing for HEV would miss acute infections and cause a large donor loss in most regions

Effectiveness of Blood Safeguards:

Direct Testing for the Agent

- Direct virologic testing is required for detection of acute infections that do not typically become chronic, and to close window periods of serologic testing
 - NAT and/or antigen testing is useful to address serologic window periods for HIV, HCV and HBV due to significant “residual risks” of virus transmission
 - Minipool NAT testing for WNV misses low titer infections, necessitating Individual Donation NAT testing
 - Testing for HAV and human parvovirus B19 helps to assure safety of plasma derivatives, but is controversial as a routine donation test due to low risks from transfusion
- Sensitivity of NAT for parasitic diseases (e.g. malaria, Chagas Disease) is limited by sample volume due to low titer infections and may require a cellular specimen instead of plasma

Effectiveness of Blood Safeguards: “Multiplex” Donation Testing Platforms

- Current donor screening technologies have limitations in regard to number of concurrent analytes, volume sampled and logistics of multiple testing
- Newer technologies are in development for multiple simultaneous (“multiplex”) detection of TTID markers
- Microarrays (DNA/Protein)
 - Nano technology
 - Aptamer technology
 - Open Arrays
 - New Generation Sequencing
 - Nanofluidics
 - New visualization methods
 - Target-capture technology

Effectiveness of Blood Safeguards: Quarantine

- Quarantine pending review of donor and donation records is a safeguard against inadvertent release of unsuitable units
- Strategies to quarantine blood components and release them after additional donor testing or symptom reporting have been effective to prevent some disease transmissions
 - Risks of HIV, HCV and HBV in plasma can be controlled by quarantine of products pending donor retesting after the window period; but, this strategy is not practical for platelets and RBCs due to the shorter shelf lives
 - Risk of chikungunya has been partially reduced by quarantine of collected blood pending recontact of donors to ask about symptoms post-donation

Effectiveness of Blood Safeguards: Steps in Collection and Processing

- Bacterial contamination of platelets is now the leading cause of morbidity/mortality from transfusion transmitted infections in the developed world
 - Risks are partially reduced by improved skin preparation, diversion of the initial collection, and leukocyte removal after warm incubation
 - Significant residual risks can be substantially reduced by bacterial detection using culture based and rapid immunologically based tests and nucleic acid targeted pathogen reduction technologies
- Leukocyte reduction is effective in reducing risks from leukocyte associated agents including HTLV, CMV and vCJD; prion reduction filters may provide an additional safeguard for vCJD

Effectiveness of Blood Safeguards: Pathogen Reduction

- Several pathogen reduction technologies (methylene blue, Solvent/Detergent, caprylate, Intercept, Mirasol) are in use to eliminate risks from enveloped viruses in plasma
- Pathogen reduction technologies that target nucleic acids appear to inactivate most bacteria, viruses and parasites in both plasma and platelets
- Widespread, routine adoption of pathogen reduction for platelets has progressed slowly out of variable concerns related to product quality (safety and efficacy) and cost
 - Limitations exist for bacterial spores, non-enveloped viruses and TSE agents
- Pathogen reduction technologies for Whole Blood and RBCs are still in development

IBS Pathogen Reduction Performance in Platelets Stored in 65% InterSol/35% Plasma

Pathogen	Log ₁₀ Reduction (pfu/mL) ^a
HIV-1 IIIB, cell-associated	≥5.4
HIV-I IIIB, cell-free	≥5.6
HIV-1 Z84 (clinical isolate)	≥3.3
HIV-2 CLB-20 (clinical isolate)	≥2.4
DHBV ^b	≥4.8
BVDV ^c	≥4.4
HTLV-I	4.7
HTLV-II	≥5.1
West Nile virus (WNV)	≥5.7
Cytomegalovirus (CMV)	≥4.9
Chikungunya virus (CHIKV)	≥5.7
Dengue virus (DENV)	≥4.3
Influenza A virus	≥5.9
Calicivirus (model non-enveloped virus)	2.1
Adenovirus	≥4.9
Blue tongue virus (model non-enveloped virus)	4.4

Table from
the IBS
Package
Insert

Variable and Limited reduction of model non-enveloped viruses (poliovirus (data not shown) and calicivirus) implies potential lack effectiveness against HAV, HEV, and parvovirus B19

Pathogen	Log ₁₀ Reduction (cfu/mL) ^a
Gram-Negative Bacteria	
<i>Klebsiella pneumonia</i>	5.8
<i>Escherichia coli</i>	≥6.3
<i>Serratia marcescens</i>	≥6.7 ^b
<i>Pseudomonas aeruginosa</i>	≥3.9
<i>Salmonella choleraesuis</i>	6.2
<i>Enterobacter cloacae</i>	5.5
<i>Yersinia enterocolitica</i>	≥5.9
Gram-Positive Bacteria	
<i>Staphylococcus epidermidis</i>	≥6.1
<i>Staphylococcus aureus</i>	≥5.4
<i>Listeria monocytogenes</i>	≥6.3 ^b
<i>Corynebacterium minutissimum</i>	≥5.3
<i>Streptococcus pyogenes</i>	≥6.8 ^b
<i>Bacillus cereus</i> (vegetative)	≥5.5
<i>Bacillus cereus</i> (spore forming)	3.7 ^b
Anaerobic Gram-Positive Bacteria and Spirochete Bacteria	
<i>Bifidobacterium adolescentis</i>	≥6.0
<i>Propionibacterium acnes</i>	≥6.5
<i>Clostridium perfringens</i> (vegetative)	≥6.5
<i>Lactobacillus species</i>	≥6.4
<i>Treponema pallidum</i>	≥6.4
<i>Borrelia burgdorferi</i>	≥6.8

IBS Bacterial Reduction Performance in Platelets
(Table from Package Insert)

Bacterial spores are resistant to inactivation; safety margin could be low if organisms grow to high titer before IBS treatment

IBS Pathogen Reduction Performance in Platelets Stored in 65% InterSol/35% Plasma

Pathogen	Log ₁₀ Reduction (pfu or cfu/mL) ^a
<i>Plasmodium falciparum</i>	≥5.6
<i>Babesia microti</i>	≥4.9
<i>Trypanosoma cruzi</i>	≥5.3
<i>Leishmania mexicana</i> (metacyclic promastigote stage)	≥5.0

Table from IBS Package Insert

Pathogen reduction technology offers a theoretical advantage over direct detection of parasitic agents due to the limitations of sampling for agents that may be present in blood only at low titer.

Summary - I

- General strategies to address EIDs have had variable effectiveness based on the pathogenesis and epidemiology of the disease agent
- Early interventions with partial effectiveness warrant consideration pending advancement of scientific knowledge
- There is no one-size-fits-all solution to emerging and unforeseeable threats from EIDs!
- Response and prevention for emerging threats and unforeseeable risks continues to require a systematic and flexible approach

Summary – II

- Multiplex testing of TTID analytes may decrease the number of tests, reduce the required sample volume and simplify the logistics of donation testing
- Leukocyte reduction is known effective against some agents and may add a safeguard against a leukocyte associated EID
- Pathogen reduction technologies targeting nucleic acids address several limitations of current screening and testing (e.g. window periods, assay insensitivity) and add a precautionary dimension to control of some potential EIDs
 - Pathogen reduction technologies are not yet available for Whole Blood or RBCs

References

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