

The Safety of the Blood Supply — Time to Raise the Bar

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Existing and emerging pathogens including viruses, bacteria, protozoa, and prions continue to threaten the safety of the blood supply. Blood-collecting facilities, including community and hospital blood banks, have typically relied on a reactive approach to these threats, developing and implementing screening tests after potential pathogens are identified. During this often slow and laborious process, pathogen transmission through transfusion is inevitable. The Food and Drug Administration (FDA) recently approved three new pathogen-reduction technologies (see table). These systems are capable of inactivating a wide variety of pathogens in donated blood components, potentially eliminating threats — including some for which no other intervention exists. We believe the FDA should mandate a proactive approach, ensuring ongoing blood safety by requiring treatment of blood components by approved pathogen-reduction technologies.

One of the newly approved systems treats plasma by using a solvent and detergent to dissolve lipid membranes, thereby rendering pathogens noninfectious. Another technology, approved for treatment of plasma and platelets, uses a psoralen compound, amotosalen, which binds and cross-links nucleic acids when exposed to ultraviolet A (UVA) light. A third technology using ultraviolet light and riboflavin (vitamin B₂) is being tested in trials. Numerous studies demonstrate little substantive negative

effect from pathogen reduction on plasma proteins or platelets. Hemoglobin absorption of UVA light prevents treatment of red cells with current pathogen-reduction technologies, but alternatives are in development.¹

In 2008, the Advisory Committee on Blood and Tissue Safety and Availability (which advises the secretary of health and human services) determined that “accumulating evidence for the efficacy and safety of pathogen reduction warrants a commitment and concerted effort to add this technology as a broadly applicable safeguard.”² Yet despite data supporting the efficacy of such technologies in reducing or eliminating transfusion-transmitted pathogens, no mandate exists for their use.

The FDA has committed to releasing draft guidance in 2015 allowing men who have sex with men to donate blood after a 1-year period of sexual abstinence. Some observers have expressed concern that this change may increase the risk of transfusion-transmitted infections, despite current testing protocols. Use of pathogen-reduction technologies may mitigate these concerns by introducing an additional layer of safety. Similarly, bacterial contamination and associated septic transfusion reactions — a serious threat to platelet recipients since platelets are stored at room temperature, which favors bacterial growth — could most likely be eliminated through the use of licensed pathogen-reduction technologies.

Currently, blood-collecting fa-

cilities voluntarily test platelet units for contamination using FDA-approved culture techniques. Nevertheless, clinical sepsis is reported after 1 in every 100,000 platelet transfusions, and 1 in every 3000 units harbors clinically relevant bacterial concentrations. To address this substantial risk, the FDA recently released draft guidance requiring pre-release platelet screening for bacterial contamination and encouraging enhanced bacterial testing by hospitals (i.e., on the day of platelet transfusion), owing to the high false-negative rate during early screening (www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm). Because of cost and logistic considerations, such recommendations will probably not be adopted unless they are mandated.

Current reactive screening for pathogens is limited by its failure to detect low levels of known transfusion-transmitted agents (e.g., human immunodeficiency virus [HIV] and hepatitis B and C viruses) soon after infection, during the so-called window period. Transfusion-transmitted HIV and hepatitis occur at rates of approximately 1 per 1 million units of transfused blood components. The use of pathogen-reduction technology would inactivate these viruses in blood components with low viral loads, closing the window period. A review of cases from countries with safeguards similar to those in the United States showed that 6 of 15 HIV transmissions and 12 of 19 hepatitis B virus trans-

Pathogen-Reduction Technologies Approved and in Development in the United States and Europe.*				
Component and Source	Manufacturer and Technology	Treatment Process	Manner of Inhibiting Replication	Regulatory Status
Platelets				
Individual volunteer donors	Cerus Intercept Blood System	Psoralen (amotosalen) and UVA light exposure	Formation of DNA and RNA monoadducts and cross-linkage	FDA approved; CE marked
	Terumo BCT Mirasol Pathogen Reduction Technology (PRT) System	Riboflavin and ultraviolet light exposure	Direct DNA and RNA damage and guanine modification	Phase 3 study planned in the United States; CE marked
	Macopharma Theraflex ultraviolet platelets	UVC light exposure	Direct DNA and RNA damage and thymine dimer formation	CE marked
Plasma				
Pools of volunteer and paid donors	Octapharma Octoplas	Plasma pools treated with solvent, tri- <i>n</i> -butyl phosphate and detergent (octoxynol)	Lipid membrane disruption of enveloped viruses	FDA approved; CE marked
Individual and minipools of volunteer donors	Cerus Intercept Blood System	Psoralen (amotosalen) and UVA light exposure	Formation of DNA and RNA monoadducts and cross-linkage	FDA approved; CE marked
Individual volunteer donors	Macopharma Theraflex MB Plasma System	Filtration, methylene blue treatment and visible light exposure	DNA and RNA damage by type I and type II redox reactions	CE marked
	Terumo BCT Mirasol PRT System	Riboflavin and ultraviolet light exposure	Direct DNA and RNA damage and guanine modification	CE marked
Whole blood				
Individual volunteer donors	Terumo BCT Mirasol PRT System	Riboflavin and ultraviolet light exposure	Direct DNA and RNA damage and guanine modification	Phase 3 studies planned in the United States, completed in Africa
Red cells				
Individual volunteer donors	Cerus Intercept Blood System	Frangible Anchor-Linker Effector (S303) and glutathione	Formation of DNA and RNA monoadducts and cross-linkage	U.S. phase 2 and European phase 3 studies complete

* The downsides of pathogen reduction vary by technology and include relative loss of component yield and reduced functionality, unknown residual infectivity of agents with pathogen loads that exceed validated inactivation efficacy, and resistance by certain pathogens (e.g., non-enveloped viruses, for certain technologies, and spore-forming bacteria). Short-term and long-term clinical adverse events have not been reproducibly documented. A listing of countries using each technology is available at www.aabb.org/tm/eid/Pages/pathogen-reduction-systems.aspx. CE (Conformité Européenne) denotes compliance with requirements in the European Union, FDA Food and Drug Administration, UVA ultraviolet A, and UVC ultraviolet C.

missions in which the component type was documented were linked to platelets or plasma collected during the window period.³ Current estimates suggest that these reported cases represent a small fraction of actual transmissions.

In the past 15 years, blood centers have implemented numerous screening tests in response

to transfusion threats. However, pathogens continue to emerge, and each incident calls transfusion safety into question. Potential threats include, but are not limited to, Ebola, dengue, chikungunya, hepatitis E, pandemic influenza, and SARS (severe acute respiratory syndrome) viruses. During the recent epidemics of dengue and chikungunya in the

Caribbean, approximately 1 in every 500 blood donations was shown to contain viral RNA.^{4,5} Proactive pathogen reduction for platelets and plasma may defuse many emerging threats; with appropriate investment, we should someday be able to do the same for red cells. Continued use of a reactive approach to addressing each threat is not viable. With

the use of pathogen-reduction technologies for platelets, plasma, and red cells, new screening tests would be needed only for pathogens that lack susceptibility to these techniques or that are present at concentrations exceeding the capacity of these techniques.

Critics believe that a policy mandating this process would increase the already high costs of donation screening. But with the adoption of pathogen-reduction techniques, certain screening tests, along with their costs, could be eliminated. Current users of this technology consider the resulting products to be safe with respect to bacteria, cytomegalovirus, and graft-versus-host disease, eliminating the need for

validation, and licensure. Blood centers that implement a new assay will typically not be able to recover the cost from hospitals until, often years later, the FDA decides to require testing by all centers.

Blood management and utilization programs ensuring that blood is used only when needed and in the smallest quantity possible have become widespread, but their adoption is a double-edged sword. Blood centers are facing a 20% decline in blood use, which translates into decreased cost recovery. Consequently, centers are downsizing infrastructure, reducing staff, closing facilities, and merging to remain fiscally sound. Individual centers are unable to absorb the

finding it increasingly difficult to change practice by setting new standards that increase cost, without changes in reimbursement. Diagnostics manufacturers no longer view developing tests for voluntarily donated blood as commercially viable, since uncertainty regarding the scope of testing and testing mandates creates untenable investment risks. However, the ongoing safety of the U.S. blood supply relies on industry innovation, including the development of conventional screening assays, highly multiplexed testing platforms (e.g., next-generation sequencing and microarrays), and pathogen-reduction technologies.

The historical process of reactive, pathogen-specific test development is not sufficient to protect patients. The time has come for proactive pathogen reduction. Only the federal government can drive adoption by mandating universal implementation of available technologies. This mandate should be supported by a reimbursement process that recognizes the benefits of proactive strategies and offsets the costs. In addition, we believe that pathogen reduction for red-cell components should become a national research priority. We now have the means to protect patients from existing and emerging blood-borne threats — all we need is the will.

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bacterial detection, cytomegalovirus screening, and irradiation. Critics also raise concerns about the safety of adding chemicals to blood products, but few published reports have linked pathogen reduction to adverse events, and to date, no such finding has been reproducible.

Implementing new or improved technologies for bloodborne pathogens is difficult in an increasingly cost-constrained health care environment. Under the current approach, recognition of a transfusion-transmitted pathogen triggers the diagnostics industry to invest in assay development,

additional costs of implementing new blood-safety interventions unless they are reimbursed by hospitals. Hospitals are not directly reimbursed for blood products and will purchase blood from the lowest-cost provider. All these factors inhibit the pursuit of safety innovations. Hospitals seeking to ensure their own fiscal solvency often view unmandated safety innovations as research they are not obligated to subsidize, an attitude that results in variable adoption of safety innovations and inconsistent safety standards.

Accrediting associations are

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