CONFERENCE REPORT

Pathogen inactivation: making decisions about new technologies

Report of a consensus conference

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Methods to remove and inactivate pathogens, used extensively in the manufacture of plasma protein fractions, have all but eliminated transmission of infectious agents by these products.[1] Technologies for reducing the risk of infection from single donor blood components have not been embraced as enthusiastically. Several methods have been introduced in Europe. Treatment with solvent/detergent (S/D) or methylene blue have both been applied to plasma components, and psoralen treatment of platelets (PLTs) has begun in several countries.[2-4] Although S/D-treated pooled plasma has been approved for use in the United States and Canada, none of these methods has been adopted for single-donor products in North America. Reasons for slow acceptance include 1) the current safety of the volunteer blood supply; 2) the success of surveillance and development of screening tests to deal with emerging pathogens; 3) the inability of current technologies to inactivate some agents such as spores, prions, and certain small nonencapsulated viruses; 4) concerns regarding remote risks from the residual chemical agents used during the pathogen inactivation (PI) process; 5) absence of any single method to treat whole blood or all components; and 6) the cost-effectiveness of these technologies especially compared to strategies to reduce noninfectious risks of transfusion.[5] The Canadian Blood Services and Héma-Québec, with support from the Biomedical Excellence for Safer Transfusion (BEST) Collaborative, organized a consensus conference entitled, "Pathogen Inactivation: Making Decisions About New Technologies," in Toronto, Ontario, Canada, March 29 through 30, 2007, to provide recommendations and guide decision-making in this area. The term "inactivation" was intended to include methods that reduce pathogen risk by any means, including physical removal.

The conference format was based on the model developed by the National Institutes of Health.[6] The steering committee was aware of the potential weaknesses of the consensus process and made every effort to minimize selection bias, particularly with respect to the choice of questions and panelists.[7] The Consensus Panel, selected by the steering committee, had been provided background materials regarding transfusion risk and PI technology as well as a series of six questions designed by the committee to focus debate on the major issues involving pathogen reduction of blood components. The Panel convened immediately before the conference to clarify objectives, principles, and roles. On the first conference day, invited experts made formal presentations on a variety of relevant topics including transfusion risks, inactivation technology, toxicology, regulatory approaches, risk analysis, and cost-benefit considerations. An open forum audience of approximately 270 international attendees participated. The audience and the nine-member independent Consensus Panel, which included a wide range of disciplines (transfusion medicine, hematology, epidemiology, microbiology, toxicology, critical care medicine, medical policy, and ethics) as well as a chronic transfusion

ABBREVIATIONS: PI = pathogen inactivation; WNV = West Nile virus.

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TABLE 1. Risk per unit of selected transfusion-transmitted pathogens

Pathogen	Component	United States	Canada	Europe
HIV	All	1:2,000,000	1:7,800,000	1:900,000-5,500,000*
HCV	All	1:2,000,000	1:2,300,000	1:2,000,000-4,400,000*
HBV	All	1:277,000	1 in 153,000	1:77,000-1,100,000*
WNV	All	1:350,000	Rare	No reported cases
HTLV-I and/or -II	RBCs and/or PLTs	1:3,000,000	1:4,300,000	Not tested
Bacterial transmission	RBCs	1:40,000-1:5,000,000		
Bacterial sepsis	PLTs	1:59,000 single-donor	1:41,000 single-donor	1:11,000 (pooled)
Malaria	RBCs	1:1,000,000-1:5,000,000	Three cases in 10 years	11 cases in 10 years

* Variation between low and medium endemic areas. Modified from Bihl et al.[21]

recipient had an opportunity to question the presenters and add comment. The Consensus Panel reconvened in the evening to address the conference questions and prepare recommendations that could be applied both in Canada and internationally. On Conference Day 2, the Panel's draft statement was presented in its entirety to the experts and the audience for public comment. The Panel finalized the statement within a few weeks of the conference. A preliminary report has been published.[8]

This final Consensus Panel report is based on the information provided to the panelists before and during the conference, a review of background literature, and continued postconference discussion. The Panel by intent did not address advantages, disadvantages, current status, or cost of specific inactivation and/or reduction technologies or commercial products, although data regarding several technologies and trials were provided as background reading and presented at the conference. Several published summaries are available.[5,9-11] The conference questions and conclusions are summarized below.

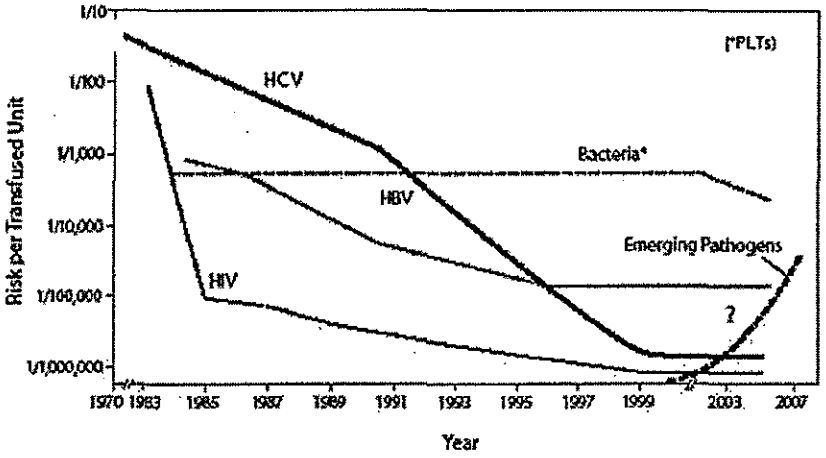

Fig. 1. Risks of transfusion-transmitted infections in the United States. Risk per unit transfused.

IS THE CURRENT RISK OF TRANSFUSION-TRANSMITTED DISEASES ACCEPTABLE IN RELATION TO OTHER RISKS OF TRANSFUSIONS?

Dramatic advances in the safety of allogeneic blood transfusion have been made during the past quarter of a century. At present, the estimated residual risk of transmission through transfusion of human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), and human T-lymphotropic virus (HTLV) in Canada is, respectively, 1 in 7.8 million donations, 1 in 2.3 million donations, 1 in 153,000 donations, and 1 in 4.3 million donations.[12] Risks still vary substantially even between low-endemic and high-endemic areas around the world (Table 1). For example, the residual risk of HBV per million blood donations is calculated to be 0.75 in Australia, 3.6 to 8.5 in the United States, 0.91 to 8.7 in Northern Europe, 7.5 to 13.9 in Southern Europe, and up to 200 in Hong Kong.[13-20] Nevertheless, the strategy of donor screening, testing, and deferral has proved remarkably successful in reducing the risk of transmission of the major viral pathogens (Fig. 1).[21]

Bacterial contamination of blood components was among the first recognized risks of transfusion.[22] The introduction of sterile interconnected plastic container systems and controlled refrigeration of blood components seemed to eliminate this risk by the 1960s; however, this conclusion proved illusory. Contamination of PLTs, the blood component stored at room temperature and therefore most susceptible to microbial growth, has been reported between 1 in 2000 and 1 in 5000 PLT collections (active surveillance in the United States) before the implementation of bacterial testing of PLTs, and bacterial sepsis has occurred on the order of 1 in 41,000 transfusions (voluntary reporting in Canada) after the introduction of screening cultures.[23-25] In the United States the frequency of septic reactions from single-donor (apheresis) PLTs before routine culture has been measured at 1 in 15,000 infusions.[26] Introduction of routine "in-process" culture of

PLTs has reduced the risk by about 50 percent. The American Red Cross now reports a residual risk of a septic transfusion reaction from a culture-negative single-donor unit at 1 in 50,200 (20 reported cases of sepsis including 3 fatalities associated with 1,004,000 single-donor PLT components tested).[27] These results are consistent with the Canadian experience. During the same period (2004-2006), septic transfusion reactions from whole blood–derived PLTs that were released without culture approached 1 in 33,000 (30 reported cases of sepsis in 1 million whole blood–derived PLT components released).[28]

Although Chagas disease, babesiosis, and West Nile virus (WNV) have been recent transfusion threats in the United States and Canada, published transmissions of other pathogens, such as hepatitis E and other viruses, other parasites, or prions that result in clinically important illness are very uncommon in the developed world.[21,29-31]

Hemovigilance data from developed countries suggest that the recognized noninfectious risks in aggregate are substantially higher than the current infectious risks of transfusion.[32] Transfusion-related acute lung injury (TRALI), which claims an estimated 50 to 100 lives in the United States each year, has been cited as the most frequent transfusion-related cause of death.[33,34] Acute transfusion reactions resulting from mistransfusion are fatal in about 1 in 1 million transfusions.[35] The frequency of acute and delayed hemolysis alone far exceeds that of clinically important pathogen transmission.[32] Based on the relatively low rates of existing infectious transfusion-related complications alone, the Panel does not recommend immediate introduction of PI with its attendant unknown risks. Even active surveillance, however, cannot estimate the risk of an emerging transfusion-transmitted pathogen. The Panel recognizes that such agents have been detected in blood donors at an increasing rate since the HIV epidemic.[36] The reactive strategy of surveillance, identification, test development, and screening permits a pathogen to disseminate widely even before clinical disease is recognized as was the case with HIV.[37] Furthermore, estimates presented at this conference by Dr Harvey J. Alter suggest that as many as 4.8 million cases of hepatitis, with an ensuing 768,000 cases of cirrhosis, resulted from transfusion in the 1970s and 1980s before a specific test for HCV was introduced. In addition to causing morbidity and mortality, the emergence of new pathogens also undermines public confidence in the blood supply. The Panel believes that such risks require a proactive approach in accordance with the precautionary principle (when facing public health threats for which the outcome can reasonably be predicted based, for example, on similar past issues, the precautionary principle dictates a risk assessment [which compares possible consequences of the action against the consequences of no action, according to available evidence and the rules of science], that favors a proactive approach, taking into account society's expectations that responsible actions be taken to circumscribe the threat. Under such circumstances, risks assessment that would favor inaction could be argued to be irresponsible and unethical, putting the public safety and the safety of future generations at greater risk. The active form of application of the principle places the burden of proof on those who propose a restrictive measure), which provides for a distinctive way of making decisions for managing serious threats to public health where there is scientific uncertainty to meet society's expectations that risks be addressed.[38,39]

If so, under what new circumstances should PI be implemented?

Given the recognition of transfusion-transmitted agents that are entering the blood supply and the risk of emerging infectious threats, the Panel believes that PI should be implemented when a feasible and safe method to inactivate a broad spectrum of infectious agents is available.

The Panel acknowledges that noninfectious hazards of transfusion can entail serious safety issues and deserve specific consideration. Blood services should direct attention to, and supply the necessary resources for, their resolution. For example, existing technology can provide a unified database for the patient's transfusion history, so that multiple collaborating hospitals could access patient blood type, antibody history, reactions to transfusion, and special transfusion needs in real time; one such system is operating in Quebec. Bedside bar-code systems and other technologic solutions have been introduced to improve positive patient identification and reduce transfusion errors.[40,41] The risk of TRALI can be reduced by excluding high-risk donors, limiting plasma use, and developing screening test technology.[34] All of these strategies are currently underfunded and underdeployed. A cost estimate by Dr Sunny Dzik presented to this conference, however, suggested that substantial risk reduction in TRALI and hemolytic transfusion reactions could be accomplished for $14 to $28 per unit, a sum that would raise the cost of blood in the United States by less than 10 percent (Table 2). Introduction of PI technology should not preclude vigorous efforts to reduce these noninfectious risks.

Should the criteria be the same for red cells, PLTs, and fresh-frozen plasma?

The same criteria of safety, feasibility, and efficacy should apply to all blood components. A single method for inactivating pathogens in all blood components would be ideal. No such system is likely to be introduced in the foreseeable future. The absence of an integrated system, however, does not imply that PI of any one component should be delayed until a method is proven satisfactory for all components.

TABLE 2. Costs to reduce noninfectious hazards*

Cost drivers	Patient bar code	Unified online database	TRALI: exclusion and/or HLA testing of high-risk donors	Total
Incremental cost/unit	$10-$20	$3-$6	$1-$2	$14-$28
× 27 million units†	$392 million	$90 million	$40 million	$432 million
Number of major events (hemovigilance data)†				295
Cost per event avoided				$1.5 million

* Adapted from S. Dzik as presented at Consensus Conference.
† Data from Stains by et al.[32]

Should different criteria be used for certain patient populations?

Once the decision has been made to move forward with a method for PI for a specific blood component, the treated product should be used universally. Traditionally, premature infants, children, and pregnant women have been considered "vulnerable populations." The same patients may be at particular risk for transfusion-transmitted pathogens, however, and might arguably derive special benefit from PI blood components. The Panel recognizes that there are few current data available on which to individualize risk-benefit assessment. For example, infection with HBV in infancy or early childhood may lead to a high rate of persistent infection (25%-90%) with significant morbidity.[42] Cytomegalovirus (CMV), in contrast, is readily transmitted by transfusion; however, infection does not necessarily result in increased morbidity and mortality, even for low-birth-weight and premature infants.[43] Similarly, blood component transmission of hepatitis C to neonates and children was common, but the epidemiologic data, histologic findings, and clinical outcomes are conflicting.[44,45] Even fewer data address the potential risk of trace amounts of residual additive, photoderivatives, or metabolites from the current inactivating agents. Until additional new information identifies groups of patients who should not receive the PI product, the Panel concluded that the product should be made universally available.

WHAT MINIMUM ACCEPTABLE SAFETY AND EFFICACY CRITERIA SHOULD BE PUT INTO PLACE FOR THE PREAPPROVAL ASSESSMENT OF PATHOGEN-INACTIVATED PRODUCTS? SPECIFICALLY:

What criteria should govern acceptable toxicology standards and how should they be assessed?

The Panel recognizes that the different regulatory authorities have established their own standard approaches to these assessments. Each agency has specific protocols and criteria for determining safety and efficacy. The Panel endorses the rigorous application of standards for safety and efficacy, particularly in the area of toxicology.[46,47] Established toxicology methods of systematically estimating hazards, anticipated exposure levels, and relevant dose-response relationships should be followed, to ensure a very high margin of safety for transfusion recipients. PI technologies that target nucleic acid should, for example, undergo careful scrutiny to assess the potential for genotoxicity, carcinogenicity, reproductive toxicity, and germline toxicity. These studies should be peer-reviewed and published.[48-50] The Panel strongly recommends that clinically relevant endpoints be selected when studying the direct toxicity of PI techniques on the blood product itself, rather than merely considering, for example, functional assays of oxygen delivery that have been proposed at this conference as one endpoint for evaluating PI of red cells (RBCs). The Panel recognizes that regulatory agencies may be constrained by issues of confidentiality in their ability to share proprietary information with the public.[48,49,51-53] The Panel encourages the harmonization of approaches and sharing of data among the various regulatory agencies internationally, however.[54]

What type of postmarketing surveillance should be required (if any) with the implementation of pathogen-inactivated blood components?

New drugs, biologics, and devices, such as modified blood components, blood containers, and anticoagulant-preservative solutions, undergo careful evaluations for efficacy and safety before approval. The premarketing randomized clinical trials are generally small, short-term studies that may fail to detect toxicities of low frequency (Table 3). New technologies are typically either approved or rejected based on these studies. In most countries, postapproval safety is monitored by a voluntary adverse event reporting system in which health-care professionals report adverse events thought to be related to the drug or biologic.[55] This collection of voluntarily submitted case reports represents the weakest link in the regulatory process. The Panel recognizes the difficulty of postmarketing surveillance studies.[56] Well-designed studies, however, should be mandated by the regulatory authorities and supported by the manufacturers and/or the blood

TABLE 3. Estimates of study size to rule out an adverse event frequency*

Study size to rule out an adverse event†	Adverse event frequency
100	1/33
300	1/100
1,000	1/333
3,000	1/1,000
10,000	1/3,333
225,000	1/75,000

* From Hanley and Lippman-Hand.[80]
† 95 percent upper confidence limit.

suppliers as a condition of approval. Postmarketing surveillance for adverse reactions to PI products should be linked to the national hemovigilance systems such as the Transfusion Transmitted Injuries Surveillance System (TTISS) in Canada. Depending on the new PI technologies implemented, specific additional surveillance outcomes may be identified. Annual reports on adverse reactions to specific products should be prepared, analyzed, and communicated to users.[56,57] In the case of PI, comparisons should be made to historical rates of adverse reactions with non-PI products. The Panel is uncertain as to what extent such information is proprietary or how quickly it is made available to regulatory agencies in different countries, but strongly recommends sharing of hemovigilance data across jurisdictions.

Research should be encouraged to identify rare and long-term consequences of transfusion of PI products. Chronically transfused patients might serve as an ideal surveillance population to identify long-term toxicities of PI products.

FOR PI TECHNOLOGIES THAT HAVE BEEN APPROVED BY THE REGULATORY AUTHORITIES, WHAT IMPLICATIONS SHOULD BE CONSIDERED BEFORE THEIR WIDESPREAD ADOPTION?

Regulatory agencies approve technologies based on their safety and efficacy. In Canada, and in many other countries, a distinction exists between regulatory authorization to market a drug and common practice.[58] Widespread implementation of novel technologies such as PI will have a number of implications for blood services (and beyond). Several technologies are already approved for fresh-frozen plasma treatment in some countries, and it is possible, even likely, that more than one technology will be approved for each of the labile blood components.[5] Suppliers will require a process to select the most appropriate PI technology. The Panel did not address the desirability of licensing or introducing any specific manufacturer's technology, but concentrated on the desirability of a PI technology and the process of implementation. The process should include the detailed review of the available safety and effectiveness data along with determination of how the adoption of a new technology will impact the processes of the organization. Collection methods, management of components, training of personnel, storage and transport, waste disposal, and methods of quality control may all be affected.

Treatment of a nation's blood supply requires societal informed consent. The Panel endorses the need for broad public consultation. Consultation with appropriate patient and physician stakeholder groups is essential. Consultation with hospital physician and transfusion groups is also a necessity. Inventory management is an important issue, particularly at the time of crossover from the current to the new technology. Once the final selection process has occurred, a detailed educational program should be put in place for blood centers, hospitals, healthcare providers, and patients before the introduction of the new product.

Initially, the new PI procedure should be introduced as a pilot project in one geographic area to work out logistical, environmental, and occupational health issues before the process is implemented more widely. For instance, a staged introduction of PI for PLTs is currently being conducted in France.

Should PI components differ in function from available non-PI products, this information should be disseminated to physicians and health-care providers and communicated to patients through an appropriate informed consent process. The manufacturer, the supplier, and provincial departments or ministries of health have the responsibility to ensure that this information is conveyed to physicians and health-care providers in a timely and effective manner. Finally, cost-effectiveness studies should be conducted by agencies such as the Canadian Agency for Drugs and Technologies in Health.[58]

IF PI WERE TO BE IMPLEMENTED FOR ALL COMPONENTS; IN PRINCIPLE:

What criteria would allow changes in donor deferral or testing?

After the implementation of PI for all components, it is possible that existing procedures could be modified to reduce costs or reduce donor deferrals. The rationale for PI implementation should be independent of these considerations, however. Specifically:

What criteria would allow the relaxation of any current donor deferral and/or exclusion policies?

The regulatory agencies and blood collectors should review the donor screening questionnaire to eliminate or modify questions that are believed to be of marginal value, such as tattooing and certain travel deferrals.[59,60]

What criteria would allow the cessation of any currently undertaken screening tests?

1. Screening tests for agents that are not readily transmissible by transfusion, for example, *Treponema pallidum* (syphilis).
2. Screening tests for agents of low infectious titer and high log kill by PI, for example, WNV.
3. Screening tests for agents that are sensitive to PI and for which redundant safety measures are in place, such as CMV, HTLV, and hepatitis B core antibody.
4. Screening tests for agents that are exquisitely sensitive to PI and for which the current tests have poor specificity and sensitivity, such as bacteria.
5. Although not a screening test, gamma irradiation of cellular blood components could be eliminated if nucleic acid–targeted PI technology were introduced. These technologies appear to inactivate contaminant lymphocytes and eliminate the risk of transfusion-associated graft-versus-host disease.[61-63]

What criteria would allow a decision not to implement new screening tests for agents susceptible to PI?
A candidate agent that is shown to be adequately inactivated by an implemented PI technology would not require screening tests, unless of unusually high infectious titer. Ideally PI treatment should reduce the pathogen load in a blood component by 6 to 10 log as measured with appropriate isolates in an in vitro assay of infectious units.[64] In certain cases virus-infected primate models may be desirable to define the efficacy of PI treatment in transfusion-mediated transmission.

Should multiple inventories be considered for each component and if yes how should allocation be decided?

The Panel recommends universal implementation of PI (or universal implementation for a particular component if PI methods for all components are not available). Consequently, unless special patient populations are identified which should not receive newly implemented PI components (see "Should different criteria be used for certain patient populations?" above), the Panel recommends against multiple inventories.

HOW SHOULD THE COSTS AND/OR BENEFITS OF PI BE ASSESSED?

The Panel appreciates that precaution must be tempered by the logic of cost-benefit analysis with its focus on scarcity and estimates of risk.[65] Country-specific studies of different PI technologies have been published, and the strengths and limitations of the existing studies were analyzed at this conference.[66-72] Economic evaluations of all PI procedures should be conducted. Implementation of PI, however, should be based on other considerations in addition to the results of an economic analysis; this practice is consistent with how economic evaluation results are used to assist with decisions in other areas of health care. For PI, the costs are currently unknown and the benefits are difficult to quantify. Even with perfect data, a decision should be made with the economic evidence as just one factor. Unlike many therapeutic interventions, PI is an intervention with "broad-spectrum" potential to reduce multiple infectious and noninfectious threats. Furthermore, blood safety interventions often do not conform to the traditional norms of cost effectiveness.[73,74] Economic evaluation is but one tool, albeit an important one, for assisting policy makers in arriving at a decision acceptable to their constituencies.[75]

Costs and benefits should be assessed with a societal perspective, examining both direct and indirect costs in accordance with published recommendations.[76] Analysts should strongly consider presenting the results in a disaggregate fashion with a cost consequence analysis in addition to a cost-effectiveness analysis.[75,77] Methods and models should be transparent with assumptions highlighted and tested for their effect on the results. Sensitivity analysis, at a bare minimum, should focus on variations in price and effectiveness. Uncertainty about these analyses should be considered, not only for the incremental cost-effectiveness ratio but also for the budget impact.

How should these be aligned with other blood safety interventions and/or other health-care interventions?

A judgment about whether the extra benefits outweigh the extra costs is context-specific. The Panel believes that it may be inappropriate to assign a single number as a cutoff threshold for the cost-effectiveness analysis.[75] Decision makers, however, should clearly state their reasoning for decisions with special emphasis on budget impact, the extra cost for improved patient outcome, and opportunity costs (i.e., what other safety improvements could be introduced for the cost of PI). Reasoning used for past decisions may not be applicable for current or future decisions involving new, expensive technologies. It is of utmost importance that decisions about scarce resources be made that are consistent with the values of the decision makers and the patients whom they represent.

WHAT OTHER INFORMATION, CONSIDERATIONS, AND RESEARCH-RELATED QUESTIONS WOULD NEED TO BE ANSWERED TO DECIDE WHETHER OR WHEN A PARTICULAR PI PROCEDURE SHOULD BE IMPLEMENTED?

The Panel recommends that consideration be given to robust governmental support for a large-scale investment