参考資料３

感染因子低減化技術導入に係る費用対効果分析に関する文献集

文献②　・・・・・・・・・・・・・・・・・・・・・・・・・・・・１０

Cost-effectiveness of pathogen inactivation for platelet transfusions in the Netherlands

文献①

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Economics of Pathogen Inactivation Technology for Platelet Concentrates in Japan

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Abstract

Residual risk of transmitting recognized and emerging blood-borne pathogens via blood transfusion in Japan persists despite advances in blood safety screening. The INTERCEPT Blood System (IBS) for platelets was developed to inactivate a broad spectrum of pathogens to reduce the risk of transfusion-transmitted infections. In this study we assessed the economic impact of the IBS on platelet transfusion costs. An economic analysis model was used to assess both net cost and cost-effectiveness of the IBS for the patient populations accounting for most of the platelet use in Japan. Pathogen exposure included viruses currently recognized to cause transfusion-transmitted infections and emerging pathogens of potential significance for transfusion-transmitted infections. Economic assessment of the full potential of the IBS revealed that only a small increase in net cost can be expected with implementation. The cost-effectiveness of the IBS for platelets is comparable with and potentially better than that of other blood safety interventions (eg, nucleic acid testing) and, in general, other recently implemented safety interventions (eg, chemical regulations and traffic safety measures) accepted as valuable in Japan. Thus a preventive approach using pathogen inactivation with the IBS may be considered a desirable strategy for improving the current safety of platelet transfusions in Japan.

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Key words: Pathogen inactivation; Japan; Economics; Cost; Cost-effectiveness

1. Introduction

The safety of the blood supply in Japan has achieved a high level since the widespread introduction of sensitive screening tests [1]. However, residual risks of transfusion-transmitted infections remain [2]. Despite the use of highly sensitive minipool nucleic acid tests (NAT) implemented in the late 1990s, the Japan Red Cross recently reported the detection of 210 contaminated blood units and 6 patients with hepatitis C virus (HCV) or human immunodeficiency virus (HIV) infection from blood transfusions [3]. Furthermore, other reports have emphasized the challenge of detecting low levels of viruses, owing to the presence of occult hepatitis B virus (HBV) infection, among healthy blood donors [4]. These events have brought blood safety back into the forefront of the health policy agenda for Japan.

In addition to the currently recognized blood-borne pathogens (HIV, HCV, HBV, and human T-lymphotropic virus [HTLV]), newly emerging viruses [5], such as West Nile and severe acute respiratory syndrome, as well as migrating agents such as plasmodia [6], may pose a threat to the blood supply. These new threats necessitate consideration of added safety measures, previously mainly in the form of additional screening tests. However, increasing the available battery of tests makes blood banking procedures highly complex and more expensive. For example, introduction of NAT for HBV resulted in only a modest additional yield of contaminated donations, indicating that this intervention was less cost-effective [7]. In addition, the scientific data on which test to implement are not always clear [8]. On a regional geographic basis, health policy decision makers and payers must balance benefits, risks, and costs when introducing new blood safety technologies [9].

Pathogen inactivation technologies, such as the INTERCEPT Blood System (IBS) for platelets, now registered with the European Conformité Européne (CE) mark, are expected to further increase the cost of blood and blood components. Therefore the cost-effectiveness for this type of intervention is of concern to health policy makers [10]. At the same time, pathogen inactivation technology is expected to comprehensively improve blood

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Table 1.
Estimated Residual Risk of Viral and Bacterial Contamination of Blood Components on a Per Donation Basis in Japan

Pathogen	Risk Per Donation*
Human immunodeficiency virus	1/2,668,696 [1,12]
Hepatitis B virus	1/51,988 [1,12]
Hepatitis C virus	1/348,091 [1,12]
Bacteria	1/50,000-500,000 (1/225,000)† [13]

*After the introduction of nucleic acid testing.
†Midpoint of range estimate for fatality due to bacterial sepsis based on data from Wagner [13].

safety and may ultimately allow a paradigm shift from testing to proactively preventing transfusion-transmitted disease [11].

Clinical benefits as well as potential blood banking economics must be evaluated in an overall and comprehensive manner in which all costs and benefits of this technology are considered before conclusions about broader economic impact can be drawn. To address these considerations, we analyzed from both a cost-consequence and a cost-effectiveness point of view the economics of pathogen inactivation with the IBS for platelets in Japan. The objectives of this study were aimed at providing information on the net cost and cost-effectiveness of the introduction of the IBS in Japan and thereby facilitating the decision-making process for implementing a novel blood safety technology.

2. Materials and Methods

A comprehensive literature analysis search of Medline and PubMed was conducted to retrieve information on current data about viral transmission due to blood transfusion as well as the associated costs of the clinical consequences. In addition, a questionnaire was designed to capture the current Japan Red Cross blood banking procedures and their associated unit costs to evaluate the impact of IBS platelets on the blood banking "value chain" to calculate the cost consequences (net cost) and cost-effectiveness of the IBS.

2.1. Estimation of Current Residual Risks for Viral and Bacterial Contamination of Blood Components in Japan

In Japan blood is generally safe. Residual viral contamination rates for HIV, HBV, and HCV are of the same order of magnitude as in European countries and the United States (Table 1) [1,12]. No data on bacterial contamination of platelet components and associated mortality from platelet transfusion were found in the literature. Therefore for the purpose of this analysis we used available data from international and US studies [13].

2.2. Potential Costs and Efficiencies of Blood Banking Operations with the IBS

The Japan Red Cross collects all platelet components in Japan, the great majority being prepared as single-donor apheresis platelets (AP) [14]. Introduction of pathogen inactivation with the IBS offers the opportunity for various blood banking process efficiencies based on experience in Europe [15].

The cost of the IBS for a therapeutic platelet dose in Japan was assumed to be approximately ¥9495. This estimate included the cost of the system (hardware and disposables) as well as the costs for material and personnel to perform the procedure. Experience had shown that use of the IBS may result in a small loss of platelets during the process, so additional platelets may have to be collected to compensate for this loss. This rate was conservatively estimated at 10% [16]. However, recent experience in European blood centers with the commercial system demonstrated minimal impact on platelet doses prepared with the IBS, and additional platelets have not been required [15]. Use of the IBS offers several potential cost efficiencies, including replacement of donor plasma with platelet additive solution, replacement of gamma irradiation for prevention of transfusion-associated graft-versus-host disease, replacement of bacterial detection assays, and replacement of future screening tests (Table 2). Estimates for these

Table 2.
Potential Blood Banking Efficiencies with Adoption of the Intercept Blood System (IBS) in Japan

Test or Procedure	Reasoning and Assumption	Potential Cost Savings, ¥
Gamma irradiation	Almost all platelets are treated with gamma irradiation for the prevention of graft-versus-host [18]. The IBS is as effective as gamma irradiation for inactivation of T-cells [39]. Implementation of the IBS would replace gamma irradiation.	900*
Use of platelet additive solution	Platelets treated with the IBS would be collected and stored in additive solution that would allow saving up to 200 mL of plasma per platelet dose. The saved plasma can be processed as fresh frozen plasma.	11,014* †
Bacterial testing	The IBS effectively inactivates bacteria in platelet concentrates [40-42]. Bacterial testing would not be required.	3363‡
Future screening tests	The IBS has been shown to inactivate a broad spectrum of emerging viruses, such as West Nile. For example, the IBS could replace introduction of a test for West Nile virus.	1631

*M. Satake, MD, written personal communication, July 2004.
†Based on the price of 160 mL of fresh frozen plasma.
‡Estimate based on European data.

Table 3.
Cost Consequences and Estimation of the Net Cost for the Intercept Blood System (IBS) in Japan

Cost Parameter	Cost, ¥	
Potential savings		
Avoidance of gamma irradiation	(900)	
Plasma savings due to use of additive solution	(11,014)	
Avoidance of bacterial testing	(3363)	
Avoidance of future screening tests	(1631)	
Additional cost		
Pathogen inactivation costs (IBS unit price)		9495
Potential additional platelet collections (10%)*		11,311
Subtotal	(16,908)	20,806
Net-cost when treating apheresis platelets with IBS	3898	

*Ten percent as additional cost of the base price of ¥113,190 per 3×10^{11} platelets.

costs were obtained from information supplied by the Japan Red Cross.

2.3. Cost-Consequence and Net-Cost Analysis Methods

The economic impact of introducing a new technology can be expressed in a so-called cost-consequence analysis. This analysis includes the initial cost of implementing the technology as well as potential downstream savings associated with use if adopted. By presenting the relevant parameters and their cost, decision makers and payers can estimate the net impact of an intervention, thereby facilitating assessment of a health technology intervention without necessarily combining all cost and outcome categories into a single ratio of cost-effectiveness, such as cost per life-year (LY) gained or cost per quality-adjusted life-year (QALY) gained as used in traditional cost-effectiveness analysis. In a cost-consequence analysis, the relevant parameters must be identified and cost values assigned. The cost consequences of implementing the IBS in a systematic fashion in Japan were estimated on the basis of available information from published and personal communication sources (Table 3).

2.4. Cost-effectiveness Analysis Methods

Health care product economic value is important and of increasing concern as health care systems struggle to deliver the highest quality health care within increasing budget constraints. To understand the economic value of new products, governmental authorities and private decision-making committees for new interventions, such as improvements in transfusion safety, frequently require formal cost-effectiveness analyses. This relationship of cost to benefit is typically measured with a cost-effectiveness ratio, such as QALY saved per cost incurred. The lower the cost-effectiveness ratio (eg, the lower the cost per unit of health gained), the better is the value of the intervention. Cost-effectiveness analysis is used to allow comprehensive comparisons between alternative medical technologies (eg, NAT versus pathogen inactivation), combining clinical effectiveness and cost, and will therefore add additional information that cannot be captured in cost-consequence analysis.

2.4.1. Model Overview

A literature-based decision-analytic model was developed to assess the economic costs and clinical outcomes associated with the use of single-donor AP treated with the IBS for platelets (AP+IBS). The analysis was based on the decision-analytic model developed by Bell et al [17] in which the incremental cost (dollars/QALY) associated with the use of AP was evaluated. Similarly, this study simulated the possible transfusion-related events and outcomes in the patient populations that account for most platelet use in Japan [18]. Patients undergoing hematopoietic progenitor cell transplantation (HPCT) for acute lymphocytic leukemia (ALL) and non-Hodgkin's lymphoma (NHL), patients undergoing coronary artery bypass grafting (CABG), and patients undergoing hip arthroplasty were chosen to be representative of patients who commonly receive platelet transfusions. Correspondingly, 4 reference patients were selected to represent the populations of all patients undergoing each procedure: (1) a 10-year-old boy undergoing HPCT for ALL, (2) a 50-year-old woman undergoing HPCT for NHL; (3) a 60-year-old man undergoing CABG; and (4) a 70-year-old woman undergoing hip arthroplasty.

A decision tree (Figure 1) was constructed for patients receiving AP+IBS versus conventional AP. The baseline model included the current risks of infection with HIV, HCV, HBV, and an emerging virus as well as bacterial agents for each platelet donor exposure. The model simulated the subsequent transfusion-related events and outcomes, as well as events that would occur naturally (ie, patients may experience morbidity and mortality due to several causes, such as underlying disease, transfusion-related complications, or general mortality for populations of the same age and sex). Clinical outcomes as a result of the underlying disease and transfusion-related complications were assigned a treatment cost and utility. Life expectancy estimates were calculated according to the declining exponential approximation of life expectancy method with consideration of competing mortality from disease-specific and naturally occurring causes [17]. The direct medical costs attributable to the use of AP+IBS and the present value of future costs attributable to treating transfusion-related complications were incorporated in the baseline model. No indirect costs such as work productivity losses were considered. Economic costs and health benefits incurred in future years were discounted at 3% per annum, consistent with current practice.

The model was used to estimate the incremental cost and health benefit (QALY) of using AP+IBS as opposed to untreated AP. The incremental cost-effectiveness ratio was then calculated as $(\text{cost}^{\text{AP+IBS}} - \text{cost}^{\text{AP}})/(\text{QALY}^{\text{AP+IBS}} - \text{QALY}^{\text{AP}})$, representing, in this case, the incremental cost per QALY gained by using AP+IBS as opposed to untreated AP.

2.4.2. Data Sources

Costs related to platelet transfusions and treatment costs were obtained from official sources (Japan Red Cross) and published literature. The net costs associated with the IBS for platelets were obtained from the preceding cost-consequence analysis. Japanese life tables from official pop-

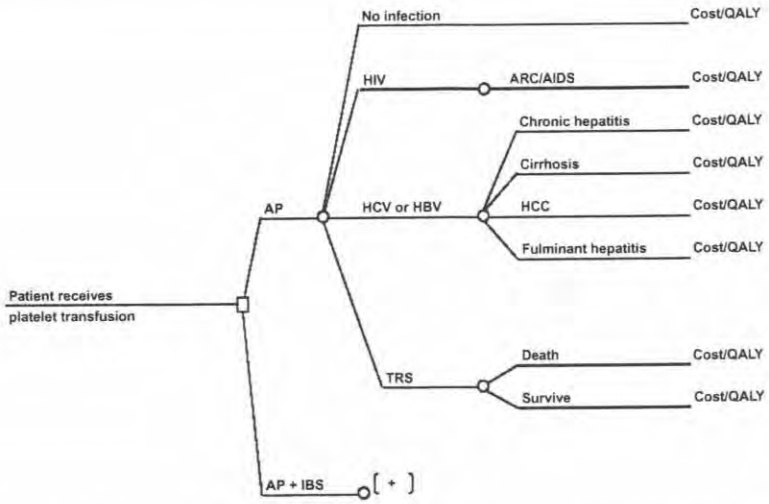

Figure 1. Decision-analytic model. AP indicates apheresis platelets; HIV, human immunodeficiency virus; ARC/AIDS, AIDS-related complex/acquired immunodeficiency syndrome; QALY, quality-adjusted life-year; HCV, hepatitis C virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TRS, transfusion-related sepsis; [+], repetition of subtree as shown for AP.

ulation statistics were applied to calculate life-years gained [19]. Data on mortality due to underlying disease as well as excess mortality caused by viral or bacterial infection and number of platelet units transfused were derived from the previously described US model [17]. Because blood transfusion safety practices are commonly shared among developed countries, only small differences in these data can be expected between countries, and therefore we applied these data to this model analysis. Furthermore, the general outcomes of the model are not overly sensitive to small variations in these parameters. Data on risk of transfusion-transmitted disease were derived from Japanese medical literature sources and international studies (Table 1). Cost data for treatment of viral disease were mainly derived from the Japanese literature and augmented with US data when no Japan-specific data could be obtained. The cost of platelet concentrates was obtained from the Japan Red Cross. Cost input data were summarized on the basis of previous sources (Table 4).

2.4.3. Sensitivity Analysis

Sensitivity analysis was used to determine the robustness of the cost-effectiveness analysis by testing plausible ranges of estimates for key independent variables (eg, costs, outcomes, probabilities of events) to determine whether such variations would make meaningful changes in the results of the analysis. As reported in our US publication about the model [17], the cost-effectiveness of use of the IBS was expected to be most sensitive to the rate of bacterial contamination and to the risk of emerging pathogens. To explore the effect of these variables on the results, we analyzed the effect of such variables in various scenarios.

2.5. Emerging Virus

It must be kept in mind that current safety measures have an impact on safety only with regard to the blood-borne pathogens for which tests are in use. They do not protect the

Table 4.
Cost Data for the Cost-effectiveness Model with Intercept Blood System (IBS) Implementation in Japan*

Parameter	Cost, ¥	Reference
Apheresis platelet cost	113,119	M. Satake, MD, personal written communication, July 2004
Net cost of IBS	3898	Net-cost calculation from Table 3
ARC/AIDS care costs per case	7,200,000	[43]
HCV or HBV care costs per case		
Chronic infection	2,228,000	[44]
Cirrhosis	267,000	[44]
HCC	1,326,000	[44]
Fulminant infection	1,557,000	[44]
TRS		
Hospitalization	700,000	[17]

*ARC/AIDS indicates AIDS-related complex/acquired immunodeficiency syndrome; HCV, hepatitis C virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TRS, transfusion-related sepsis.

transfusion recipient against untested or unknown infectious agents. Therefore the blood supply remains vulnerable to newly identified or emerging infectious agents. A primary example is the West Nile virus epidemic in the United States from 1999 to 2002 [20]. Although a number of recently examined new agents (hepatitis G and TT viruses) with a potential impact on blood safety appear to be nonpathogenic, or not to be transmitted through transfusion (human herpes virus type 8), every discovery of an agent necessitates investigation for the potential of transfusion-associated transmission [21,22]. Transfusion-related pathogenicity requires an asymptomatic viremic phase during which the infected donor can donate undetected by current screening methods, and that the virus can survive in blood components during preparation and storage [23].

Historical as well as contemporary data confirm that this risk of emerging infection is not hypothetical. With the model, we examined the health economic consequences of implementation of the IBS for different potential situations with regard to the transfusion-related infection risk of a new emerging virus. The risk was programmed at different levels, which were based on historical HCV infection rates [24]. The following transfusion-associated residual risk levels were evaluated: 1 per 100,000 and 1 per 10,000 donations.

2.6. Bacterial Contamination

Bacterial contamination is currently the most prevalent residual risk associated with platelet transfusion [13]. Several surveillance systems exist (United Kingdom Serious Hazards of Transfusion report, US Food and Drug Administration) in various countries; however, inherent with all of the systems is a certain degree of underreporting [25]. Several recent European reports of data on systematic bacterial cultures at time of preparation for more than 130,000 platelet components indicated the contamination rates is approximately 0.7% (7 cases per 1000 components) [26,27]. To analyze the effects of bacterial contamination, we used sensitivity analyses to explore mortality data from the literature applicable to bacterial contamination. Of note, this analysis dealt only with mortality and not with less severe infections that arise owing to transfusion of contaminated platelet components with attendant health- and care-related consequences [28].

3. Results

3.1. Net-Cost Impact of IBS Adoption

The IBS, as most innovative technologies, will require a net cost to the Japanese health care system. At the same time, potential savings in current tests and procedures will offset this investment so that the additional net cost for the IBS amounts to only ¥3898 per platelet therapeutic dose. This calculation includes an assumed cost that 10% more platelet doses have to be collected to compensate for processing losses. This imputed added cost due to collection of additional platelets is a conservative assumption based on recent data from a clinical trial and postmarketing experience in Europe that indicated the IBS may not require collection and transfusion of additional platelet doses [29,30].

With approximately 700,000 platelet units transfused annually in Japan, use of the IBS at a net cost of ¥3898 per platelet transfusion would result in an increase of only 0.02% (¥2.7 billion) of the total hospital budget (¥11,342 billion) [31] and only an additional 0.89% increase in the cost for labile blood components in Japan. Moreover, this conservative calculation does not include potential benefit from extension of platelet storage from 3 to 5 days, benefit from avoidance of disease due to platelet transfusion and the long-term consequences associated with adverse events, benefits from avoidance of legal claims (in Japan ¥56,100,000 was awarded per hemophiliac patient with HIV infection due to exposure to contaminated clotting factors) [32] and associated judicial costs, and benefit from avoidance of indirect costs due to work loss and premature death. Furthermore, in phase 3 clinical trials, transfusion of IBS platelets resulted in a significantly reduced rate of acute transfusion reactions [33], thus the costs of care associated with transfusion reactions may be reduced. Similarly, suspension of the IBS in a reduced concentration of allogeneic plasma may reduce the incidence of transfusion-associated acute lung injury with additional savings in transfusion-related care costs [34].

3.2. Cost-effectiveness Analysis for IBS Adoption: Analysis Using Baseline Assumptions

When analyzing our previously developed cost-effectiveness model with Japanese risk factors and cost data, adding the net cost of the IBS to the current AP price, we found the cost-effectiveness of the IBS ranged from ¥99,000,000 for the pediatric ALL patient to ¥1,076,000,000 for the hip surgery patient (Table 5). The wide range of cost-effectiveness ratios can be explained by the better survival prognosis for pediatric and heart surgery patients and their age. The better prognosis allows more life-years gained by prevention of transfusion-transmitted disease compared with the situation for patients with end-stage cancer and relatively older orthopedic surgery patients.

3.3. Sensitivity Analysis

Increasing the number of deaths due to bacterial contamination of platelet components from 1 in 225,000 to 1 in 112,500 improved the range of cost-effectiveness by 30% to 40%. The same held true for the impact of emerging viruses. Cost-effectiveness improved markedly with increasing risk of viral transmission (Table 5). Given that we mimicked an HCV-like emerging virus scenario, the impact was greatest in pediatric patients receiving platelet transfusion owing to the natural history of posttransfusion hepatitis. Most cases of hepatitis C (70%-80%) are asymptomatic and do not lead to significant medical problems. In contrast, prevention of transfusion-transmission of an HIV or West Nile virus type of emerging pathogen would yield great benefits in terms of life-years gained and associated cost avoided and would lead to a highly favorable cost-effectiveness ratio.

Table 5.
Cost-effectiveness of Intercept Blood System in Japan: Cost in Yen per Quality-Adjusted Life-Year Gained*

Analysis	ALL, 10-Year-Old Boy	NHL, 50-Year-Old Woman	CABG, 60-Year-Old Man	Hip Arthroplasty, 70-Year-Old Woman
Baseline	99,000	433,000	263,000	1,076,000
Baseline plus higher risk of bacterial fatality rate: 1/112,500	69,000	267,000	163,000	605,000
Baseline plus emerging virus scenario: 1/100,000	84,000	238,000	237,000	1,022,000
Baseline plus emerging-virus scenario: 1/10,000	35,000	127,000	127,000	702,000

*In thousands of yen, rounded. ALL indicates acute lymphocytic leukemia; NHL, non-Hodgkin's lymphoma; CABG, coronary artery bypass grafting.

3.4. Interpretation of Cost-effectiveness Ratios

Cost-effectiveness ratios can be interpreted in 2 ways. First, if national health policy makers have established a certain threshold of cost-effectiveness, new technologies could be evaluated against that cutoff point. Several countries have determined official criteria for cost-effectiveness. For example, in the United States interventions that yield a cost-effectiveness ratio of more than US$100,000 per QALY gained are considered unfavorable and should ideally not be implemented. The United Kingdom National Institute of Clinical Excellence uses a similar "threshold" of approximately £30,000 per QALY gained. According to these "decision rules," none of the recently used blood safety measures should have been implemented because their cost-effectiveness ratios are much higher than the designated thresholds [35,36]. Cost-effectiveness is a relative concept and should be applied to in-group comparisons. In other words, new blood safety technologies should be evaluated against technologies in the same area (eg, NAT screening, plasma pathogen inactivation treatment). Transfusion medicine is in a situation in which additional benefits gained for protection against selected pathogens are marginal and come at a cost leading to higher cost-effectiveness ratios ranging from $300,000 (solvent detergent plasma) to $85,000,000 per QALY (HCV NAT in France) [37,38]. However, society has decided to pay for these interventions given the paramount interest in blood safety, especially in Japan, where patients expect 100% safety [14]. Comparing the cost-effectiveness of the IBS to current safety measures in Japan and elsewhere, we found the IBS is an equal and even more cost-effective intervention in preventing transfusion-transmitted disease and injury (Figure 2).

4. Discussion

In our analysis we examined the economic impact of use of the IBS in Japan. We examined both the net cost to a blood center for use of the technology and the broader health-care implications of use of the IBS by use of cost-effectiveness analysis. The net-cost analysis provided valuable information about the ultimate potential of the IBS for

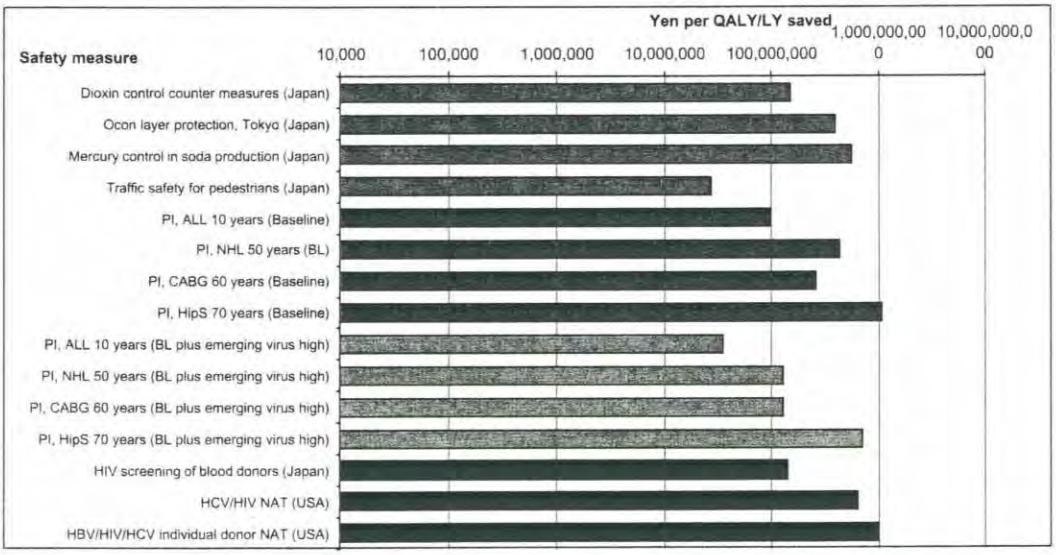

Figure 2. Cost-effectiveness of the Intercept Blood System (IBS) compared with other blood, environmental, and transport safety measures. QALY indicates quality-adjusted life-year; PI, pathogen inactivation; ALL, acute lymphocytic leukemia; NHL, non-Hodgkin's lymphoma; CABG, coronary artery bypass grafting; HipS, hip arthroplasty; BL, baseline; HIV, human immunodeficiency virus; HCV, hepatitis C virus; NAT, nucleic acid test; HBV, hepatitis B virus.

reducing the cost of platelet transfusion for the blood center by replacing several current practices (Table 3). Moreover, if additional platelets were not required for use of the IBS, consistent with the European experience to date, then introduction of the IBS could actually reduce the cost of platelet transfusion by ¥7413 per therapeutic dose (Table 3). In addition, other savings, not factored into this analysis, are possible through avoidance of additional tests such as cytomegalovirus (CMV) serologic tests and tests for other emerging pathogens, such as dengue virus.

Cost-effectiveness analysis provides another perspective from which to examine the economic impact of use of the IBS. Whereas the risk of transfusion-transmitted infections has been greatly reduced by existing safety measures, zero risk has not yet been attained. New safety interventions that can reduce bacterial and viral transfusion risks still are needed to improve blood safety. As evidenced by the cost-effectiveness ratios of reviewed studies [38], society places a high value on reducing the number of unintentional deaths and injuries. New transfusion safety measures should be evaluated by use of higher cost-effectiveness thresholds that accurately reflect the value to society of reducing unintentional deaths and injuries from a therapeutic modality presumed to be free from infectious agents, as are other parenteral medications.

In addition, we must bear in mind that cost-effectiveness analysis is limited in its ability to capture all the benefits that improved blood safety has to offer. Results of cost-effectiveness analysis actually may be misleading, underestimating the true cost-effectiveness of an intervention. Many cost-effectiveness analysis models do not account for the economic benefit of eliminating potentially redundant blood safety measures (eg, gamma radiation, CMV testing, p24 testing, HTLV testing, or testing for bacterial contamination). Furthermore, new safety measures may offer other benefits, such as increased shelf life of blood, avoidance of having to compensate infected patients, and lost productivity due to premature death following infection with lethal viruses (such as HIV). These aspects, and the peace of mind that increased safety offers to all transfusion recipients, should not be overlooked in evaluation of new blood safety interventions.

Implementation of the IBS in Japan came at a net cost to society. According to our analysis, however, realizing the full potential of the technology has reduced the additional cost to a relatively small cost considering the wide array of benefits that allow cost offsets elsewhere in the blood banking operating scheme. If the initial European experience that use of the IBS did not necessitate collection of more platelet doses is confirmed with broader experience, then the net cost of the IBS is very reasonable. Use of the IBS may initiate a paradigm shift from testing to prevention, thereby harnessing additional long-term cost savings far beyond the immediate benefits of disease prevention. Use of the system may avoid implementation of multiple new screening tests, extend the shelf life of platelet components, and broaden the donor base by avoiding travel-related donor exclusions. The greatest benefit of the IBS, however, is the potential to protect against emerging and migrating pathogens. The system therefore should be a valuable technology for enhancing blood safety in Japan.

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ORIGINAL ARTICLE

Cost-effectiveness of pathogen inactivation for platelet transfusions in the Netherlands

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SUMMARY. The objective of this study is to estimate cost-effectiveness of pathogen inactivation for platelet transfusions in the Netherlands. We used decision tree analysis to evaluate the cost-effectiveness of the addition of pathogen inactivation of pooled platelets to standard procedures for platelet transfusion safety (such as, donor recruitment and screening). Data on transfusions were derived from the University Medical Centre Groningen (the Netherlands) for 1997. Characteristics of platelet recipients (patient group, age, gender and survival) and data/assumptions on viral and bacterial risks were linked to direct and indirect costs/benefits of pathogen inactivation. Post-transfusion survival was simulated with a Markov model. Standard methods for cost-effectiveness were used. Cost-effectiveness was expressed in net costs per life-year gained (LYG) and estimated in baseline- and sensitivity analysis. Sensitivity was analysed with respect to various assumptions including sepsis risk, reduction of the discard rate and discounting. Stochastic analysis to derive 90% simulation intervals (SIs) was performed on sepsis risk. Net costs per LYG for pathogen inactivation were estimated €554 000 in the baseline-weighted average over the three patient groups (90% SI: €354 000–1092 500). Sensitivity analysis revealed that cost-effectiveness was insensitive to viral risks and indirect costing, but highly sensitive to the assumed excess transfusions required and discounting of LYG. Given relatively high net costs per LYG that are internationally accepted for blood transfusion safety interventions, our estimated cost-effectiveness figures for pathogen inactivation may reflect acceptable cost-effectiveness in this specific area. Two main assumptions of our model were that the pathogen inactivation was 100% effective in preventing transmission of the pathogens considered and was not associated with major and/or costly adverse reactions. Validation of several crucial parameters is required, in particular the Dutch risk for acquiring and dying of transfusion-related sepsis.

Key words: cost-effectiveness, pathogen inactivation, pharmacoeconomics, platelets.

In the Netherlands, safety of transfusion of blood and blood products is largely determined by supply of available technology. The major goal of public health authorities in this field has been to achieve maximum transfusion safety. For example, newer and better tests for blood-borne infectious diseases are rapidly introduced in screening procedures for blood donors, such as nucleic acid amplification testing (NAT) for the human immunodeficiency virus (HIV). Next to the 'maximum-safety' criterion, cost-effectiveness is becoming an important issue in judging new technologies, also in blood transfusion. Relatively high cost-effectiveness ratios are seemingly accepted in the blood transfusion area (Van Hulst *et al.*, 2002; Yeh *et al.*, 2002). For example, at estimated current Dutch levels of risk for HIV transmission through transfusion, HIV NAT costs several millions per life-year gained (LYG) (Postma *et al.*, 2001). This finding is in line with

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estimates of NAT for HIV and hepatitis C virus (HCV) in other countries (Pereira & Sanz, 2000; Loubière *et al.*, 2001; AuBuchon *et al.*, 2002).

Despite high levels of safety achieved in Dutch blood transfusion, risks still remain. Relatively small residual risks have been estimated for HIV, HCV and hepatitis B virus (HBV) (Müller-Breitkreutz, 2000). Particularly, for platelets relevant risks of bacterial infection and subsequent sepsis are estimated, with significant mortality rates being reported (Sazama, 1994; Ness *et al.*, 2001). Estimated sepsis risk after transfusion is highest for pooled platelets, with risks being suggested up to one per 2000 units transfused (Sazama, 1994; Lopez-Plaza *et al.*, 1999). In the Netherlands, pooled platelets reflect almost all utilization of platelet transfusions (Sanquin, 2000).

A new pathogen inactivation technology-the INTERCEPT® Platelet Systems-achieves reductions in pathogen loads in platelets below detection limits for all relevant enveloped viruses – such as HIV-1, HIV-2, HBV and HCV – and many bacteria – such as *Staphylococci* and *Escherichia coli* (Corash, 2000). The INTERCEPT® Platelet Systems (further: pathogen inactivation) is based on psoralen treatment. Application of pathogen inactivation for platelets may achieve benefits accruing at various levels:

- Elimination of risk for parasites and viral infections, such as HIV, HCV and HBV.
- Elimination of risk for sepsis due to bacterial infection.
- Blood bank processing benefits, such as improved discard rate of platelets due to prolonged shelf-life and potential elimination of gamma irradiation.
- Elimination of risks for yet unknown emerging pathogens.
- Potential reductions in judicial claims following fatal transfusion-transmitted infections.

In the present study, we assess the cost-effectiveness of pathogen inactivation in platelets. The scope of this article is limited to elimination of risks for known bacterial and viral infections and improvements in blood bank processing with regard to elimination of gamma irradiation. Benefits with respect to reduced discard rates may have already been achieved in the Netherlands with the implementation of bacterial screening in 2002. Benefits of averted spread of yet unknown emerging viruses in platelets and inclusion of judicial claims are left for discussion and further work. Future applications of the INTERCEPT® Systems, comprising the whole spectra of pathogens (including nonenveloped viruses) and products (including red cells and plasma), enhance formal consideration of such further benefits, inclusive of potential omission of any of the usual tests on donor blood for viruses and bacteria on the long-term.

MATERIALS AND METHODS

General design

We developed a pharmacoeconomic model that links characteristics of the population of platelet recipients (age, gender and outcome in terms of survival) with economic aspects of pathogen inactivation. The pharmacoeconomic model estimates cost-effectiveness in terms of net costs per discounted LYG, with inclusion of direct and indirect costs and benefits. Direct medical costs relate to the costs of pathogen inactivation. Direct benefits are related to costs of treatment and care for transfusion-related viral and bacterial infections and elimination of gamma irradiation. Indirect benefits are related to averted production losses related to averted deaths due to infections.

Patient population

The pharmacoeconomic model was developed for three separate typical patient groups, as cost-effectiveness for blood transfusion safety interventions may strongly vary between such groups (Van Hulst *et al.*, 2002). For example, application of viral inactivated plasma was estimated to cost US$59 000 per quality-adjusted LYG in trauma patients and US$122 000 in cardiac surgery patients (AuBuchon & Birkmeyer, 1994). Application of single-donor platelets instead of pooled platelets was estimated to cost US$200 000 per quality-adjusted LYG in cardiac surgery and US$470 000 in haematology (Lopez-Plaza *et al.*, 1999). In this study, we elaborate cost-effectiveness for three patient groups giving rise to the major share of platelet transfusions in the Netherlands: cardiology, haematology and paediatric oncology.

Transfusion data of patients were gathered in the University Medical Centre Groningen (UMCG, the Netherlands) in 1997. Figure 1 shows the distributions in terms of patients (Fig. 1a) and transfusions (Fig. 1b). As shown, cardiac surgery patients – primarily undergoing coronary artery bypass grafting – represented almost 41% of the patient population receiving platelets, whereas in terms of platelet transfusions their proportion is lower (23%). In terms of the number of transfusions, haematology accounts for the major share. Table 1 lists the distributions of platelet transfusions over age

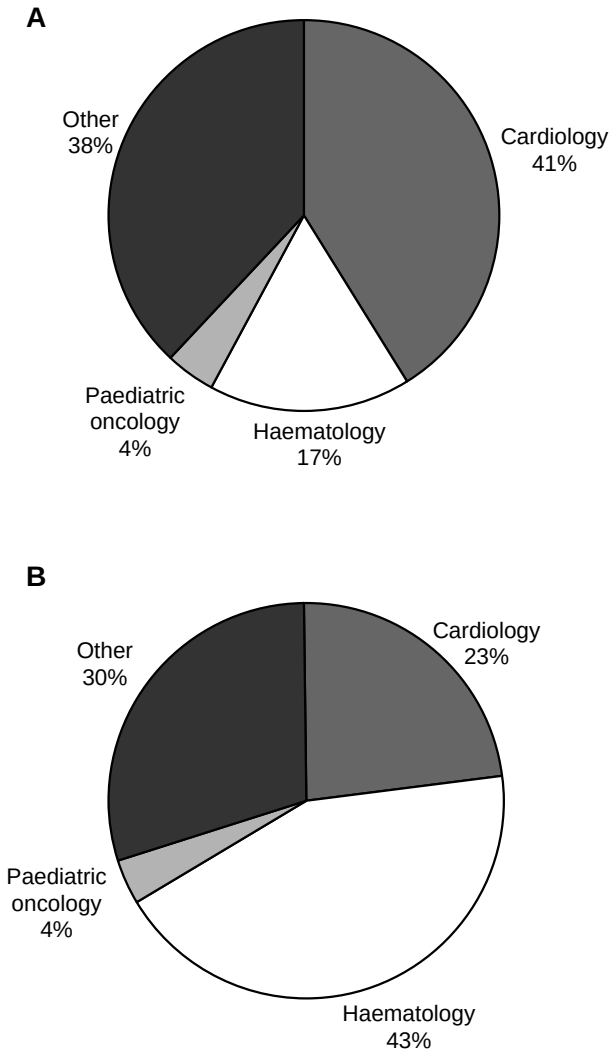

Fig. 1. Distribution of patients (upper) and transfusions (lower) over patient groups in the University Medical Centre Groningen (data for 1997).

groups and gender. This distribution is the basis for our pharmacoeconomic model below.

Risks of pathogen transmission

Given the existence of thorough donor selection and routine donation screening for HIV, HCV and HBV, virally infected donations are very rare in the Netherlands. European estimates for the risk of window period donations in 1997 were one in 2·3 million for HIV, one in 620 000 for HCV and one in 400 000 for HBV (Müller-Breitkreutz, 2000). In the model, we applied recent estimates that are considered specific to the Dutch situation at one per 200 000 for HBV and one per million for HIV and HCV (Health Council, 2003).

Transfusion-related sepsis is most often related to platelet transfusions. Approximately 80% of cases in the UK were estimated to be related to platelets (Serious Hazards of Transfusion (SHOT), 2001). An internationally published (Yomtovian *et al*., 1993; Ness *et al*., 2001) risk of 0·04% per platelet transfusion was deployed in the model as upper bound and investigated in sensitivity analysis (see below). Corresponding case fatality for sepsis was assumed at 15% (Ness *et al*., 2001). For the lower bound (also investigated in sensitivity analysis), 0·025% was taken for platelet transfusion-related sepsis with a related case fatality of 17% (Morrow *et al*., 1991; Sazama, 1994). For the baseline, the intermediate risk at 0·0325% and intermediate case fatality at 16% were assumed. On top of these estimates, we assumed that the recently implemented bacterial screening only slightly reduces the sepsis risk by approximately 5% (almost 40% of positive units are

Table 1. Percentage distribution of platelet transfusions for three patient groups in the University Medical centre Groningen in 1997 by age and gender ($n = 603$ for cardiology, $n = 120$ for haematology and $n = 30$ for paediatric oncology)

	Cardiology		Haematology		Paediatric oncology	
Age group (years)	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
<10	2·5	1·3	0·0	0·0	46·7	23·3
10–20	0·0	0·5	1·7	0·0	20·0	10·0
20–30	0·5	0·8	5·8	3·3	–	–
30–40	1·2	0·5	0·8	9·2	–	–
40–50	9·6	0·2	13·3	7·5	–	–
50–60	13·8	1·3	15·8	18·3	–	–
60–70	19·4	9·6	10·0	7·5	–	–
70–80	23·2	12·3	1·7	4·2	–	–
>80	1·0	2·3	0·0	0·8	–	–
Total	71·1	28·9	49·2	50·8	66·7	33·3

not recalled, and over 90% of recalled platelet units are already transfused) (Beckers *et al*., 2005).

Excess mortalities for HIV and HCV were set at 6 and 1% per annum, respectively (Loubière *et al*., 2001; Postma, Wiessing *et al*., 2001). Mortality due to HBV infection was neglected.

Costing aspects

All costs in our analysis were estimated at price levels of 2003. If required, annual deflators of 1·8% for direct and 2% for indirect costs were used (Oostenbrink *et al*., 2000). According to the Dutch guidelines for pharmacoeconomic research, future costs (and LYG) were discounted at 4% per annum (Riteco *et al*., 1999).

Lifetime, discounted direct costs for transfusion-related viral infections were available from the published literature (Struijs *et al*., 2000; Postma, Wiessing *et al*., 2001; Postma *et al*., 2005). Direct costs for transfusion-related sepsis were based on a recent Dutch study (Van Gestel *et al*., 2002). Table 2 lists the cost estimates as used in the model.

To enable estimation of cost-effectiveness from the societal perspective, indirect costs were included for death due to any transfusion-related infection, i.e. HIV death, HCV death and sepsis death. The societal perspective is preferred in many international guidelines for pharmacoeconomic research, including the Dutch ones (Riteco *et al*., 1999; Hjelmgren *et al*., 2001). Indirect costs were estimated using the friction costing approach, as requested by the Dutch guidelines for pharmacoeconomic research (Riteco *et al*., 1999; Oostenbrink *et al*., 2000). As opposed to the human capital approach, the friction costing approach only counts indirect costs of production losses during a period of a limited number of months required to fill in the vacancy. The human capital approach calculates production losses during all future life-years that are lost due to premature death.

Table 2. Direct costs for viral infections and bacterial sepsis in € (price level 2003) used in the model (costs for-human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV) are lifetime discounted costs) (Struijs *et al*., 2000; Postma, Wiessing *et al*., 2001; Van Gestel *et al*., 2002; Postma *et al*., 2005)

HIV	83 200
HCV	19 500
HBV	1100
Sepsis	20 600

The costs for pathogen inactivation were assumed at €116, the currently envisaged price for hospitals (including margins for required production process changes in the blood banks; personal communication with the manufacturer). Additional costs are posed by pathogen inactivation that may potentially involve yield losses. We assumed a 10% increase in the costs per platelet transfusion unit to account for this factor (McCullough *et al*., 2001; Van Rhenen *et al*., 2003). Additionally, in the trials performed for INTERCEPT®, excess transfusions were required to achieve adequate count increments. In the US SPRINT trial, such excess transfusions were more than 30%; in the European euroSPRITE trial, no significant difference was found (McCullough *et al*., 2001; Van Rhenen *et al*., 2003). In our analysis, we assumed 15% excess transfusions with pathogen inactivation (0 and 30% in sensitivity analysis). Excess transfusions were monetarily valuated at the estimated cost price per platelet transfusion unit of €458 for adult and €285 for paediatric application (Sanquin Blood Supply: price list as of 1 March 2003) plus €116 for bacterial inactivation.

Finally, benefits of elimination of gamma irradiation were inserted in the model, assuming this elimination in 10% of transfusions in haematology and paediatric oncology at €30 per irradiation.

Pharmacoeconomic model

The distribution of platelet transfusions in the UMCG was the basis for our pharmacoeconomic model. This distribution was conceived to reflect the probabilities that an individual unit is transfused to a patient of specific gender, age and patient group. For each patient group, an age- and gender-specific Markov model was developed for post-transfusion survival. Survival results from death risks due to viral/bacterial infection through transfusion, post-cardiac surgery death risks and those due to other causes (natural mortality). Details on transfusion-related infections are listed below; mortality for cardiac surgery, haematology and paediatric oncology patients was estimated at 17, 38 and 37%, respectively, in the first year (data from the UMCG for 1997) and 1, 5 and 0·5%, respectively, in subsequent years (The Bypass Angioplasty Revascularization Investigation (BARI) Investigators, 1996; Lopez-Plaza *et al*., 1999; Coebergh *et al*., 2001). Natural mortality was taken from the national statistics (source: Dutch Central Bureau of Statistics, Voorburg, the Netherlands).

For the three patient groups considered, a weighted average for cost-effectiveness was also calculated (proportions of transfusions as weights;

Fig. 1). As shown in Fig. 1, the patient groups in our model are estimated to consume 70% of Dutch platelet transfusions.

Figure 2 shows above in the concept of a decision tree.

Cost-effectiveness was expressed in net costs per LYG. Net costs reflect the costs of pathogen inactivation minus its monetary benefits. Monetary benefits were related to either the elimination of risks for viral and bacterial infection or gamma irradiation. Monetary benefits and LYG were estimated by comparing two options in the model. In a first step, the financial costs and life-years lost were estimated in the absence of pathogen inactivation with risks for transfusion-related viral and bacterial infections as specified above. In the next step, pathogen inactivation was simulated, corresponding with zero risks for infections of pathogens considered in this analysis. In addition, elimination of gamma irradiation was assumed. Differences in costs and life-years in both options were compared subsequently.

Cost-effectiveness was estimated in the baseline and sensitivity analysis. Deterministic sensitivity analysis was performed with respect to viral risks, bacterial risk, reduction in discard rate and discounting of LYG. For stochastic sensitivity analysis, Monte-Carlo simulation was performed with respect to the annual number of transfusion-related sepsis cases (Poisson distribution) allowing calculation of 90% simulation intervals (SIs) for cost-effectiveness. Microsoft Excel 97, @RISK 3·5 for Excel (Palisade, London, UK) and DATA 3·5 for Health Care (TreeAge Software, Williamstown, MA, USA) were used for computer implementation and presentation.

RESULTS

As an example, estimated annual monetary benefits of pathogen inactivation in the baseline accrued to €69 300 per 10 000 transfusions in cardiac surgery (10 000 also approximately reflects the annual number of Dutch platelet transfusions in cardiac surgery). Of these benefits, 96% referred to averted cases of sepsis (also for the other patient groups, sepsis accounts for the major share of benefits; however, additional benefits come in for elimination of gamma irradiation at approximately 30% of total benefits). Furthermore, per 10 000 transfusions in cardiac surgery, approximately 4·4 discounted life-years were gained and costs of €2169 200 were made, rendering net costs of €2099 900 and net costs per LYG at €474 000 in the baseline (90% SI: €302 500–€940 300). Baseline estimates for the other patient groups – haematology and paediatric oncology – were €678 600 (90% SI: €434 000–€1338 300) and €260 700 (90% SI: €166 800–€511 200), respectively. The weighted average over the three patient groups was estimated at €554 000 (90% SI: €354 000–€1092 500) As mentioned, SIs formally represent potential annual fluctuations in cost-effectiveness.

Sensitivity analysis revealed that our results are insensitive to the exclusion of averted viral infections and exact levels of assumed indirect costs (not shown). Model results were sensitive to sepsis risk and related case fatality, the assumed excess transfusions through inactivation and discounting of LYG (Table 3 lists results for weighted average over patient groups). In percentage changes, results were most sensitive to higher excess transfusions assumed (+74% of baseline) and nondiscounting of LYG (−38% of baseline).

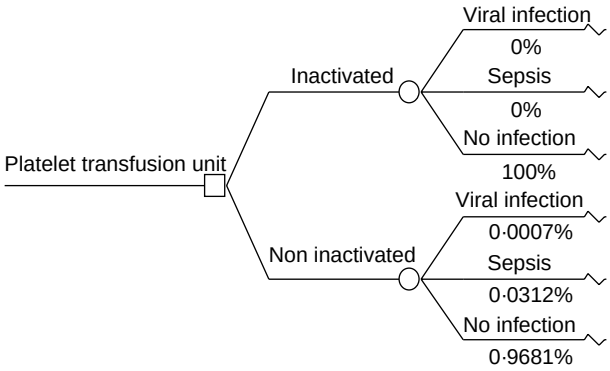

Fig. 2. Decision tree for the cost-effectiveness analysis of pathogen inactivation.

DISCUSSION AND CONCLUSIONS

Cost-effectiveness of pathogen inactivation of platelet transfusions was estimated at €554 000 per LYG in the baseline as an average over three major patient

Table 3. Sensitivity analysis for the cost-effectiveness ratio in net costs per life-year gained (LYG) (in €; price level 2003) on sepsis risk (and related case fatality), excess transfusions and discount rate for the weighted average over the three patient groups considered (cardiology, haematology and paediatric oncology)

Baseline (sepsis risk 0·0325%; case fatality 16%; 15% excess transfusions; discounting of LYG)	554 000
Sepsis risk 0·04%; case fatality 15%	476 900
Sepsis risk 0·025%; case fatality 17%	682 700
No excess transfusions required	393 500
Excess transfusions required at 30%	961 500
Nondiscounting of LYG	341 200

groups, accounting for 70% of Dutch platelet transfusions. Averted cases of sepsis were identified as major drivers of benefits of pathogen inactivation. In sensitivity analysis, a range around €554 000 from €341 200 to €961 500 was indicated, by assuming nondiscounting LYG and 30% excess transfusions due to inactivation, respectively.

In the frameworks of statin treatment for high cholesterol and several vaccination studies, a Dutch threshold for acceptable net costs per discounted LYG of approximately €20 000 has been suggested (Postma, Heijnen *et al*., 2001). Such thresholds differ between societies and between interventions (Owens, 1998). For example, for transplantation services, relatively high thresholds for cost-effectiveness are implicitly applied with transplantations of the liver and the lung costing approximately €100 000 per discounted LYG (Michel *et al*., 1994; Al *et al*., 1998). Also for transfusion safety, relatively high net costs per discounted LYG – up to one million €'s – seem to be accepted in the Netherlands and other countries (Postma, Staginnus *et al*., 2001; Van Hulst *et al*., 2002; Yeh *et al*., 2002). For example, we recently estimated cost-effectiveness of NAT of Dutch donors for HIV at €200 000 to over one million €'s (Postma *et al*., 2002). From this perspective, our estimated cost-effectiveness figures for pathogen inactivation may reflect acceptable net costs per LYG.

Our analysis primarily focused on results using discounted life-years (gained). Nondiscounting of LYG reduces net costs per LYG up to almost two-thirds in our analysis. For preventive services such as the one investigated here, discounting of LYG is subject to debate among pharmacoeconomists (Gold *et al*., 1996), and one may argue to focus on net costs per nondiscounted LYG for pathogen inactivation, i.e. €341 200 (Bos *et al*., 2002).

We analysed the risk for transfusion-related sepsis over a plausible range from 0·025 to 0·04% per pooled platelet unit transfused. Lower risks have been reported, for example in the BACTHEM and BaCon studies (Kuehnert *et al*., 2001; Perez *et al*., 2001). The authors of the former study commented on their findings on incidence rates of life-threatening bacterial contaminations that these probably are underestimated due to underreporting and overestimation of the denominator in the calculus (issued numbers instead of transfused units) (Perez *et al*., 2001). The latter study has been argued to have identified merely the top of the iceberg (Yomtovian, 2002). Another study estimated approximately one adverse reaction per 2000 platelet transfusions, higher than our baseline assumption (Robillard & Karl Itaj, 2001). Finally, we note that our assumptions on risks for bacterial infections are in line with a consensus of opinion that was expressed in an open letter to the Blood Collection Community (Brecher *et al*., 2002).

During the conduction of our research, bacterial testing was implemented in the Netherlands and was used in Dutch blood banks during 2002 (BacTAlert®, Oreganon Teknika BV, Boxtel, The Netherlands). Bacterial testing has reduced the risk for transfusion-related bacterial infection in the Netherlands. Recent research, however, indicates that this reduction may be only limited, as mentioned in the section entitled 'Materials and Methods'. Also, for serious infection (ICD code 999·8: 'septic shock due to transfusion or transfusion reaction NOS'), no reduction in the annual number of cases was, seen in the national hospital registration data (Primant Utrecht). During 1998–2001, approximately 20 cases were registered annually (case fatality: 16%), whereas 2002 had 24 cases (case fatality: 21%) (Primant Health Care, 2002). We believe that these data do currently not support the formal inclusion of a more prominent risk reduction due to bacterial screening than the current 4% on our baseline sepsis risk of 0·0325%.

Further benefits of pathogen inactivation may be related to the occurrence of a new emerging virus of which the spread through platelet transfusion may be averted. The historic example of transfusion-related HIV in the Netherlands may serve as an illustration. Primarily, during the first 5 years of the Dutch HIV epidemic, approximately five HIV infections may have been directly caused by platelet transfusions annually (Op de Coul, 2001). Aversion of such an epidemic would translate into direct benefits of averted lifetime HIV treatments, indirect benefits and LYG for both index cases and spouses.

Our current analysis is limited to the Netherlands. Differences in health care systems, treatment patterns for viral and bacterial infections, cost prices and costing guidelines complicate country-to-country transition of pharmacoeconomic models (Welte & Leidl, 1999; Schmid *et al*., 2001). Also, national blood banking policies and infection risks differ between European Union (EU) countries. For example, we note that the transfusion-related HIV epidemic in the Netherlands has been limited compared to that in other EU countries (Postma, 1998) and the US. A preliminary evaluation of the pathogen inactivation process for the US indicates that inclusion into the analysis of averting of an HIV-like emerging virus, to be transmitted through platelet transfusion, may result in overall life- and cost savings (Bell *et al*., 2002).

Obviously, we cannot test definitively the validity of the assumption that spread through platelet

transfusions of the next virus that comes along is averted. Its plausibility is based on the observation that this pathogen inactivation technology has been effective against all the enveloped viruses tested (Lin *et al*., 1997). Furthermore, we know from studies on the HIV viruses using inhibition of molecular amplification that these viruses are highly modified after psoralen treatment and that the titre of virus that can be inactivated is far greater than the 6-log inhibition of infectivity (Lin *et al*., 1992).

Two of the main assumptions of this cost-effectiveness analysis were that the pathogen inactivation for platelets was 100% effective in preventing transmission of the pathogens used in the model and was not associated with any adverse reactions. We note that the INTERCEPT® Blood System for platelets was not effective although for nonenveloped viruses that are not in our current analysis. Clinical studies conducted in the US and Europe have evaluated the efficacy and safety of the INTERCEPT® Blood System for platelets, and no excess treatment-related adverse reactions were detected in patients receiving platelet components treated with pathogen inactivation technology (McCullough *et al*., 2001; Van Rhenen *et al*., 2003). Also, we note that a carcinogenicity study using a sensitive and validated heterozygous p53 mouse model has been completed, and treated platelets were not carcinogenic at 1000-fold the clinical exposure (Ciaravino, 2001). This study was reviewed by federal drug administration (FDA) and EU regulatory authorities who concurred with the observation of no carcinogenicity. However, inherent to the assumed benefit of platelets treated with the pathogen inactivation process is a level of uncertainty, as with any new medical intervention, and any benefit gained from the use of pathogen-inactivated platelets may be offset by the incidence of an unanticipated adverse reaction or any other treatment-related hazard.

Finally, we note that our cost-effectiveness analysis could be based on three patient groups only, leaving 30% of platelet transfusions uncovered by our model. These transfusions may involve multitrauma with poor short-term prognosis, i.e. patient groups whose inclusion in the model may worsen cost-effectiveness.

Cost-effectiveness of pathogen inactivation of platelet transfusions was estimated at €554 000 per LYG in a weighted average for three patient groups, accounting for 70% of Dutch platelet transfusions. Given relatively high net costs that are internationally accepted for an LYG in blood transfusion safety interventions, our estimated cost-effectiveness figures for pathogen inactivation may reflect acceptable cost-effectiveness in this specific area.

Averted cases of sepsis were identified as the major driver of health gains of pathogen inactivation. Validation of several crucial parameters is required, in particular the Dutch risk of acquiring transfusion-related sepsis and subsequent case fatality. Further work should extend the model to other countries as well as including further potential benefits of pathogen inactivation. The relevance of this inclusion is enhanced if pathogen inactivation is to cover the whole spectra of pathogens and blood products.

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ORIGINAL ARTICLE

Assessment of the economic value of the INTERCEPT blood system in Belgium

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SUMMARY. Emerging pathogens continue to threaten blood safety, requiring novel safety approaches. INTERCEPT Blood System for platelets (IBSP) inactivates pathogens, aiming at eliminating the risk of transmitting current and emerging pathogens. The objective was to evaluate the incremental cost-effectiveness ratio (ICER) for IBSP in Belgium.

A decision model comparing a 'world with IBSP' to a 'world without IBSP' calculates lifetime costs and 'quality adjusted life years' (QALYs) following platelet transfusion in different indications. Disease-specific life expectancy and consequences of transfusion-transmitted infections were obtained from literature. Transfusion safety and costs were obtained from official sources. Hepatitis C virus-like emerging pathogen was simulated.

A wide range of ICERs was observed, highly sensitive to the risk of emerging pathogen transmission, underlying disease and age. In the most conservative approach, ICER ranged from 3,459,201€/QALY in absence of emerging pathogen to 195,364€/QALY. The mean threshold of emerging infection risk for IBSP dominance (saving money and producing health gains) ranged from 1/1,079 to 1/2,858 transfusions.

Considering the high value authorities appear to place on preventing accidental injury, and ICER of recent implementations in transfusion medicine (NAT: up to €2·3 million per lifeyear), IBSP can be considered cost-effective, taking into account the potential risk of emerging pathogens.

Key words: emerging, INTERCEPT, pathogen inactivation, platelets, safety, transfusion

The risk of transfusion-associated viral infections has been significantly reduced by the introduction of donor-screening and blood-screening tests in routine practice. However, some residual risk of transfusion-related infections remains. This is because of the window period between infection and positive test results on the one hand and to some pathogens which could potentially be transmitted via transfusion, but for which screening tests are not performed today on the other hand (e.g. Cytomegalovirus [CMV], Human T-lymphotropic virus [HTLV]...). In addition, viral screening tests may produce false-negative results (Laperche *et al.*, 2003; Busch, 2003). Recently, safety measures have been increased by including NAT tests for hepatitis C virus (HCV) and HIV detection in routine screening programs. However, current safety initiatives consisting of serological or viral antigen tests address only one or few selected pathogens at a time. Any new pathogen requires new safety measures in addition to the already established system.

Historical as well as contemporary data confirm that the risk of newly emerging infections is not hypothetical (WHO, 1998 (www.who.int); Leiby, European Parliament hearing June, 2003; Biggerstaff & Petersen, 2003). Depending on their clinical characteristics and modes of transmission, these emerging infections may present an enormous threat to transfusion safety. Scientific information is often limited at the time of emergence, and the development of diagnostic screening tests takes time. Therefore, these emerging agents require novel approaches to prevent transmission (Leiby, European Parliament hearing June, 2003).

As they are stored at room temperature, platelets are particularly vulnerable for bacterial contamination. Therefore, bacterial screening is routinely performed on platelet samples in Belgium; however, a potential risk of false-negative results remains.

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The INTERCEPT Blood System for platelets (IBSP) is a new technology which inactivates different types of pathogens through irreversible binding to RNA/DNA in the blood (*BioDrugs*, 2003).

When new safety measures are introduced, there is clearly a need to accurately define the value of these new initiatives, and decisions regarding blood-screening policies must be based on accurate estimates of the incremental safety balanced against cost and taking into account the potential loss of donors (Busch *et al*., 2003).

The objective of our study was to analyse the health and economic consequences of pathogen inactivation using the IBSP in Belgium, taking a perspective directed to the future, including the risk of emergence of a new transfusion transmittable virus.

SUBJECTS STUDIED

The target population included patients with haematological malignancies undergoing bone marrow or peripheral stem cell transplantation [acute lymphoid leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML) and non-Hodgkin's lymphoma (NHL)], breast cancer patients undergoing stem cell transplantation and patients undergoing cardiac surgery, whereby coronary artery bypass graft (CABG) was selected as case. These populations are considered to receive most commonly platelet transfusions (Bell *et al*., 2003).

MATERIALS AND METHODS

We performed a cost-effectiveness analysis in Belgium from a societal perspective, including both direct medical costs and productivity related costs (expressed in euro), as well as legal and liability costs.

A decision analytical model was developed simulating the clinical outcomes of patients requiring platelet transfusion, in a world with and in a world without the INTERCEPT blood system.

Model

The model was developed using TreeAge data™ software. The model starts at the time of platelet transfusion and simulates the evolution of a cohort of patients receiving transfusions of platelets inactivated with the INTERCEPT blood system compared with the same cohort receiving untreated platelets, taking into account the risk of bacterial infection, HCV, hepatitis B virus (HBV) and HIV infection. These infections are currently tested for in Belgium and their residual transfusion-related infection risk has been assessed.

In addition, the risk of a possible newly emerging viral infection is included in the framework.

The overall risk of infection per patient is calculated in the model as the residual risk per transfusion multiplied with the average number of transfusions per patient.

If no transfusion-related infection occurs, the average life expectancy is the one of the underlying diseases. If transfusion-related infection occurs, the life expectancy is reduced because of the mortality associated with the infection. The main decision analytical model structure is outlined in Fig. 1.

Life expectancy in the absence of transfusion-related infection

The average life expectancy associated with the considered underlying diseases was calculated based on published mortality rates. By applying yearly mortality rates, average life expectancy can be calculated as the surface below the survival curve.

For both ALL and AML, 1 year mortality was 44% (Dini *et al*., 2001). During subsequent years, the relative mortality rates as reported by Socié *et al*. (1999) were applied to age-matched general mortality rates in Belgium (1997).

In patients with NHL undergoing early stem cell transplantation, a 5-year overall survival rate of approximately 65% is reported (Dresse *et al*., 1999; Martelli *et al*., 2003). Patients surviving more than 5 years were assumed to have normal life expectancy.

In CML patients, based on review of recent literature (Carreras *et al*., 2000; Davies *et al*., 2001; Elmaagacli *et al*., 2002; Gaziev *et al*., 2002; Pigneux *et al*., 2002; Radich *et al*., 2003), an average cumulative mortality rate of 50% by year five was estimated. For the remainder 50%, long-term relative mortality rates were applied to the age-matched general population (Socié *et al*., 1999).

For CABG patients, a weighed average life expectancy was calculated from data published by Weintraub *et al*. (2003), including mortality rates up to 20 years post-intervention. Although these patients were operated many years ago, the short-term mortality was not higher than reported in more recent studies (Calafiore *et al*., 2000; Taggart *et al*., 2001).

For breast cancer patients undergoing Peripheral Stem Cell Transplantation (PSCT), life expectancy was estimated equal to the weighed (for study size) average median survival reported in PSCT patients (Farquhar *et al*., 2003).

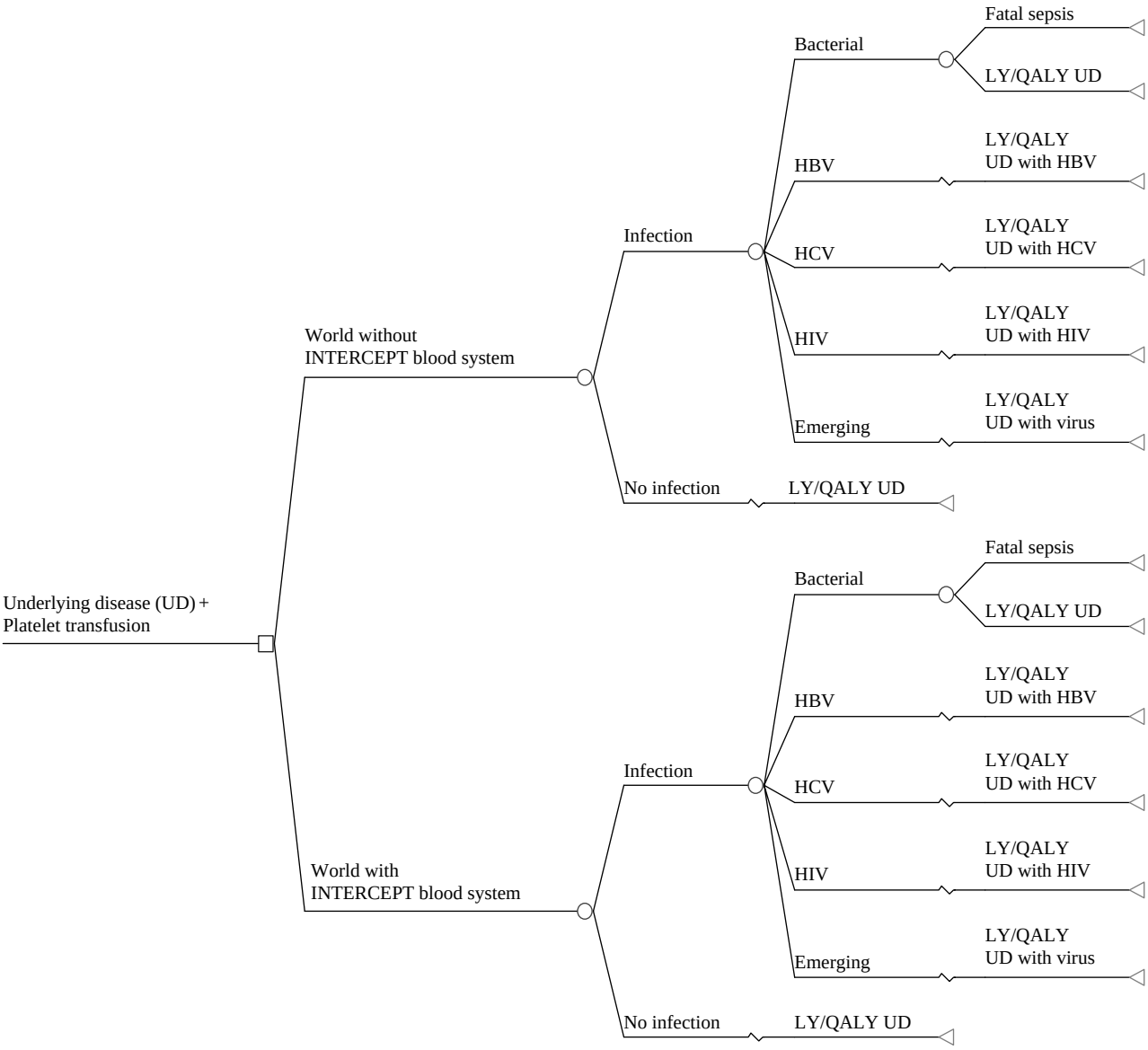

Fig. 1. Basic structure of decision tree. QALY, quality adjusted life years.

Table 1 summarizes the obtained average life expectancy per underlying disease.

Risk of known infections with untreated platelet components

Table 2 provides an overview of viral safety tests performed on blood components in Belgium today, the frequency of positive tests and the respective residual risks of viral transmission per transfusion (Belgian Red Cross 2003, see Acknowledgements). As they are stored at room temperature, platelets are particularly vulnerable for bacterial contamination. Therefore, in Belgium, a sample of the platelet component is monitored for bacterial contamination throughout storage time using the 'BactAlert system'. Because of the absence of mandatory reporting of any transfusion-related events, there is limited information on the actual risk of transfusion-associated bacterial infections in Belgium. For the current analysis, Red Cross and clinical expert estimates were collected. The most conservative estimate, reported by the Red Cross, was a rate of transfusion-associated bacterial infections of one in 5000 transfusions.

Risk of emerging pathogens

To assess the potential health economic consequences of the INTERCEPT blood system, the risk of future

Table 1. Average life expectancy in the absence of transfusion related infection

Type	Average life expectancy (years)
AML adults	1·7
AML childhood	31·9
ALL adults	3·1
ALL childhood	15·6
NHL adults	5·9
NHL childhood	26·3
CML	9·6
CABG	16·1
Breast cancer	2·7

ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; CABG, coronary artery bypass graft; CML, chronic myeloid leukaemia; NHL, non-Hodgkin's lymphoma.

known or unknown emerging infections were taken into account. Because the characteristics of a new emerging virus are unknown, it was decided to simulate an economic, morbidity and mortality impact comparable with HCV. The simulation of infection risk for this new emerging virus can be based on the historical evolution of HCV virus transmission through transfusion, although it could be argued that, compared with the 1990s, a new virus today would be identified sooner after its emergence because of scientific progress, and hence, that transmission rates will probably not reach the level observed for HCV at the time. But, on the other hand, a lot depends on the disease characteristics. A long asymptomatic period following initial infection may significantly increase the time to identification and the time to linking the infection with blood transfusion. The American Medical Association (2000, see Chamberland, 2002) described the historical evolution of transfusion-related transmission of HCV in the United States. In the 1970s, the risk of HCV infection was very high (>1/100). The improvements in donor screening and testing have combined to result in substantial decreases in transfusion-transmitted infections during the 1980s and 1990s. On the other hand, other factors also contribute to the incidence rates of transfusion-related infections that may be reached such as the window period for the emerging pathogen, its incidence and prevelance in the donor population... (Chamberland, 2002). Our economic evaluation was performed for different levels of emerging viral infection risk between 1/100 and 1/100,000 transfusions.

Efficacy and safety of IBSP

The following pathogens are inactivated by the system (approved indications): HIV 1, HIV 2, HBV, HCV, CMV, MCMV and aerobic bacteria.

The following inactivation claims have been recently approved by the Irish Medicines board: HTLV I, HTLV II, *Treponema pallidum* (Syphilis), protozoa (*Trypanosoma cruzi*, Chagas disease, *Plasmodium falciparum,* malaria) and anaerobic bacteria.

Other inactivation studies on alternative pathogens are ongoing (Leishmaniasis, Babesiosis, *Candida albicans*, *Borrelia bugdorferi*, West Nile virus, Parvovirus B19 – last update July 2004).

The results of an extensive series of *in vitro* and *in vivo* studies have not demonstrated any toxicologically relevant effects on platelet concentrates prepared by the INTERCEPT Blood System (Ciaravino *et al.*, 2001).

In the model, the inactivation system is programmed to eliminate the risk of the considered known transfusion transmittable infections as well as to eliminate transmission of the simulated emerging virus. Two main assumptions underlying the model were that

Table 2. Viral safety measures and residual risk of platelet transfusions (Belgium)

		Donations (Wallonia, 2002, see Acknowledgements)		Donations (Flanders, 2000, see Acknowledgements)		
Virus	Screening test	Tested +	True +	Tested +	True +	Residual risk*
HBV	HbsAg	54/100,000	17/100,000	121/100,000	10/100,000	<1/200,000
HCV	Anti-HCV	93/100,000	17/100,000	119/100,000	6/100,000	<1/200,000
	NAT					1/703,571
HIV	Anti-HIV1 and 2	111/100,000	0/100,000	103/100,000	0·3/100,000	<1/2–3 mio
	NAT HIV1					<1/4–6 mio

HBV, hepatitis B virus; HCV, hepatitis C virus.
Source: Belgian Red Cross.
*Risk of transmission per 'transfusion'.

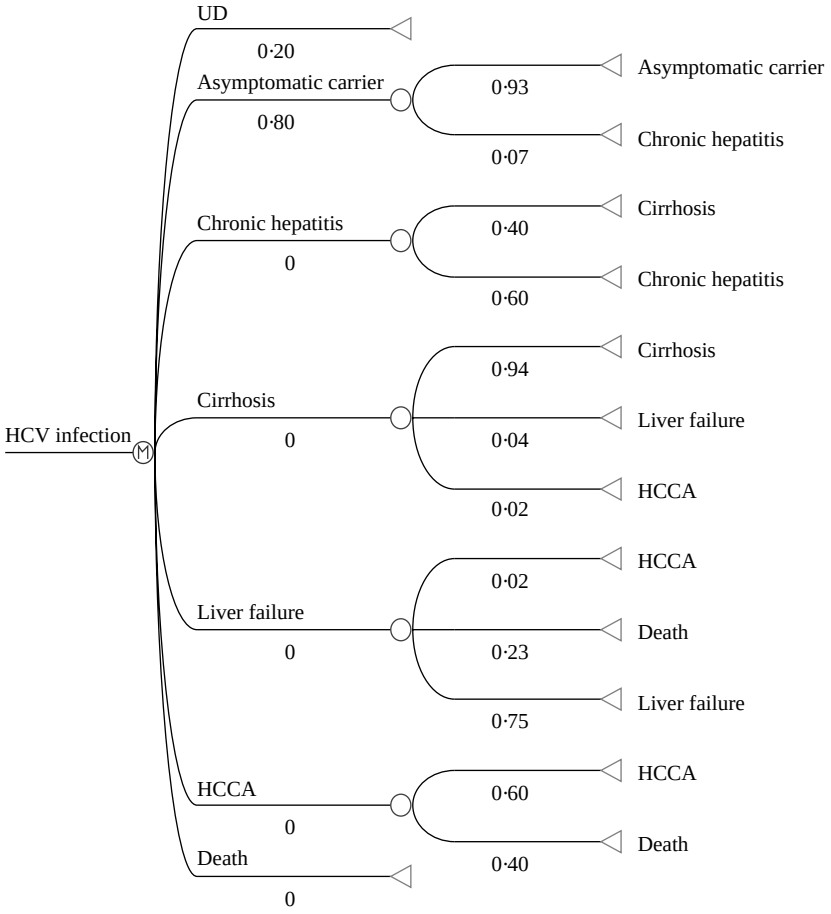

Fig. 2. Structure of subtree related to transfusion-transmitted infection with hepatitis B or C. Under each branch, the probability of transition from the left to the right health state are shown. The probabilities under the left hand side branches represent possible pathways at model start, at the time of infection. At this time, patients can either have only acute infection without becoming a carrier (20%) or become carrier (80%). Subsequently, carriers may develop chronic complications, possibly evolving over chronic hepatitis to cirrhosis, liver failure or carcinoma. The probabilities shown under the right hand side branches represent the likelihood of possible transitions from one state to another. The probabilities were obtained from published literature (Pereira, 2000; Sevinir, 2003; Gordon, 1998; Hu, 1999; Tong, 1995). Only the probability of developing chronic hepatitis is different for HCV versus HBV: 0·212 (Sevinir, 2003; Pereira, 2000) and 0·224 (Sevinir, 2003; Gordon, 1998) respectively. Other disease progression rates were programmed equally for HCV and HBV. HCCA, hepatocellular carcinoma.

pathogen inactivation is 100% effective and is not associated with major or costly adverse events.

Additional benefits of the IBSP

The INTERCEPT blood system is anticipated to have an additional number of future benefits, supported by a recent international forum of experts (Engelfriet *et al.*, 2003).

First, it is estimated that, in the future, some of the currently applied screening tests, leading to platelet waste, may be eliminated. These may include BactAlert testing, NAT testing (given the high burden and low yield) and Alkaline Phosphatasis (ALT) testing. It must be noted that, at present, the elimination of NAT testing is only possible for single donor platelets, because for random donor platelets, the tests are needed to ensure safety of the obtained red cells and plasma. However, pathogen inactivation for red cells may become available in the future. Nevertheless, given the uncertainty of its timing, in a secondary analysis (not in the basecase), we considered this potential benefit only for Single Donor Platelets (SDP) platelets. Secondly, studies have demonstrated that the INTERCEPT blood system is at least as effective as γ-irradiation for the inactivation of T-cells (Lin *et al.*, 1997; Grass *et al.*, 1998). Hence, the second potential benefit may be to make γ-irradiation, which is performed on the majority of platelet components in Belgium today, obsolete. The third benefit consists of a reduction of platelet waste. Today, in Belgium, of the 45,808 platelet transfusion bags donated annually, approximately 8% are wasted because of storage time overdue and 1·9% because of contamination or positive viral screening tests (Red Cross Belgium). In the past, the platelet storage time initially set at 7 days was reduced to 5 days mainly for increasing risk of bacterial contamination. With the INTERCEPT blood system, the previously applied limit of 7 days could potentially be re-introduced. In addition to the above-mentioned current potential benefits, pathogen inactivation may avoid a proportion of supplementary tests in the future for potential emerging pathogens, which will not be required for SDP. Conservatively, the latter benefit is not considered in the economic evaluation.

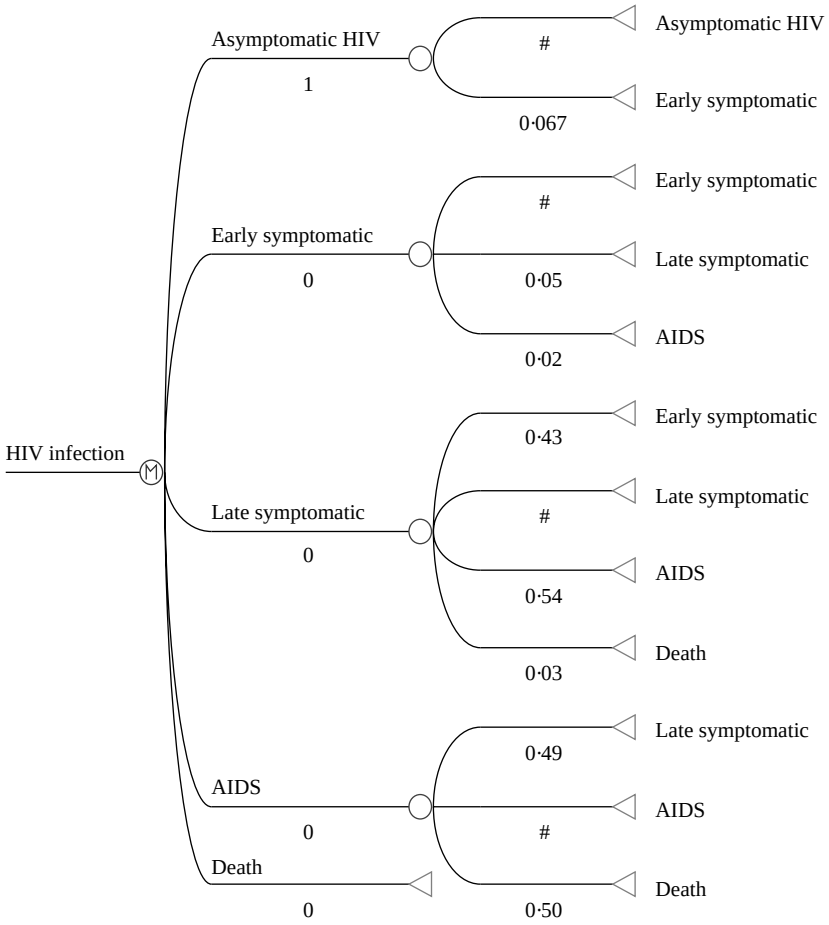

Fig. 3. Structure of subtree related to transfusion-transmitted infection with HIV. Under each branch, the probability of transition from the left to the right health state is shown. The probabilities were obtained from published literature. (Miners, 2001).

Impact of transfusion-transmitted infections

The impact of transfusion-transmitted viral infections was calculated by simulating the clinical progression rates over different disease states (Figures 2 and 3) obtained from literature and assigning costs (Table 4) and utilities to each state. Utilities are values representing the quality of life in a certain health status. Utility values can range between 0 and 1, with 0 representing death and 1 representing a state of perfect health. The time spent in a certain health state is multiplied by the corresponding utility weight to account for the quality of life in that particular state. The utility values applied in the model were obtained from previous published research (Table 3).

Regarding bacterial infections, 9·7% have been reported fatal and 26·5% life threatening (France, Andreu *et al*., 2002). For the current analysis, non-fatal infections were not attributed any reduction in quality of life given their limited duration. Fatal or life-threatening bacterial infections were attributed a management cost derived from previous research related to severe sepsis, showing a total cost per sepsis episode of €17,988 (SE = 1145) (Laterre *et al*., 2002).

Table 3. Utility weights applied for disease stages related to viral infection

	Utility (95% CI)
HIV	
Asymptomatic (CD4 >500 cells mm^{-3}) (Tengs 02)	0·94
CD4 200–500 cells mm^{-3}	0·82
CD4 <200	0·79
Aids	0·77
Hepatitis	
Viral negative	1
Chronic Hepatitis	0·82 (0·6–0·9)
Compensated Cirrhosis	0·78 (0·5–0·9)
Decompensated Cirrhosis	0·65 (0·3–0·88)
Hepatocellular Carcinoma	0·25 (0·1–0·5)
Liver transplantation, 1st year	0·5 (0·11–0·7)
Liver transplantation, subsequent years	0·7 (0·24–0·87)

The same utility values were applied for hepatitis C virus as for hepatitis B virus related health states (Dusheiko *et al*., 1995)

Table 4. Cost data for disease stages related to viral infection

	Annual cost (€) (SD)
HIV*	
Stage A: Asymptomatic	2231 (1955)
Stage B: Symptomatic	7899 (7070)
Stage C: Aids	25,736 (20,766)
Hepatitis	
Viral negative	
Acute hepatitis C†	2300
Chronic hepatitis ‡	125
Compensated cirrhosis‡	250
Decompensated cirrhosis‡	8060
Hepatocellular carcinoma‡	10,000
Liver transplantation, 1st year‡	50,000
Liver transplantation, subsequent years‡	8700

*Decock *et al.* (2001).
†Occurring in approximately 25% of HCV transmissions (Harbarth *et al.*, 2000).
‡Wong & Nevens (2002).

Finally, the calculation of indirect costs incurred from transfusion-associated infections is summarized in Table 5.

Cost data

The costs per transfusion of €371·84 for SDP and €274 for average Random Donor Platelets (RDP) were obtained from official sources (RIZIV/INAMI, Red Cross Belgium). These costs include γ-irradiation and donor screening tests except NAT.

The cost of inactivation using the INTERCEPT blood system is estimated as €125 per inactivation session, hence per platelet transfusion. This cost includes the cost for the system itself (€ 90, including VAT) as well as the costs for material and personnel to perform the procedure (potential savings at the level of platelet processing not taken into account). In the model, the average transfusion cost per patient is calculated considering the basic transfusion cost, the cost of the INTERCEPT blood system and the average number of transfusions per patient.

With regard to legal costs, we assumed an average cost of €100,000 per transfusion-associated infection with HIV or with emerging virus, based on law suits or governmental action reports from different countries, including Belgium (Press conference Minister of Public Health Belgium, 19 September 2001, Hof van beroep, Gent, 1e kamer, 24 April 1998). Although for other infection types, there have been legal procedures started in Belgium, we have not included these costs in the model, because none of the law suits have been finalized (some are ongoing for up to 10 years).

Scenarios evaluated

In the basecase scenario, the implementation of the INTERCEPT blood system is assumed to eliminate the risk for HIV, HCV, HBV and bacterial infection.

Table 5. Methods for indirect cost calculations (adults)

Productivity loss calculations	Haematological cancer	Breast cancer	CABG
Employed prior to underlying diagnosis*	48%	39%	25%
Average *n* days per year active*	218	167	218
Percent resume activity post treatment†	67	67	100
Annual *n* days lost if infected‡	70	44	55
Duration of productivity loss	From month 6 to end stage§	From month 6 to end stage§	5 years¶
Unit costs			
Unit cost per hour (€)	23**		

CABG, coronary artery bypass graft.
*Age and sex matched national data (National Institute for Statistics, 2001, available at www.statbel.fgov.be).
†Bradley & Bednarek (2002).
‡The annual number of days lost if infected = % active previously × *n* working days/year × % who would resume activity despite underlying disease in the absence of infection (e.g. 48% × 218 × 67% = 70).
§Because the employment rate applied is based on calculations for the entire adult population up to all ages, the age at diagnosis does not need to be taken into account for programming duration of activity. However, during the end stage of the underlying disease, no productivity is assumed in the absence of infection; hence, no productivity loss can be attributed.
¶70% of patients are under 60 years of age at the time of intervention. 25% of these are active for an estimated further duration of 5 years. Beyond this duration, no productivity is assumed in the absence of infection; hence, no productivity loss can be attributed.
**Includes direct wages + employers charges (National Institute for Statistics, 1996, available at www.statbel.fgov.be)

Additional processing benefits (see further scenarios) are not considered in this scenario. Given the evidence, it is clear that a risk of emerging viruses in the future is existent; however, the timing and level of risk is unknown. Therefore, the assumption of neither the presence of viral risk nor the absence of viral risk can be supported as a reflection of reality. Therefore, it was decided to present the basecase scenario as a double scenario, taking into account a similar probability of absence and presence of an emerging virus. To the emerging virus, different levels of risk were attributed between 1 in 100,000 and 1 in 1000. The highest and lowest risks are shown in the first scenario in Tables 1 and 2.

In the second and third scenarios, the implementation of the INTERCEPT blood system is assumed to eliminate the risk for HIV, HCV, HBV, bacterial and emerging HCV like virus, and in addition, a set of processing benefits are considered. In scenario 2, the elimination of BactAlert testing (corresponding cost and platelet waste reduction), the storage time prolongation to 7 days, leading to 50% decrease in overdue platelets waste, the elimination of SDP ALT testing on SDP platelets and the elimination of γ-irradiation were assumed to be associated with the INTERCEPT blood system. In a third scenario, the following benefits were assumed in addition to the benefits in scenario 2: the elimination of NAT tests and syphilis tests (VDRL) on SDP units leading to reduced costs (NAT costs eliminated). Scenarios 2 and 3 imply a reduction in the cost for platelet processing and testing.

RESULTS

The cost-effectiveness ratio is highly sensitive to the risk of infection with the emerging pathogen and to the indication and age group considered.

Scenario 1: In the absence of emerging virus, the cost-effectiveness ranges between 3,459,201€ per quality adjusted life year (QALY) to 195,364€/QALY. At the lowest simulated risk of the emerging pathogen contamination (1/100,000), the cost-effectiveness ratios range between 3,355,308€/QALY and 165,051€/QALY, depending on the underlying disease (Table 6). With increasing risk of emerging pathogen transmission, the cost-effectiveness ratios steadily decrease (improve), with a maximum of 2,594,120€/QALY at 1/10,000 and of 223,255 at 1/1000 (Table 7) and INTERCEPT being dominant in the majority of cases, meaning cost saving and producing extra QALYs. At 1/100, the INTERCEPT blood system strategy becomes dominant in all cases.

Including processing benefits of INTERCEPT, resulting in a reduced cost for platelet processing and testing, leads to lower cost-effectiveness ratios (Table 8) and dominance of INTERCEPT already at an emerging infection risk of 1/1000.

The following thresholds of emerging infection risk for the INTERCEPT system to become dominant in all indications are observed. Dominance is present as from an emerging risk of 1/1074 transfusions in scenario 1, 1/1697 transfusions in scenario 2 and 1/1791 in scenario 3 (Table 9).

DISCUSSION

The objective of this study was to assess the cost-effectiveness of the INTERCEPT blood system. For this purpose, a health economic model was developed, comparing the overall outcome in a world with INTERCEPT, where infections because of blood transfusions are prevented, to a world without INTERCEPT where infections may occur.

Three scenarios were developed including different levels of INTERCEPT benefits from the prevention of infections up to multiple processing benefits: redundancy of bacterial testing, viral screening and γ-irradiation and reduction of platelet waste. Two main assumptions underlying the model were that pathogen inactivation is 100% effective and is not associated with major or costly adverse events. The INTERCEPT blood system has not only been shown to effectively inactivate current pathogens, but the main benefit of an inactivation system versus safety measures based on screening for infections is that it prevents the transmission of new pathogens before they have been identified. In the absence of the INTERCEPT blood system, the identification of the pathogen, the development and implementation of diagnostic screening tests would take time, during which the pathogen can emerge and might cause numerous transmissions.

Historical data on the rise of transfusion-associated infections with HCV, HBV and HIV have shown that the risk can reach very high levels before screening measures have been developed for implementation in donor-screening schedules. Also recently, there has been an epidemic of West Nile virus in the United States, a virus which was shown to be transmittable via blood transfusion. The risk of transmission through transfusion at the epicentre of the epidemic (1999) has been estimated as high as one in 3700 to one in 5555 transfusions in high-risk areas (Harrington *et al*., 2003). Estimated mean risks in 2002 ranged from one in 6667 to one in 811 donations for several high incidence geographical areas (Biggerstaff & Petersen 2003). This has lead to the

Table 6. Cost effectiveness (cost/QALY) scenario 1 – no emerging virus or emerging virus 1/100,000

Type	Emerging virus	Strategy	Cost*	Marginal cost*	Efficacy†	Marginal efficacy†	Incr C/E (ICER)‡
AML-A	Absent	Without INTERCEPT	4279		1·99953		
		With INTERCEPT	5915	1636	2·00000	0·00047	3,459,201
	Present	Without INTERCEPT	4292		1·99952		
		With INTERCEPT	5915	1623	2·00000	0·00048	3,355,308
AML-C	Absent	Without INTERCEPT	4277		31·99162		
		With INTERCEPT	5915	1638	32·00000	0·00838	195,364
	Present	Without INTERCEPT	4295		31·99019		
		With INTERCEPT	5915	1620	32·00000	0·00981	165,051
ALL-A	Absent	Without INTERCEPT	4290		2·99929		
		With INTERCEPT	5915	1625	3·00000	0·00071	2,280,181
	Present	Without INTERCEPT	4304		2·99927		
		With INTERCEPT	5915	1611	3·00000	0·00073	2,196,998
ALL-C	Absent	Without INTERCEPT	4275		15·99602		
		With INTERCEPT	5915	1640	16·00000	0·00398	411,522
	Present	Without INTERCEPT	4290		15·99562		
		With INTERCEPT	5915	1624	16·00000	0·00438	370,981
NHL-A	Absent	Without INTERCEPT	4502		5·99850		
		With INTERCEPT	6161	1659	6·00000	0·00150	1,105,343
	Present	Without INTERCEPT	4522		5·99843		
		With INTERCEPT	6161	1639	6·00000	0·00157	1,045,085
NHL-C	Absent	Without INTERCEPT	4455		25·99302		
		With INTERCEPT	6161	1706	26·00000	0·00698	244,591
	Present	Without INTERCEPT	4473		25·99200		
		With INTERCEPT	6161	1688	26·00000	0·00800	210,949
CML	Absent	Without INTERCEPT	3638		9·99797		
		With INTERCEPT	4929	1291	10·00000	0·00203	636,067
	Present	Without INTERCEPT	3659		9·99784		
		With INTERCEPT	4929	1270	10·00000	0·00216	586,459
CABG	Absent	Without INTERCEPT	360		15·99968		
		With INTERCEPT	493	133	16·00000	0·00032	422,784
	Present	Without INTERCEPT	361·3		15·99967		
		With INTERCEPT	492·9	132	16·00000	0·00033	395,535
BRCA	Absent	Without INTERCEPT	1000		2·99984		
		With INTERCEPT	1380	381	3·00000	0·00016	2,328,169
	Present	Without INTERCEPT	1003		2·99983		
		With INTERCEPT	1380	377	3·00000	0·00017	2,285,263

A, adults; ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; C, childhood; CABG, coronary artery bypass graft; CML, chronic myeloid leukaemia; ICER, incremental cost-effectiveness ratio; NHL, non-Hodgkin's lymphoma; QALY, quality adjusted life year.
*Cost and marginal cost in €.
†Efficacy and marginal efficacy in number of QALYs.
‡Marginal cost-effectiveness in €/QALY gained.

prompt introduction of expensive screening tests in the US transfusion safety programme (NAT tests). However, considering the time of first detection of West Nile virus in the US (1999) and the time of implementation of NAT tests in routine blood screening (2002), the lag time between emergence and blood safety measures was 3 years (Allain *et al.*, 2005). In our study, the rate of infection with an emerging virus was set at different levels representing different stages of emergence.

In the absence or at very low-risk levels of emerging virus, of <1 in 100,000 transfusions, the cost-effectiveness ratios were high in some populations, depending on the underlying disease and age

Table 7. Cost effectiveness (cost/QALY) scenario 1 – no emerging virus or emerging virus 1/1000

Type	Emerging virus	Strategy	Cost*	Marginal cost*	Efficacy†	Marginal efficacy†[$]	Incr C/E (ICER)‡
AML-A	Absent	Without INTERCEPT	4279		1·9995		
		With INTERCEPT	5915	1636	2·0000	0·0005	3,459,201
	Present	Without INTERCEPT	5568		1·9985		
		With INTERCEPT	5915	347	2·0000	0·0016	223,255
AML-C	Absent	Without INTERCEPT	4277		31·9916		
		With INTERCEPT	5915	1638	32·0000	0·0084	195,364
	Present	Without INTERCEPT	6079		31·8486		
		With INTERCEPT	5915	−164	32·0000	0·1514	−1084
ALL-A	Absent	Without INTERCEPT	4290		2·9993		
		With INTERCEPT	5915	1625	3·0000	0·0007	2,280,181
	Present	Without INTERCEPT	5736		2·9973		
		With INTERCEPT	5915	179	3·0000	0·0028	64,960
ALL-C	Absent	Without INTERCEPT	4275		15·9960		
		With INTERCEPT	5915	1640	16·0000	0·0040	411,522
	Present	Without INTERCEPT	5781		15·9565		
		With INTERCEPT	5915	134	16·0000	0·0435	3086
NHL-A	Absent	Without INTERCEPT	4502		5·9985		
		With INTERCEPT	6161	1659	6·0000	0·0015	1,105,343
	Present	Without INTERCEPT	6492		5·9918		
		With INTERCEPT	6161	−331	6·0000	0·0083	−40,109
NHL-C	Absent	Without INTERCEPT	4455		25·9930		
		With INTERCEPT	6161	1706	26·0000	0·0070	244,591
	Present	Without INTERCEPT	6251		25·8903		
		With INTERCEPT	6161	−90	26·0000	0·1097	−817
CML	Absent	Without INTERCEPT	3638		9·9980		
		With INTERCEPT	4929	1291	10·0000	0·0020	636,067
	Present	Without INTERCEPT	5791		9·9845		
		With INTERCEPT	4929	−862	10·0000	0·0155	−55,479
CABG	Absent	Without INTERCEPT	360		15·9997		
		With INTERCEPT	493	133	16·0000	0·0003	422,784
	Present	Without INTERCEPT	522		15·9979		
		With INTERCEPT	493	−29	16·0000	0·0021	−14,039
BRCA	Absent	Without INTERCEPT	1000		2·9998		
		With INTERCEPT	1380	381	3·0000	0·0002	2,328,169
	Present	Without INTERCEPT	1317		2·9997		
		With INTERCEPT	1380	63	3·0000	0·0003	190,448

A, adults; ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; C, childhood; CABG, coronary artery bypass graft; ICER, incremental cost-effectiveness ratio; NHL, non-Hodgkin's lymphoma; QALY, quality adjusted life year.
*Cost and marginal cost in €.
†Efficacy and marginal efficacy in number of QALYs.
‡Marginal cost-effectiveness in €/QALY gained.

group. In children, the results were much more favourable.

Considering the cost-effectiveness of other, recently established interventions in transfusion medicine, the INTERCEPT blood system compares well with these interventions, especially taken into account that only the economic implications of currently tested pathogens were included, whereas currently not tested pathogens may also induce costs. This result is confirmed by the results of a previous health economic evaluation of the INTERCEPT system for platelets within the US health care system (Bell *et al.*, 2003), as well as in a European setting (Postma *et al.*, 2005). For example, NAT tests, recently

Table 8. Cost effectiveness (cost/QALY) scenarios 2 and 3 – emerging virus 1/100,000

Type	Scenario	Strategy	Cost*	Marginal cost*	Efficacy†	Marginal efficacy†	Marginal C/E (ICER)‡
AML A	2	Without INTERCEPT	4292		1·9995		
		With INTERCEPT	5329	1037	2·0000	0·0005	2,143,435
	3	Without INTERCEPT	4292		1·9995		
		With INTERCEPT	5276	984	2·0000	0·0005	2,032,636
AML C	2	Without INTERCEPT	4295		31·9902		
		With INTERCEPT	5329	1034	32·0000	0·0098	105,389
	3	Without INTERCEPT	4295		31·9902		
		With INTERCEPT	5276	981	32·0000	0·0098	99,924
ALL A	2	Without INTERCEPT	4304		2·9993		
		With INTERCEPT	5329	1025	3·0000	0·0007	1,398,458
	3	Without INTERCEPT	4304		2·9993		
		With INTERCEPT	5276	971	3·0000	0·0007	1,325,297
ALL C	2	Without INTERCEPT	4290		15·9956		
		With INTERCEPT	5329	1039	16·0000	0·0044	237,275
		Without INTERCEPT	4290		15·9956		
		With INTERCEPT	5276	985	16·0000	0·0044	225,028
NHL A	2	Without INTERCEPT	4522		5·9984		
		With INTERCEPT	5552	1029	6·0000	0·0016	656,438
	3	Without INTERCEPT	4522		5·9984		
		With INTERCEPT	5496	973	6·0000	0·0016	620,812
NHL C	2	Without INTERCEPT	4473		25·9920		
		With INTERCEPT	5552	1079	26·0000	0·0080	134,763
	3	Without INTERCEPT	4473		25·9920		
		With INTERCEPT	5496	1023	26·0000	0·0080	127,783
CML	2	Without INTERCEPT	3659		9·9978		
		With INTERCEPT	4441	782	10·0000	0·0022	361,091
	3	Without INTERCEPT	3659		9·9978		
		With INTERCEPT	4397	737	10·0000	0·0022	340,449
CABG	2	Without INTERCEPT	361		15·9997		
		With INTERCEPT	444	83	16·0000	0·0003	248,647
	3	Without INTERCEPT	361		15·9997		
		With INTERCEPT	440	78	16·0000	0·0003	235,227
BRCA	2	Without INTERCEPT	1003		2·9998		
		With INTERCEPT	1244	241	3·0000	0·0002	1,459,408
	3	Without INTERCEPT	1003		2·9998		
		With INTERCEPT	1231	228	3·0000	0·0002	1,383,572

A, adults; ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; C, childhood; CABG, coronary artery bypass graft; CML, chronic myeloid leukaemia; NHL, non-Hodgkin's lymphoma; QALY, quality adjusted life year.
*Cost and marginal cost in €.
†Efficacy and marginal efficacy in number of QALYs.
‡Marginal cost-effectiveness in €/QALY gained.

implemented in routine donor-screening programmes in many countries, including Belgium, showed cost-effectiveness ratios ranging from €25,000 to €2·3 million per life year gained (Yeh *et al*., 2002). NAT tests for HIV have consistently been associated with cost-effectiveness ratios over €1 million per QALY (Jackson *et al*., 2003; Marshall *et al*., 2004).

Hence, these very high cost-effectiveness ratios have not prevented these blood safety measures to be introduced in many countries. When considering also the cost-effectiveness ratios for other interventions to prevent accidental injuries or death such as traffic safety measures, it seems that society or at least authorities tend to place a very high value on

Table 9. Threshold values emerging virus risk for INTERCEPT dominance

	Threshold emerging infection risk		
Type	Scenario 1	Scenario 2	Scenario 3
AML A	1/789	1/1230	1/1297
AML C	1/1107	1/1722	1/1816
ALL A	1/895	1/1400	1/1476
ALL C	1/925	1/1439	1/1510
NHL A	1/1205	1/1905	1/2004
NHL C	1/1057	1/1644	1/1738
CML	1/1675	1/2692	1/2858
CABG	1/1222	1/1932	1/2037
BRCA	1/838	1/1306	1/1380
Mean	1/1079	1/1697	1/1791

A, adults; ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; C, childhood; CABG, coronary artery bypass graft; CML, chronic myeloid leukaemia; ICER, incremental cost-effectiveness ratio; NHL, non-Hodgkin's lymphoma.

measures to reduce unintentional deaths and injuries (Yeh *et al*., 2002). Therefore, it was suggested by Yeh *et al*., (2002) that transfusion safety measures should be evaluated using cost-effectiveness thresholds that are higher than those typically used by healthcare decision makers, reflecting the higher value placed on such types of interventions, where it is considered 'unfair' if patients have no access to the best possible protection (Yeh *et al*., 2002).

Also the cost-effectiveness analyses should take into account all potential benefits of a new intervention such as processing benefits, indirect costs from productivity loss (Yeh *et al*., 2002).

When a more pro-active viewpoint is taken, from a public health perspective, the apparent risk for emerging viruses should be taken into account. At emerging viral risks beyond 1/1000 to 1/2300 transfusions, the INTERCEPT strategy becomes dominant, that is saving money and producing health gains.

In conclusion, considering the apparently applied thresholds for cost-effectiveness in the field of blood transfusions, the implementation of the INTERCEPT blood system can be considered cost-effective and even a dominant strategy taking into account the potential risk of emergence of a new pathogen in the future.

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文献④

The cost-effectiveness of pathogen reduction technology as assessed using a multiple risk reduction model

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BACKGROUND: Pathogen reduction technology (PRT) for labile blood components has the potential to reduce the risk of many adverse events associated with transfusion. Because of the potential broad-spectrum risk reduction capability of PRT, the health economics of PRT could be an important consideration in decision making for this technology.

STUDY DESIGN AND METHODS: Decision analytic models comparing current blood safety screens and interventions to riboflavin-based whole blood PRT (currently in development) and separately to platelets (PLTs)-and-plasma PRT from the health care system perspective in Canada were used to assess the cost-utility of PRT in reducing the following adverse events: human immunodeficiency virus, hepatitis B virus, hepatitis C virus, human T-lymphotropic virus, syphilis, West Nile virus, bacteria, Chikungunya virus, cytomegalovirus, *Trypanosoma cruzi*, graft-versus-host disease, febrile nonhemolytic transfusion reactions, and transfusion-related immunomodulation. PRT was modeled as an addition to rather than a replacement for current interventions. The potential of PRT to reduce the risk of an unknown pathogen was not assessed.

RESULTS: Whole blood PRT was estimated to have a cost-effectiveness of $1,276,000/quality-adjusted life-year (QALY; 95% confidence interval [CI] approximation, 600,000-3,313,000) compared to current screens and interventions. PLTs-and-plasma PRT was estimated to have a cost-effectiveness of $1,423,000/QALY (95% CI approximation, 834,000-2,818,000) on an all-transfusions basis.

CONCLUSIONS: Because of the complexity of transfusion risks and practices, the cost-effectiveness of whole blood or PLTs-and-plasma PRT can be modeled provided that assumptions and simplifications are made. Uncertainty remains with respect to the risk reduction that can be achieved for some adverse events. Nevertheless, the results of this cost-effectiveness analysis can be used to inform policy decisions regarding PRT technology in the context of other initiatives designed to improve transfusion safety.

Two methods for pathogen reduction technology (PRT), also known as pathogen inactivation, use a photoactive compound (riboflavin or amotosalen) and ultraviolet (UV) light treatment to prevent DNA or RNA replication. These methods are being adopted for the treatment of platelets (PLTs) or plasma in some European countries. Consensus statements from the panel of the Canadian Consensus Conference on Pathogen Inactivation in 2007 and summary statements, such as from one of the 2008 US Advisory Committee on Blood Safety and Availability meetings, indicate that economic evaluations of PRT should be conducted and included as part of the information used for making implementation decisions.[1,2] Previous economic analyses of photoactive compound/UV light PRT focused on human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotropic virus (HTLV), and bacteria.[3-6] These analyses assumed that the treatment process is 100% effective (residual risk of these pathogens is eliminated in PRT-treated PLTs) and reported results for specific patient populations likely to receive such transfusions. The likelihood that these same patients would receive untreated red blood cells (RBCs) and/or plasma transfusions was not addressed. Moreover, while analyses restricted to specific patient populations

ABBREVIATIONS: FNHTR(s) = febrile nonhemolytic transfusion reaction(s); PRT = pathogen reduction technology; QALY = quality-adjusted life-year; TRIM = transfusion-related immunomodulation; WNV = West Nile virus.

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based on transfusion indication are informative for assessing who is most likely to benefit,[7] they do not help blood safety decision makers faced with selecting interventions to enhance the safety of components intended for all transfusion recipients.

We developed a new health economics model to assess the cost-effectiveness of riboflavin-based PRT (Mirasol PRT system, CaridianBCT, Lakewood, CO) in mitigating the risk of transfusion-associated infectious and some noninfectious threats. The first model examines the cost-effectiveness of a technology in development, whole blood PRT.[8] To model the technology that is currently available in some settings, PLTs-and-plasma PRT, we modified the whole blood PRT model, incorporating data on PLT preparation procedures and transfused components to adjust the risk reduction achieved.

MATERIALS AND METHODS

Overview

The models simulate the costs and consequences of the following infectious and noninfectious adverse events: HIV, HBV, HCV, HTLV, syphilis, West Nile virus (WNV), bacteria Chikungunya virus, cytomegalovirus (CMV), *Trypanosoma cruzi*, graft-versus-host disease (GVHD), febrile nonhemolytic transfusion reactions (FNHTR), and transfusion-related immunomodulation (TRIM). Both the set of and the prevalence of adverse events included in each version of the model can be adjusted to reflect setting-specific epidemiology or disease. In this analysis we neither included an unknown, emerging pathogen nor retrospectively included a scenario for HIV or HCV when either virus had the highest prevalence in blood donors. Our reason for not including these pathogens or scenarios is that it is relatively easy to construct a set of outcomes with a disease burden profile that is favorable to PRT. However, such a scenario in the context of trying to address or mitigate current risks could cloud the assessment of the efficiency of PRT.

We analyzed the cost-utility of PRT for Canada. Canada represents an appropriate country for such an analysis because there are 1) nationally representative health care data, 2) active hemovigilance and transfusion surveillance systems in some Provinces, and 3) interest in implementation of PRT. Similar to other economic analyses in blood safety, this analysis is from the health care system perspective and costs are limited to the costs of the safety interventions and the direct medical costs associated with infections or other adverse events.[9] The results reported here do not include the cost of lost productivity or related indirect costs incurred because of transfusion-associated adverse events. We used 2007 as the analysis year, so all monetary values are adjusted to 2007 Canadian dollars using the health and personal care component of the Canada consumer price index.[10] Data sources for disease occurrence, outcomes, and costs come from published literature specific to Canada. When data were not available for a specific disease or condition, we used data from other countries with preference for US data when available. In accord with the recommendations of the US Panel on Cost-effectiveness in Health and Medicine, future costs and effects are discounted at 3% per year[11,12] and were allowed to vary independently between 1 and 5% in sensitivity analysis. We constructed the model and performed analyses using computer software (TreeAge Pro 2009, TreeAge Software, Inc., Williamstown, MA). Aspects of the model not covered in detail under Materials and Methods, such as annual mortality probabilities and disease-specific models and variable values, are provided as an electronic Technical Appendix (available as supporting information in the online version of this paper).

Structure of the model

The model has a decision analytic format and is a cohort simulation with separate disease-specific Markov submodels to track the progression of each adverse event. Each version of the model consists of four sections. The first section is a two-armed decision tree: current screens and interventions compared with PRT added to current screens. The second section is focused on two characteristics of blood recipients that influence the likelihood of survival: age at transfusion and immunocompetence. The model can be run using survival data for three age groups: 1) an overall group that reflects the age distribution of the entire transfused population, 2) persons 0 to 39 years of age, and 3) persons 40 years or older. These categories were defined based on available posttransfusion data that indicate that the probability of survival is similar within these latter two broad age categories.[13-15] The population of blood recipients is also separated into those with and without underlying immunocompromise, because a subset of the population requiring transfusion may be immunocompromised due to a medical condition, such as cancer, organ transplantation, or specific infections like HIV. These patients may be at increased risk for more severe adverse outcomes from transfusion.[16] Estimates of the size of the immunocompromised subpopulation are not available for Canada. Data from the National Blood Service in the United Kingdom suggest that as many as 50% of blood recipients are immunocompromised to some degree, with 25% having moderate or severe immunocompromise.[17] We included immunocompromise in our analysis by assuming that 25% of the transfused population has underlying immunocompromise. In the model this patient group is at increased risk of mortality and faster disease progression, which we included as 50% increased posttransfusion mortality in the first year after transfusion, and increased risk of morbidity from each adverse event.

TABLE 1. Percentage of patients receiving transfusions by component combination from British Columbia and Yukon transfusion registry data and assumed risk reduction achieved in the PLTs-and-plasma PRT model

Transfused labile component combinations for 2007 (n = 184,842 components)	Percentage receiving each type of a component	Assumed PRT risk reduction adjustment factor (PRT AF)
RBCs only	75.7	None
Plasma-containing transfusions	9.9	Mixed
Plasma only	6.0 (61)	100% of PRT AF
RBCs with plasma (no PLTs)	3.9 (39)	50% of PRT AF
PLT-containing transfusions	14.4	Mixed
PLTs only	8.2 (57)	100% of PRT AF
PLTs and plasma (no RBCs)	0.6 (4)	100% of PRT AF
RBCs with PLTs and plasma	2.1 (15)	50% of PRT AF
RBCs with PLTs (no plasma)	3.5 (24)	50% of PRT AF

TABLE 2. Blood safety interventions and assumed costs

Cost	Cost element	Per donation cost	Range for sensitivity analysis
Current screens	HIV antibody		
	HIV NAT		
	HCV antibody		
	HCV NAT		
	HBV surface antigen		
	HBV core antibody		
	WNV NAT		
	HTLV(I/II) antibody		
	Serologic test for syphilis		
	Total	44.00	33.00-55.00
Bacterial culture after diversion	Bacterial culture[9]	25.00	18.75-31.25
CMV antibody		10.30	7.72-12.88
Gamma irradiation		5.00	3.75-6.25
PRT		100.00	75.00-125.00

The third section of the model differentiates recipients into three groups based on the type of blood components received. Published data consistently show that recipients of PLTs or plasma alone or in combination with RBCs have reduced long-term survival compared to RBC-only recipients.[18,19] Data on the percentage of transfusion episodes that include each blood component type were provided by the British Columbia Provincial Blood Coordinating Office for the year 2007 (Table 1). We assumed that the component combinations transfused in British Columbia and Yukon are representative of those for the entire country. We adjusted the mortality probabilities for PLT recipients and separately for plasma recipients using data published by Wallis and colleagues.[19]

The fourth section of the model addresses transfusion outcomes through detailed accounting of disease and adverse event progression and costs. Details of how each adverse event is modeled are provided in the Technical Appendix.

In the model each transfusion recipient is assumed to experience a single transfusion episode consisting of 1 unit of whole blood or the equivalent as RBCs, PLTs, and plasma. Components are not assumed to come from the same blood donor and so carry the independent risk of each adverse event, but the adverse risks for each component would be mitigated in a single inactivation if whole blood PRT becomes available. The number of transfusions received in an episode has not been modeled. Although the risk of specific infectious agents and of noninfectious hazards varies according to the type of blood component transfused, component-specific residual risks are mostly unreported and are not included in the whole blood PRT analysis.

Effectiveness of PRT

Current blood safety interventions used in Canada are listed (Table 2). In this analysis, we assumed that all of these interventions would continue and that universal leukoreduction would continue. The effectiveness of PRT at reducing the risk of each transfusion-associated adverse event is dependent on the interventions already in place, the likelihood of adverse event occurrence, and the pathogen-specific performance of riboflavin-based PRT. Actual estimates of the effectiveness of PRT under conditions of normal use will only be available after sufficient post-marketing surveillance data have accumulated. To project the effectiveness of PRT we assumed pathogen-specific risk reduction factors (Table 3). Risk without PRT is based on the observed frequency of the event, the yield of screening, or estimated residual risk given current safety measures. For example, the current estimated residual risk of HBV infection is 1 per 153,000 transfusions.[20] Good animal models to demonstrate a specific level of pathogen inactivation for HBV are not available. Studies of riboflavin-based PRT have shown that it can successfully prevent polymerase chain reaction amplification of HBV at concentrations up to 29,400 geq/mL.[21] We assumed that the risk reduction achieved by PRT would be 10-fold greater than current testing (hepatitis B surface antigen and anti-hepatitis B core antigen) giving an estimated residual risk after use of PRT of 1 per 1,530,000.

Costs

The cost of current screens and interventions applied to every donation in total sum to $44.00 per donation (Table 2). No serologic intervention for *T. cruzi* was used in

TABLE 3. Current transfusion risks in Canada and assumed residual risks using PRT

Pathogen or condition	Prevalence or yield of testing if known	Current residual or assumed risk	Source for prevalence or residual risk estimates	PRT risk reduction factor (triangular distribution values for probabilistic sensitivity analysis)	Estimated risk after PRT	Source for PRT performance
Bacteria (PLTs)	1/10,000	1/47,000	Ramirez-Arcos et al.,[39] Laupland et al.[40]	50 (10-90)	1/2,350,000	Goodrich et al.[28]
Bacteria (other components)	*	1/50,000	International Forum: Haemovigilance[22]	50 (10-90)	1/2,500,000	Goodrich et al.[28]
CHIKV	*	1/10,000,000	Assumption	1.5 (1.01-1.99)	1/15,000,000	Assumption
CMV	1/40,000	1/80,000	Blajchman et al.[41]	2 (1.25-2.75)	1/160,000	Assumption
FNHTR	1/375	1/750	International Forum: Haemovigilance[22]	2 (1.01-2.99)	1/1500	Assumption
GVHD	*	1/2,400,000	Serious Hazards of Transfusion—Annual Report Summary 2007[42]	2 (1.25-2.75)	1/4,800,000	Assumption
HBV	8.08/100,000†	1/153,000	O'Brien et al.[20,43]	10 (5-15)	1/1,530,000	Assumption
HCV	8.49/100,000†	1/2,300,000	O'Brien et al.[20,44]	10 (5-15)	1/23,000,000	Assumption
HIV	0.41/100,000†	1/7,800,000	O'Brien et al.[20]	10 (5-15)	1/78,000,000	Ruane et al.[27]
HTLV	0.93/100,000†	1/4,300,000	O'Brien et al.[20]	10 (5-15)	1/43,000,000	Assumption
Syphilis	2.8/100,000†	1/2,000,000	Assumption	10 (5-15)	1/20,000,000	Assumption
T cruzi	*	1/200,000	Based on Bern et al.[45]	20 (10-30)	1/4,000,000	Cardo et al.[29]
TRIM	*	1/150,000	Assumption	1.5 (1.01-1.99)	1/225,000	Assumption
WNV		1/1,000,000	Assumption	10 (5-15)	1/10,000,000	Ruane et al.[27]

* Not known or not applicable.
† S. O'Brien, personal communication, Canadian Blood Services, 2009.
CHIKV = Chikungunya virus.

Canada in 2007, and so no screening costs are included for this agent. CMV antibody and gamma irradiation costs are assumed to be incurred only for the units intended to be transfused to patients with underlying immunocompromise. The estimated cost of PRT ($100 on a per donation or component treated basis) covers the cost to implement the strategy including labor and overhead. In the case of bacterial culture, costs are not incurred for all components as screening is conducted only on PLTs. PLTs comprise 10-15% of all components transfused in Canada.[22] We used a currency converted, inflation-adjusted cost estimate for bacterial culture from the Netherlands[9] to determine a cost of $25 for bacterial culture per PLT preparation.

The potential risks of riboflavin-based PRT include cytotoxicity, genotoxicity, and reduced efficacy of components. It is possible processing mistakes such as under- or over-exposure to UV light may lead to these consequences, but available laboratory and animal model studies conducted to date have found only minimal evidence of these adverse events.[23] It is expected that RBC and PLT efficacy could be reduced by the treatment process, but the one available clinical study of PLTs treated with riboflavin-based PRT did not demonstrate increased transfusion in the PRT treated compared to untreated arms of the trial.[24,25] Nonetheless, we included a component use cost factor in the model to account for potential additional transfusion of components due to the PRT treatment process. We reflected increased component use by assuming a 10% increase in blood component screening and preparation costs that would be necessary to achieve the same therapeutic efficacy in the PRT arm of the model. In sensitivity analysis we varied this additional cost factor between 0 and 20%.

Sensitivity analysis

Both one-way and probabilistic sensitivity analyses were conducted. All sensitivity analyses were performed using the overall (all ages) blood recipient population, age-specific sensitivity analyses were not conducted. In one-way analysis, the influence of a single model variable over the likely range of possible values for that variable is assessed with respect to its impact on cost-effectiveness. The one-way analyses have been aggregated into tornado diagrams, one for the whole blood version of the model and one for the PLTs-and-plasma model, showing the decreasing influence of model variables. The top 18 most influential variables specific to each model are included in each tornado diagram. Uncertain variable values and assumptions such as the residual risk of each adverse event, PRT risk reduction factors, and treatment costs were varied by ±50% of the baseline estimate. The costs of blood safety interventions including PRT and annual posttransfusion mortality were varied by ±25% indicating

less uncertainty. All remaining model variables were varied within specifically defined ranges based on published literature or standardized methods.

Probabilistic sensitivity analysis (Monte Carlo simulation) allows for an overall assessment of the uncertainty given the range of possible values or probability distribution of each variable used in the model. We ran 2000 computer simulations of each analysis and obtained an approximation of the 95% Confidence Interval (CI) for the cost-effectiveness ratio, represented by the 2.5 and the 97.5 percentiles of the distribution of results from each simulation.

PLTs-and-plasma PRT

We modified the whole blood model to estimate the cost effectiveness of PRT for the technology that is currently approved for use in some European jurisdictions, PLTs-and-plasma PRT. To do so we added an additional section to the model focused on PLT preparation methods. As in the whole blood model, transfusions containing PLTs are separated from transfusions not containing PLTs; this design also allowed us to include the PLT preparation method (single donor or pooled PLTs). We assumed single donor PLTs represent 25% of the total preparations and buffy coat PLT preparations represent 75% of the total preparations (percentages that approximate the preparations issued by Canadian Blood Services). The baseline risk for PLTs in this version of the model applies to single donor preparations and a donor exposures factor is included to increase the baseline risk for each adverse event according to the number of donor exposures for recipients of pooled PLTs. In the PLTs-and-plasma analysis, except for bacterial contamination, we assumed that the risk of plasma was the same as that of PLTs and that PRT reduced those risks to the same degree in both products.

Except for transfusion episodes that include both PLTs and plasma, which are included in the PLTs arm of the model, transfusions that include plasma are considered in another separate arm of the model. PLTs and plasma account for approximately 25% of the components transfused in Canada[22] so the effective cost of PRT on an all transfusions basis would be approximately 25% of the cost of whole blood PRT if fixed costs are not considered. However, the risk reduction achieved for this cost is not 25% of the overall risk because different combinations of blood components are transfused to patients. To estimate the average expected effectiveness of PLTs-and-plasma PRT from the perspective of all components transfused, we adjusted the risk reduction achieved using whole blood PRT. We assumed that patients receiving RBC only transfusions would continue to have the same residual risk with no benefit from PRT. For patients receiving transfusions that are exclusively PLTs and/or plasma, representing nearly 15% of the transfused population, we assumed the risk reduction would be equivalent to the overall risk reduction achieved for whole blood PRT (Table 1). For the remaining 10% of the transfused patients receiving combinations of RBCs, PLTs, and/or plasma transfused, we assumed half of the current risk would be mitigated, meaning that the residual risks for recipients of RBCs with PLTs and/or plasma is the average of the current residual risk and the expected lower residual risk obtained by the use of PRT for PLTs and plasma.

RESULTS

Whole blood PRT

We report the estimated average quality-adjusted life expectancy for the transfused population overall and for specific recipient age groups, the average healthcare-related costs incurred per donation with current interventions, and incremental cost-effectiveness of whole blood PRT compared to current interventions used in Canada (Table 4). For all recipients, on average individuals are expected to gain approximately 47 quality-adjusted life minutes. In a cohort of 100,000 transfusion recipients this would represent a gain of approximately 9 quality-adjusted life years. The incremental cost-effectiveness of whole blood PRT compared to current screens and interventions is $1,276,000/quality-adjusted life-year (QALY; 95% confidence interval [CI] approximation 600,000-3,313,000). For transfused patients over 40 years of age, the incremental cost per QALY saved is higher, but similar to the overall result given that the average age of transfusion is approximately 65 years in Canada. However, for recipients 39 years of age or younger the incremental cost-effectiveness is $426,000/QALY (95% CI approximation 197,000-1,173,000).

Whole blood PRT sensitivity analysis

One-way sensitivity analyses are shown as a tornado diagram for the overall recipient population (Fig. 1). In order of decreasing influence, the model is most sensitive to the risk of bacterial contamination, annual mortality in the year of transfusion, the cost of PRT per donation, the probability of death due to sepsis, the discount rate for effects, and health state quality-adjustment preference weights for patients requiring transfusion in the years following transfusion. Bacterial contamination risk is the most influential variable and a low risk for bacteria (1:100,000) leads to a cost-effectiveness of nearly $2,200,000/QALY. The impact of posttransfusion mortality in the year of transfusion is shown in the second horizontal bar of the figure. Low annual mortality would lead to an incremental cost-effectiveness of whole blood PRT of $850,000/QALY, whereas high annual mortality would lead to an incremental cost-effectiveness of whole blood PRT of $1,550,000/QALY.

TABLE 4. Costs and effects of current interventions, with PRT and incremental cost-effectiveness of PRT by transfusion recipient age group for whole blood PRT

	Costs and effects		
Results category	Overall (all ages)	0- to 39-year-old group	40 years or older group
Total costs for current screens/interventions ($CAD)	44.77	44.92	44.76
Effects with current screens/interventions (QALY)	7.885246	19.550197	7.311080
Total cost for PRT adoption ($CAD)	158.30	158.31	158.30
Effects with PRT adoption (QALY)	7.885335	19.550463	7.311161
Incremental cost of PRT ($CAD)	113.53	113.40	113.54
Incremental effectiveness of PRT (QALY)	0.000089	0.000266	0.000081
Incremental cost-effectiveness of PRT ($CAD/QALY)	$1,276,000	$426,000	$1,405,000
(95% CI approximation)	(600,000-3,313,000)	(197,000-1,173,000)	(653,000-3,693,000)

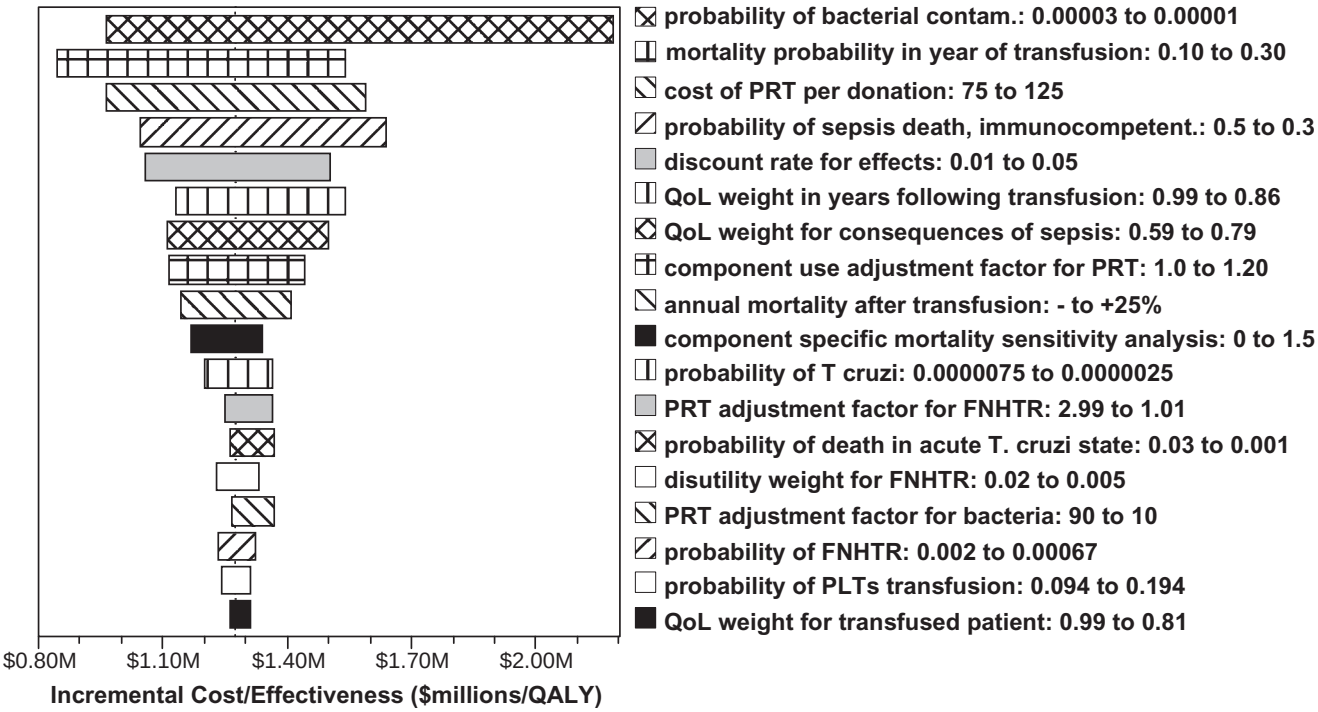

Fig. 1. Tornado diagram showing the range of values used and results from one-way sensitivity analysis of the most influential variables in the whole blood PRT model. Each horizontal bar reflects the range of adjacent values listed on the right. Ranges are provided from low to high or high to low in correspondence with the left and right ends of each horizontal bar. QoL = quality of life.

Several of the factors related to FNHTR, such as the probability of FNHTRs (attributable to residual white blood cells [WBCs] even in leukoreduced blood) and the assumed risk reduction, are influential in the whole blood PRT model. Evidence of the efficacy of UV light and photoactive compound PRT to reduce the occurrence of FNHTRs continues to emerge; both riboflavin-based and amotosalen-based PRT have demonstrated a decrease in these adverse events during active hemovigilance studies.[25,26] It is expected these benefits would be mostly limited to PLTs and RBC preparations. However, in order to assess the cost-effectiveness of PRT without considering a potential FNHTR benefit, we set the residual risk of this event to zero which removes this adverse event and associated costs from the model. The whole blood PRT result increased to $1,364,000/QALY representing nearly a 7% higher cost-effectiveness ratio.

Appropriate values for the current residual risk for pathogens that are not universally screened for are difficult to know with certainty. The influence of two infectious threats, bacteria and *T. cruzi*, was assessed jointly. If the underlying residual risk of bacterial infection for all components is 1 in 75,000 and for *T. cruzi* is 1 in 250,000, the cost-effectiveness ratio for whole blood PRT increases to $1,876,000/QALY (95% CI approximation, 812,000-5,295,000), representing a 47% higher cost-effectiveness ratio.

TABLE 5. Costs and effects of current interventions, with PRT and incremental cost-effectiveness of PRT by transfusion recipient age group for PLTs-and-plasma PRT

	Costs and effects		
Results category	Overall (all ages)	0- to 39-year-old group	40 years or older group
Total costs for current screens/interventions ($CAD)	44.37	44.55	44.36
Effects with current screens/interventions (QALY)	7.838611	19.458178	7.266893
Total costs for PRT adoption ($CAD)	72.43	72.55	72.42
Effects with PRT adoption (QALY)	7.838631	19.458243	7.266911
Incremental cost of PRT ($CAD)	28.06	28.00	28.07
Incremental effectiveness of PRT (QALY)	0.000020	0.000065	0.000018
Incremental cost-effectiveness of PRT ($CAD/QALY)	1,423,000	429,000	1,579,000
(95% CI approximation)	(834,000-2,818,000)	(256,000-805,000)	(965,000-3,174,000)

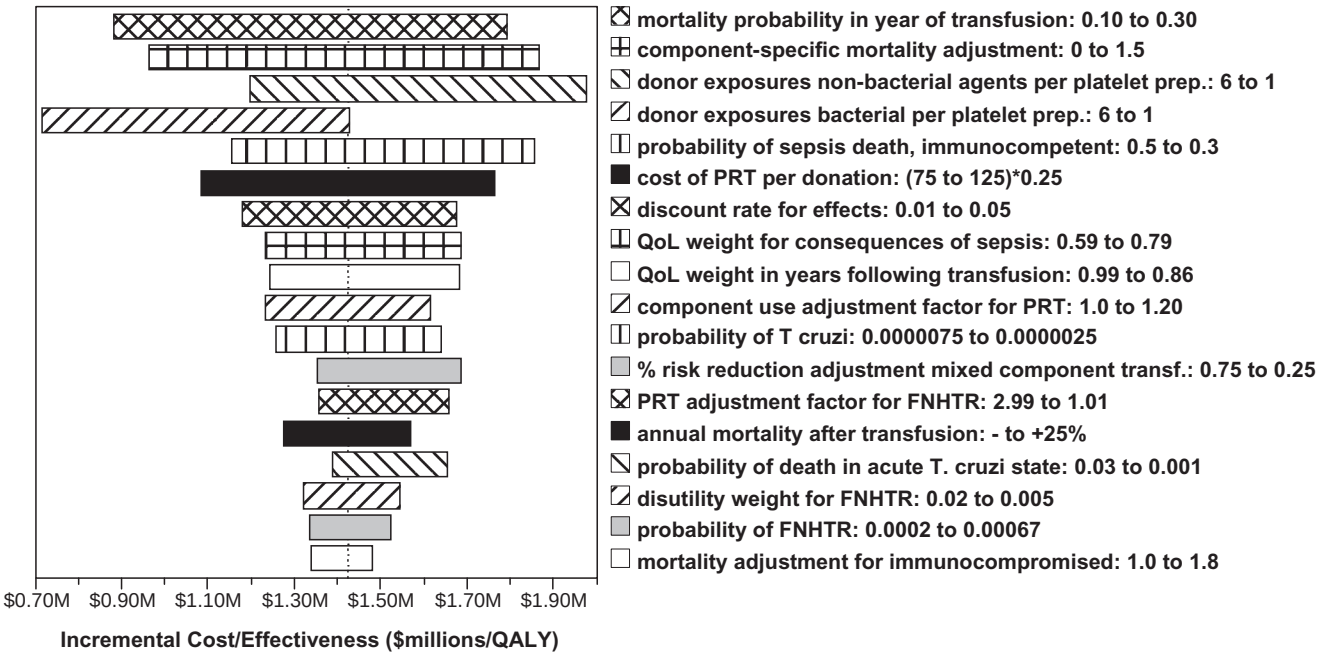

Fig. 2. Tornado diagram showing the range of values used and results from one-way sensitivity analysis of the most influential variables in the PLTs-and-plasma PRT model. Each horizontal bar reflects the range of adjacent values listed on the right. Ranges are provided from low to high or high to low in correspondence with the left and right ends of each horizontal bar. QoL = quality of life.

PLTs-and-plasma PRT

We report the costs and consequences of PLTs-and-plasma PRT compared to current screens and interventions used in Canada (Table 5). When evaluated on an all-transfusions basis, the incremental cost-effectiveness of PLTs-and-plasma PRT is $1,423,000/QALY (95% CI approximation, 834,000-2,818,000). The mean gain in quality-adjusted life expectancy is 11 minutes per patient; even though the incremental cost is also lower, the cost-effectiveness of PLTs-and-plasma PRT compared to current screens and interventions is less cost-effective than for whole blood PRT. This result is expected because of the decreased overall risk reduction achieved using PLTs-and-plasma PRT compared to whole blood PRT. The patterns of cost-effectiveness for older and younger transfusion recipients are similar to those seen for whole blood PRT with estimated cost-effectiveness of $429,000/QALY (95% CI approximation, 256,000-805,000) in transfusion recipients 39 years or younger in age.

PLTs-and-plasma PRT sensitivity analysis

In one-way sensitivity analysis, the factors that are influential in the PLTs-and-plasma PRT model in order of decreasing influence are mortality in the year of transfusion, mortality associated with type of blood components received, the number of donor exposures per pooled PLT preparation, the probability of death due to sepsis, the cost of PRT per donation, and the discount rate for effects (Fig. 2). We examined the sensitivity analysis results with respect to donor exposures in more detail by evaluating the influence of the percentage of single-donor PLT (apheresis) collections on the cost-effectiveness of PRT based when the pooled PLT method is either buffy coat or

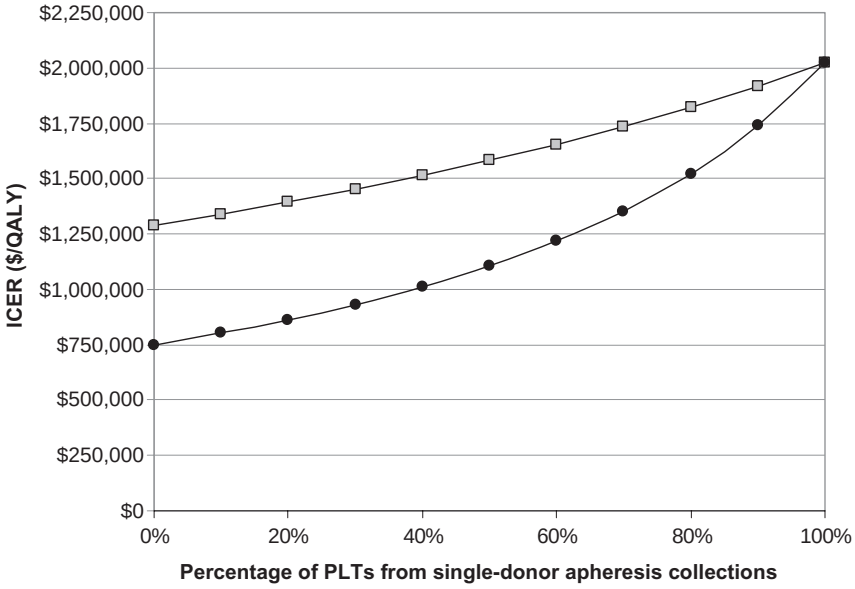

Fig. 3. Influence of the percentage of PLT preparations from single-donor apheresis collections on the incremental cost-effectiveness ratio (ICER) of PLTs-and-plasma PRT compared to current screens and interventions. (—□—) Buffy coat random-donor PLTs; (—●—) plasma-rich random-donor PLTs.

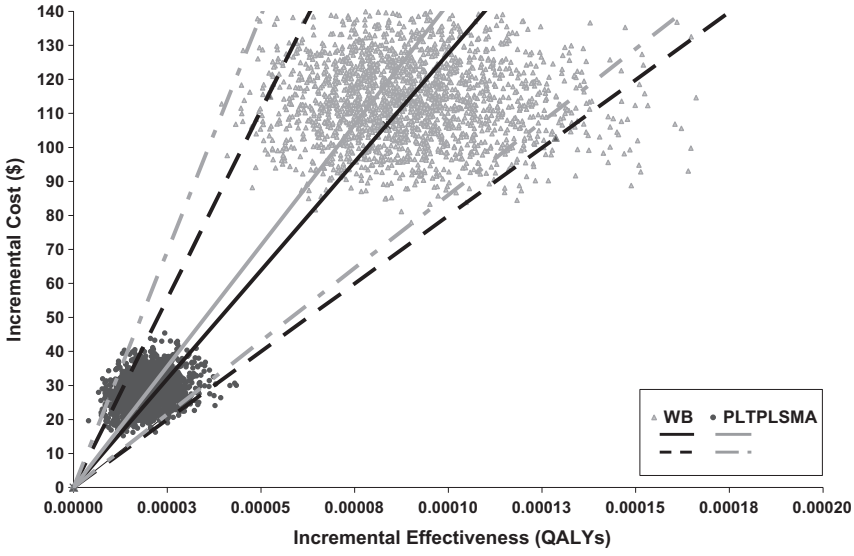

Fig. 4. Incremental cost and effectiveness scatterplots from 2000 probabilistic simulations for whole blood PRT compared to current screens and PLTs-and-plasma PRT compared to current screens. Solid lines represent the mean incremental cost-effectiveness ratio and dashed lines represent the 2.5 and 97.5% values of the cost-effectiveness ratios from the distributions of the simulations with points for whole blood PRT shown in gray and points for PLTs-and-plasma PRT in black; lines are in reverse grayscale so that they can be visualized on top of each corresponding cloud of points.

plasma-rich preparations (Fig. 3). When no PLTs are prepared using single-donor collection methods, the incremental cost-effectiveness of PLTs-and-plasma PRT is dependent on the pooled PLT preparation method. The residual risk of bacteria in plasma-rich PLT preparations is higher than in buffy coat or apheresis preparations; thus PRT treatment of PLTs prepared using this method yields greater benefit and a more favorable cost-effectiveness profile. As the percentage of single-donor apheresis collections increases, the cost-effectiveness ratio increases in a nonlinear manner, and at 100% single-donor collections, the ratio exceeds $2,000,000/QALY.

Probabilistic sensitivity analysis

The cloud diagrams of the incremental costs and effects, generated from probabilistic sensitivity analysis of whole blood PRT and PLTs-and-plasma PRT, provide an indication of overall uncertainty. As expected, the simulation result plots show that both the incremental cost and the incremental effectiveness of whole blood PRT are higher than for PLTs-and-plasma PRT (Fig. 4). In addition, the possible values for incremental effectiveness of whole blood are more uncertain than those for PLTs-and-plasma PRT as demonstrated by the greater horizontal dispersion of individual simulation results.

DISCUSSION

In this analysis, we assessed the cost-effectiveness of PRT for whole blood focused on the direct cost of blood safety interventions and medical care. While such a technology is currently unavailable, clinical studies of candidate technologies are under way. We estimated the cost-effectiveness of adding whole blood PRT in Canada to current screens and interventions to be $1,276,000/QALY. Recognizing that RBC risks would not be mitigated by currently available PRT, we modified the model and used it to estimate the incremental cost-effectiveness of adding PLTs-and-plasma PRT generating a result of $1,423,000/QALY compared to current screens and interventions. The cost-effectiveness of a PLTs-and-plasma PRT was most dependent on the PLT collection

and preparation methods used by blood centers. The most important factors driving better cost-effectiveness results are the risk of bacterial contamination and other infections resulting from higher donor exposures in pooled PLTs. Since Canadian blood centers collect and prepare PLTs via single-donor apheresis or buffy coat preparation methods PRT technology will be less cost-effective in Canada than in countries which primarily supply plasma-rich PLTs.

The analyses reported here with respect to the cost-effectiveness of PLTs-and-plasma PRT have focused on the mix of PLT preparation methods used by Canadian Blood Services. HemaQuebec, the other blood operator in Canada, which serves the Province of Quebec, uses a different combination of preparation methods. Approximately 80% of PLTs collected by HemaQuebec are from single-donor apheresis collections with the remainder of PLTs produced in 2007 being plasma-rich PLTs averaging five donor exposures. This combination of PLT preparation methods leads to a result of $1,389,000/QALY (95% CI approximation, 713,000-2,944,000) for PLTs-and-plasma PRT. The same percentages of single-donor apheresis collections and buffy coat–derived instead of plasma-rich PLTs as now used by HemaQuebec would lead to a result of $1,775,000/QALY (95% CI approximation, 1,021,000-3,364,000) for PLTs-and-plasma PRT.

On the one hand, if PRT were to be adopted it could be more cost-effective than reported here. The residual risk of transfusion-transmitted viruses of greatest concern is already very low, particularly in Canada, due to the efficacy of current screens and interventions, and in this analysis we did not assume that any of these screens or interventions would be discontinued or modified. However, it is likely that blood collection agencies would seek changes. Interventions that potentially could be eliminated include bacterial culture for PLTs and gamma irradiation. Interventions that could be modified include universal testing for WNV and HTLV. For example, with an available whole blood PRT, discontinuation of testing for WNV or elimination of outbreak season individual donation nucleic acid testing (NAT) might be possible due to the more than 5 logs kill achieved using riboflavin-based PRT,[27] and discontinuation of bacterial culture of PLTs also seems feasible for either a whole blood or a PLTs-and-plasma PRT.[28] Each of these changes would favorably alter the incremental cost-effectiveness of PRT. Avoidance of *T. cruzi* screening also seems likely given the observed ability of riboflavin-based PRT to inactivate this and other parasites.[29]

On the other hand, if PRT were to be adopted it could be less cost-effective than reported here. The potential for increased component use, adverse events for blood recipients, increased treatment costs, and increased total costs to the health care system could result from the use of riboflavin-based PRT. For example, the formation of neoantigens is possible. Based on other PRT methods that do not use riboflavin as the photoactive compound, this could be an issue for RBC units prepared from PRT-treated whole blood.[30] Another possible concern is for PLTs treated with PRT where clinical studies including the MIRACLE trial have shown that the corrected count increment (CCI) is lower for PRT-treated compared to untreated PLTs.[25] Lower CCIs could lead to increased risk of bleeding.

The current analysis does not consider other infections such as human parvovirus B19, *Babesia,* or the undefined value of PRT in preventing transfusion transmission of unknown or reemerging pathogens. The safety and health economic benefit of PRT in the face of an emerging agent could be considerable. Most infectious agents (except prions) would likely be at least partially susceptible to PRT. We elected not to include such an agent in this analysis because it is relatively easy to construct the set of assumptions regarding the pathogen so that results create a very attractive economic profile for PRT. Adopting PRT could be thought of as insurance against the risk of a future large epidemic of an unknown virus, bacteria, or parasite transmitted to transfusion recipients. In the face of a prevalent emerging pathogen it is highly likely that whole blood PRT would become much more cost-effective than PLTs-and-plasma PRT alone because of the reduction of the threat in all blood components.

The residual risk of many infectious or noninfectious threats is important for the cost-effectiveness of PRT, but limited data are available on objectively measured risks of many potential adverse events associated with transfusion. For example, the morbidity and mortality of bacteria-contaminated RBCs are not well defined. Quebec hemovigilance data report that bacterial contamination of RBCs occurs with a prevalence as high as 1 in 36,000,[22] whereas others have estimated the risk to be approximately 1 in 250,000 or lower.[31] The frequency with which such units result in detectable clinical morbidity or mortality affects the calculation of cost-effectiveness. In our analysis we assumed that the baseline residual risk of bacterial contamination was 1 in 50,000 and that 40% of nonimmunocompromised patients who received non–PRT-treated components containing bacteria would develop fatal infections. Active capture of data via hemovigilance may provide reliable estimates, but the availability of more precise data would improve the accuracy of the analysis of infectious risks across all blood component types. The importance of current residual risks of infection was also exhibited in other sensitivity analyses. When we reduced the risk of bacteria and *T. cruzi* at the same time, the overall cost-effectiveness ratio of whole blood PRT increased by 47%.

Our analysis of the cost-effectiveness of whole blood PRT has important limitations. To model the question of the cost-effectiveness of PRT we had to make several simplifying assumptions. In one simplification, we assumed

that transfusion episodes are one-time events with exposure to one whole blood unit or its equivalent components. This does not reflect clinical practice because transfused patients may receive multiple transfusions on different occasions, and even in the same transfusion episode patients could receive anywhere from 1 unit of any component type to dozens of units. The model does not account for transfusion of different numbers of components or multiple transfusion episodes. The survival of recipients of a large number of units in a single transfusion episode is significantly lower than recipients who receive a smaller number of units.[18,19] If we were able to account for this in our model, the cost-effectiveness ratio of PRT would be larger than reported here.

A key factor related to blood recipients that we cannot address in the analysis is the possibility that current posttransfusion survival across all component types, but particularly for PLT recipients, may be lower than the survival probabilities we used. Changes in practice patterns such as increased use of PLTs in patients with poor prognosis and reduced life expectancy would lead to larger cost-effectiveness ratios. While clinicians may recognize that current survival rates are lower for patients who receive specific blood components, only published longer-term survival data are appropriate to include in analyses of the cost-effectiveness of blood safety interventions. By necessity long-term posttransfusion survival data relies on transfusions that may have occurred as long as 20 years ago. Policy analyses that rely on posttransfusion survival data cannot circumvent this limitation.

Another potential limitation is the inclusion of some noninfectious adverse events such as postoperative infection that might occur as a result of TRIM. The debate is ongoing as to whether this is a real phenomenon leading to identifiable health consequences.[32,33] Nonetheless, assuming that the phenomenon is real the idea that TRIM is influenced by WBCs is less controversial. PRT will inactivate WBCs that are not removed by leukoreduction, preventing antigen presentation that could trigger recipient immune system responses. In this analysis, we assumed that PRT could achieve a 50% reduction in the residual risk of occurrence of TRIM. Moreover we modeled postoperative infection attributable to TRIM by assuming that the risk reduction could be as low as 1% or as high as a twofold increase. In sensitivity analyses, no aspect of TRIM was influential including the assumed risk reduction achieved using PRT.

Another possible limitation is that there is currently only emerging clinical data to support a reduced rate of FNHTR after the adoption of PRT. However, the mechanism for at least some FNHTRs is thought to include residual WBCs and PRT could reduce the frequency of FNHTR as has been observed in clinical studies. These benefits would be expected in components that carry higher risks of FNHTRs: PLTs and RBCs. In the model, FNHTRs are relatively high-probability and low-cost events that are somewhat influential. If FNHTR risk reduction is excluded from the model, for whole blood PRT the cost-effectiveness ratio increases by approximately 7% (meaning PRT is less cost-effective when FNHTRs are excluded). However, the 7% effect on the ratio shows that FNHTRs are not overly influential with respect to estimated cost-effectiveness.

The PLTs-and-plasma PRT model also has important additional limitations. Chief among them is that, except for donor exposures associated with PLTs, the model does not account for differential risks associated with different component types. For example, the model assigns the risk for plasma equal to that of PLTs for the transmission of enveloped viruses such as CMV or HTLV and for FNHTRs risk reduction. If other infectious or noninfectious threats differentially partition to specific labile blood components, then the model does not fully reflect these differential risks. However, we did account for one of the most important influences on the residual risk of bacterial contamination—the method of PLT preparation[34]—and showed that the cost-effectiveness of PLTs-and-plasma PRT varies depending on PLT collection and preparation methods.

Another important consideration is how we modeled the residual risk of each adverse event in the PLTs-and-plasma PRT analysis. The infectiousness of a blood component is dependent on multiple factors; these include the stage of donor's infection at the time of donation (viral load and antibody levels), the recipient's immune system, and the interaction between the two, among other factors.[35,36] An additional factor for component-specific use of PRT is also present and is related to the approach we used for modifying the residual risk of transfusion complications based on the combination of components transfused. For persons who receive transfusions that include both pathogen reduced and nonreduced components (RBCs), the residual risk of an adverse event is adjusted to reflect a blend of the lower risk in the pathogen-reduced component coupled with the residual risk of the nonreduced component.

Economic evaluations of similar PRT processes have previously been reported. For example, studies of the cost-effectiveness of amotosalen-based PRT for PLTs focused on patients with specific conditions requiring transfusion. A study conducted in the US setting reported results for four different patient groups (pediatric acute lymphocytic leukemia, hip arthroplasty, coronary artery bypass grafts, and adult non-Hodgkin's lymphoma) and with and without bacterial culture. Depending on the patient population, baseline results ranged from $4.8 to $23.0 million/QALY with bacterial culture and $1.4 to $4.5 million/QALY without bacterial culture for apheresis PLTs.[3] For pooled PLTs, the cost-effectiveness was $1.0 to $6.0 million/QALY under assumptions of low fatality attributable to bacterial

contamination and improved to $460,000 to $1.8 million/QALY assuming higher fatality due to bacterial contamination. Similar analyses for specific patient populations were conducted for Belgium, the Netherlands, and Japan.[4-6] Another study from the Netherlands found the cost-effectiveness of PRT for PLTs to be €2.8million/QALY (approx. $3.6 million/QALY) when added to bacterial culture and €382,000/QALY (~$497,000/QALY) without bacterial culture in random-donor PLTs for the average recipient.[9] The majority of these results suggest a cost-effectiveness of PRT that is less efficient than we report here. These previous analyses did not include the broad range of infectious and specific noninfectious threats that were included in our analysis. In addition, many other analysis assumptions were different, making direct comparison of our results to these studies difficult. Nonetheless, one common thread is apparent: bacterial contamination is the most important known adverse event that PRT addresses.

Our results also indicate that the age of the patient population is an important determinant of the cost-effectiveness of PRT. In the previously published cost-effectiveness studies of PRT for PLTs, the best incremental cost-effectiveness ratio was always evident for the pediatric population.[3-6] We conducted our analyses focused on different age groups to show that there are subgroups of transfused patients where PRT has a relatively attractive economic profile. These analyses are intended to indicate that for the expected benefits to accrue to subgroups of patients, it may be necessary to adopt PRT for all blood collections. Only if separate blood supply inventories were kept could recipient-specific use of PRT be an option. The complexity of maintaining separate inventories on such a large scale has not been carefully studied, but in many settings is likely not feasible.

Model variables related to the age and health status of the transfused population had important influence on cost-effectiveness results. In addition, the discount rate for effects was influential. Discount rates reflect time preference for health and money, with higher preference given to having health and money today as opposed to in the future. These model variables are not directly related to PRT and are often influential in analyses of any blood safety intervention. Moreover, the influence of life expectancy, quality of life, and discount rates is applicable to all cost-effectiveness analyses regardless of medical practice area. Both appropriately accounting for quality-adjusted life expectancy across broad population groups and determining what discount rates to use are unresolved methodologic controversies in health economics. While the influence of these variables in the analysis is evident, whether these variables have meaning with respect to decision making about PRT adoption is unclear.

Relative to the cost-effectiveness of interventions already in use in Canada and many other developed countries, such as minipool HIV and HCV NAT, which exceed $1.5 million/QALY in the United States,[37,38] the estimated preadoption cost-effectiveness of whole blood PRT and of PLTs-and-plasma PRT is consistent with established thresholds for value in blood safety. In developed countries that have very low risk of transfusion transmission of infectious diseases, even if some current screens or interventions are discontinued or modified, it is unlikely that any PRT will approach an incremental cost-effectiveness ratio threshold of $100,000/QALY. Although expensive on a cost-per-QALY basis in comparison to interventions adopted in other sectors of health care, given blood safety expectations that lean toward "zero risk" for infectious threats, commonly accepted thresholds that are regarded as cost-effective in clinical practice do not seem relevant. There continue to be multiple different hazards associated with transfusion including those considered in this analysis and other ones not amenable to the use of PRT such as transfusion-related acute lung injury and transfusion of the wrong blood type. This cost-effectiveness analysis provides additional information that was not previously available and may help to support decisions regarding this technology within the context of competing interventions and other threats to the safety of transfusion.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Technical Appendix. The cost effectiveness of pathogen reduction technology as assessed using a multiple risk reduction model.

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わが国における感染性因子低減化技術により生じる便益について（要約）

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方法

輸血用血液製剤に感染性因子低減化工程を加えた時にいかなる費用便益を生じるかについて、感染性因子低減化技術が確立している血小板製剤を含むすべての輸血用血液製剤による感染を想定した。

経済計算は、疾病や障害を有する者の生存期間を無価値的に捉えたり結果が感覚としてわかりにくい QALY(Quality Adjusted Life Year)ではなく、具体的な金額により便益を算定した。

保管検体で陽性が確認された過去約 10 年間の感染性因子の件数から 1 年当たりの予想される感染事例を算定し、感染が成立した場合の予後の推移等をもとに「直接医療費」「休業損失」および「早世による遺失利益」を求めることにより便益を算定した。HBV、HCV、HIV、細菌感染、ヒトパルボウイルス B19、HEV が対象感染性因子である。

結果

平均的勤労者（平均年齢 41.1 歳、年収 294.5 千円）をモデルとすると感染性因子低減化技術の導入により削減できる年間の「直接医療費」は 24,298,785 円、「休業損失」は 420,150 円となった。加えて「早世による遺失利益」は 1,083,669 円となり、合計 25,852,698 円が便益となる。

考察

わが国では HBV 感染者が多いが、これは「直接医療費」と「休業損失」の大半が HBV を原因としていることにも表れている。成人の HBV 感染の場合、慢性化しにくいことから 1 年目の医療費等の出費が増大するが、以後ほとんど影響を及ぼさない。HCV については、慢性化する割合が高いものの、HBV に比べると絶対数が少ないことにより、同様に経済的影響は少ないものとなった。HIV についても同様である。他の感染性因子による感染が考えられる事例についても数が少なく慢性化しないものが多いことから便益は小額になったものと考えられる。

まとめ

本稿では新興・再興感染症の流行の問題を考慮していない。いかなる感染症まで対象を広げて経済計算を行うべきか、そして血液の検査や製造工程にどの程度の経済資源を投入すべきかについても議論が必要であろう。

わが国における感染性因子低減化技術により生じる便益について

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緒言

高齢化により高騰する医療費をいかに抑制するかが、政府の主たる政策的課題であるが、医療技術の進歩も医療費を嵩じさせる要因の１つである。

現代の医療技術は、超音波、CT、MRI、PET などの診断治療技術と人工呼吸器、人工臓器、経静脈栄養、ICU などの延命的技術が主体となっている。対象疾患も長期・慢性の経過を示す生活習慣病である。治療期間が長いうえ、基盤は光学技術や電子工学などの最先端の技術で、しかも開発途上にあるため短期のサイクルで更新されていくものである。検査や血液製剤の製造技術も同様に高度かつ高価な技術基盤に基づくものである。NAT やウイルス等の感染性因子低減化技術もこうした技術に属する。しかも、旧来の検査・製造技術を併存しながら最新技術を付加しているのである。

血漿分画製剤の不活化は技術としてシステムとして確立している。論点は、輸血用血液製剤への感染性因子低減化技術の導入である。

検査技術としての NAT は、血液中のウイルスを高精度で検出する技術であり、血液製剤の信頼性の向上に大きく寄与している。しかし、費用便益面から考えると問題を有している。NAT という大規模技術の導入に当たっては医学面のみではなく経済的観点からの検討ならびに導入後の多角的評価が必要であった。しかし、それは十分にはなされてこなかった。感染性因子低減化技術も費用便益的観点からの分析・評価が十分とは言えない。こうした大規模技術は社会経済的インパクトが大きいにもかかわらず、医学的観点からの論議のみが先行し、そのほかの各分野の専門家、国民、行政、関係者を交えた議論の展開や合意の形成が欠落しているのである。

本稿は、感染性因子低減化技術などの最新技術を導入することが、医療や社会にどのようなインパクトをもたらし、導入した技術をシステムとして維持していくために検討を要する課題の一部を整理したものである。

輸血用血液製剤の安全性確保のために問診の強化や NAT が行われている。また、血漿分画製剤には不活化が製造工程で加えられ、安全性を飛躍的に向上させている。現在、これに加えて輸血用血液製剤に対しても不活化を行うべく議論が進んでいる。しかし、NAT を

はじめとする新技術の導入は一般に高コストとなるものである。

そこで、輸血用血液製剤に感染性因子低減化工程を加えた時にいかなる便益を生じるかを調べた。但し、感染性因子低減化技術が確立している血小板製剤以外の製剤も含むすべての輸血用血液製剤による感染を想定した。

なお、経済計算を行っている多くの論文では、生活の質（QOL）で重みづけを行い生存期間に加えて生活の質の評価もできる QALY(Quality Adjusted Life Year)を求めている。しかし、QALY は健康な人が 1 年生きた場合の生存期間を 1QALY とするのに対し、脳卒中などで身体が不自由になった場合の生存期間を健常人が 1 年生きる価値があるのを 0.3QALY に補正するなど障害の重み付けに主観が入ることや、疾病や障害を有する者の生存期間を無価値的に捉える問題がある。加えて結果が感覚としてわかりにくいことから、本稿では多くの方が直観的にイメージしやすいように具体的な金額により便益を算定する方法を採用した。

方法

1. NAT を行っている HBV、HCV および HIV について

輸血用血液製剤の製造の際に感染性因子低減化工程を導入することは、NAT の検出感度以下の HBV、HCV および HIV の混入による患者への感染を防ぎ得たことによる不必要な医療費出費、外来や入院にともなう休業損失、早期死亡による遺失利益を減少させるという社会経済効果をもたらすものと考えられる。

日本赤十字社には輸血後感染症情報が医療機関等から寄せられ、保管検体をもとに原因ウイルスか否か同定することになる。これら報告のうち、検体陽性が確認された件数をもとにウインドウ期等のために NAT では検出できないケースが、これら 3 つのウイルスによる感染を引き起こすものと想定した（表１）。これらの感染は輸血用血液製剤に不活化工程を導入した場合、被害を防ぐことができるものとして社会的な観点から「直接医療費」「休業損失」および「早世による遺失利益」の計算を行った。具体的には、①感染により各段階に病態が進行した際の“直接医療費”、②外来や入院に費やす時間に起因する“休業損失”、そして③期待寿命を待たずして死亡した“早世による遺失利益”を社会的コストとして算定した。

HBV については急性肝炎のステージで病態が終息するとし、HCV については慢性肝炎、肝硬変、肝細胞がんへの移行確率を Markov 連鎖モデルをもとに算出した。

HIV については予後が近年著しく向上したことから、算定する今後 10 年間においては死亡がなく、定常的な状態にあるものとした。なお、これらウイルスの陽性血液を輸血された場合、必ず感染が成立するものとした。

また、2008 年 8 月より新 NAT システム（抽出・検出機器 cobas s401　試薬 TaqScreen MPX）により 20 プールで HBV、HCV、HIV に関する検査が行われている。それ以前の NAT の検出感度と現在のそれとの差を無視するが、2000 年～2010 年 7 月までの約 10 年

余の間に献血が原因と考えられる輸血後感染症は、HBV 95 例、HCV 3 例、HIV 1 例であった。これを年間発生数で表すと下記のようになる（表１）。計算は、年間発生件数を用いて行った。

表１　検体陽性数をもとに算定した年間感染件数

ウイルス名	2000 年～2010 年 7 月までの報告数	年間報告件数
HBV	95	8.98
HCV	3	0.28
HIV	1	0.09

(1)HCV 感染の Markov 連鎖モデル

HCV 感染後の患者は、急性肝炎→キャリアー→慢性肝炎→肝硬変→肝細胞癌という自然推移をとることが多いが、必ずしもそのような推移をとるわけではなく、中には慢性肝炎から肝硬変を経ずに肝細胞癌を罹患するという症例も見られる。また、肝硬変の症例は肝細胞癌を合併する前に死亡する例も見られることから、この推移は一義的ではない。このような疾患の自然推移をモデリングするために HCV 感染者の予後データ[1]、[2]、[3]、[4]をもとに Markov 連鎖モデルを用いて、NAT 後 10 年間の遷移確率を計算し、それぞれの状態において要する医療費を当てはめた。

Markov 連鎖は別名 Markov 過程とも呼ばれる確率過程のことである。すなわち、未来の挙動が現在の値だけで決定され、過去の挙動と無関係であるという性質を持つ確率過程である。例えば、ある慢性肝炎例が肝硬変を発症する確率が、その症例がどのように（例えばどの時点で）HCV に感染したかと無関係であるとき、この確率過程は Markov 性を有するという。

上記は数式により以下のように表すことができる。時点 i における集団の状態を、

$$\mathbf{S}_i = \begin{pmatrix} s_{i1} & s_{i2} & s_{i3} & s_{i4} & s_{i5} & s_{i6} \end{pmatrix}$$

とする。ここでベクトルの要素は疾患の推移（HCV 非感染、キャリアー、慢性肝炎、肝硬変、肝細胞癌、死亡）にそれぞれ対応する。次に、時点 i におけるそれぞれの状態の人数を、

$$\mathbf{L}_i = \begin{pmatrix} l_{i1} & l_{i2} & l_{i3} & l_{i4} & l_{i5} & l_{i6} \end{pmatrix}$$

とする。時点の経過とともに、ベクトルの各要素である各状態の人数は変動する。マルコフ連鎖モデルでは、この変動を推移確率行列という行列で確率的に規定する。

$$\mathbf{P}=\begin{pmatrix} p_{11} & p_{12} & 0 & 0 & 0 & 0 \\ 0 & p_{22} & p_{23} & 0 & 0 & 0 \\ 0 & 0 & p_{33} & p_{34} & p_{35} & 0 \\ 0 & 0 & 0 & p_{44} & p_{45} & p_{46} \\ 0 & 0 & 0 & 0 & p_{55} & p_{56} \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

ここで、p_{ij} は i 番目の状態から j 番目の状態に推移する確率（推移確率）を意味する。例えば、p_{23} はキャリアーが次の時点に慢性肝炎を発症する確率を示している。上の推移行列では、疾患は進行するものの治癒することはなく（対角成分よりも下の推移確率が全て 0）、各時点で状態が推移する確率が時点によらず一定であることを仮定している。

上記のマルコフ連鎖モデルにより、時点 i におけるそれぞれの状態の人数は、$\mathbf{L}_0$ を初期状態の人数としたとき、$\mathbf{L}_i=\mathbf{L}_{i-1}\mathbf{P}=\mathbf{L}_0\mathbf{P}^i$ で表すことができ、マルコフ連鎖モデルにおける推移行列を下記のように定めることができる[1]。

たとえば、1 年単位の推移行列を下記のように推定すると、

$$\mathbf{P}=\begin{pmatrix} 0.99948 & 0.00052 & 0 & 0 & 0 & 0 \\ 0 & 0.977 & 0.023 & 0 & 0 & 0 \\ 0 & 0 & 0.957 & 0.03 & 0.013 & 0 \\ 0 & 0 & 0 & 0.923 & 0.043 & 0.034 \\ 0 & 0 & 0 & 0 & 0.697 & 0.303 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

この推移行列に対して、初期条件を$\mathbf{L}_0=\begin{pmatrix}1 & 0 & 0 & 0 & 0 & 0\end{pmatrix}$としたとき、年次の条件の推移は<u>表９、１０</u>の通りである。この$\mathbf{L}_0$ に現時点での各病態の人数を代入すれば、将来における HCV の自然経過をモデル化できる。

２．輸血後副作用報告があったその他の感染症

日本赤十字社に報告があったその他の感染症として以下のものがある（<u>表２</u>）。

これらについても年間発生件数をもとに、「直接医療費」「休業損失」および「早世による遺失利益」の計算を行った。但し、「細菌」「ヒトパルボウイルス B19」「HEV」による感染は慢性化することなく、急性期で終息するものとした。

表２　輸血後副作用報告があったその他の感染症

（製剤陽性例　報告期間　1998～2007 年）

	確認件数	感染者数／年
細菌	8	0.8（うち死亡が 0.2）
梅毒	0	0.0
HTLV-1	0	0.0
ヒトパルボウイルス B19	10	1.0
HEV	5	0.5

仮定としては、感染性因子低減化工程を取り入れた場合と取り入れなかった場合を比較して、取り入れなかった場合に 1 年間に血液製剤を輸血され感染が成立した患者群を 10 年間追跡した場合の「直接医療費」「休業損失」および「早世による遺失利益」の総コストを算定し、これを便益とした。

また、計算の対象とした年齢は、わが国の標準的な勤労者とした。当該年齢の平均賃金は、男女計 294.5 千円(平均年齢は 41.1 歳)であった。

「休業損失」については、入院の場合 1 日、外来通院の場合 0.5 日の損失があったものと仮定した。

「直接医療費」については、「2005 年疾患別医療費データ」（津谷 2007 年）、平成 20 年の厚生労働省の「患者調査」、「社会医療診療行為統計」を用いて算定した。

「早世による遺失利益」については、死亡した時点から 65 歳（収入が得られる何らかの職業に従事している上限年齢を 65 歳に設定）までの間の残余年数を求め、昨今の経済情勢を加味して賃金上昇はこの期間ないものとして算定した。

これら 3 つの因子の今後 10 年間の値は、民事事件で損害額の算定に用いられるホフマン法を採用し、現在価値に置き換えた。ホフマン法については通常法定利息（割引率）5%を用いるところ、昨今の情勢に鑑み 3%として計算した（注：参照）。

注）ホフマン法

$$X = \sum_{n=1} A／（1＋n r）$$

X：現在価格（手取額）

A：将来得ることが可能な利益

n ：利益が生じるまでの期間

r：利率（割引率）3%　（法定利率である 5%は昨今の経済状況から用いなかった。）

具体例）

$$X = 2{,}945{,}000/(1+0\times0.03) + 2{,}945{,}000/(1+1\times0.03) + 2{,}945{,}000/(1+2\times0.03) + \cdots\cdots$$

結果

１．直接医療費

HBV、HCV、HIV およびその他の感染症の医療費は「2005 年疾患別医療費データ」（津谷、2007 年）により算定した。その結果を表３、４、５に示している。

平均在院日数および平均外来日数は患者調査をもとに算定し、その結果は表６、７、８に示すとおりである。

さらに Markov モデルによる HCV の各病態への遷移確率と予想される人数を表９、１０に示している。

これらをもとに計算すると、今後 10 年間の「直接医療費」は表１１に示すように 242,987,846 円となり、1 年当たり 24,298,785 円となる。

表３　肝疾患の年間医療費（津谷　2007 年）

入院	円
急性肝炎	4,276,679
慢性肝炎	766,237
肝硬変	3,748,163
肝細胞がん	15,168,287
外来	**円**
急性肝炎	17,310,343
慢性肝炎	2,952,795
肝硬変	2,080,998
肝細胞がん	3,757,797

表４　HIV の年間医療費（津谷　2007 年）

	円
入院	14,900,000
外来	

表５　その他の感染症（細菌、ヒトパルボウイルス B19 および HEV）の年間医療費（津谷　2007 年）

入院	円
細菌感染	6,770,602
ヒトパルボウイルス B19	1,443,080
HEV	4,276,679
外来	**円**
細菌感染	1,341,824
ヒトパルボウイルス B19	6,019,502
HEV	17,310,343

- 細菌感染については、「その他の感染症および寄生虫症」、ヒトパルボウイルス B19 については「皮膚及び粘膜の病変を伴うその他のウイルス疾患」、HEV については HBV、HCV と同様に「ウイルス肝炎」の金額を用いた。
- HEV 感染については、重症化することなく急性肝炎で終焉したと仮定した。

表 6　肝疾患の平均在院日数および平均外来日数

入院	日
急性肝炎	14.2
慢性肝炎	35.5
肝硬変	40.7
肝細胞がん	22.4
外来	**日**
急性肝炎	36.7
慢性肝炎	50.0
肝硬変	44.0
肝細胞がん	38.0

表 7　HIV の平均在院日数および平均外来日数

入院	40.1
外来	25.0

表 8　入院および外来期間

入院	日
細菌感染	45.2
ヒトパルボウイルス B19	4.2
HEV	14.2
外来	**日**
細菌感染	23.3
ヒトパルボウイルス B19	36.1
HEV	54.5

表９　HCV の向こう 10 年間の遷移確率

年	1年目	2年目	3年目	4年目	5年目	6年目	7年目	8年目	9年目	10年目
急性肝炎	1	–	–	–	–	–	–	–	–	–
慢性肝炎	0	0.0230547550	0.0230804537	0.0342339653	0.0451890934	0.0558932392	0.0664036043	0.0766604108	0.0867241703	0.0965601127
肝硬変	0	0	0.0002622779	0.0006966214	0.0013290910	0.0021732487	0.0031803057	0.0043530393	0.0056487905	0.0070846315
肝細胞癌	0	0	0.0001311389	0.0002985520	0.0005235813	0.0008489253	0.0012073383	0.0016160984	0.0020626289	0.0025393709
死亡	0	0	0	0.0000497587	0.0001208265	0.0002716561	0.0005300509	0.0008862475	0.0013828989	0.0019845504

表１０　HCV 感染者の実数（0.28 人）を代入した場合の向こう 10 年間の各病態の人数

年	1年目	2年目	3年目	4年目	5年目	6年目	7年目	8年目	9年目	10年目
急性肝炎	0.28	–	–	–	–	–	–	–	–	–
慢性肝炎	0	0.0064553314	0.0064625270	0.0095855103	0.0126529462	0.0156501070	0.0185930092	0.0214649150	0.0242827677	0.0270368316
肝硬変	0	0	0.0000734378	0.0001950540	0.0003721455	0.0006085096	0.0008904856	0.0012188510	0.0015816613	0.0019836968
肝細胞癌	0	0	0.0000367189	0.0000835946	0.0001466028	0.0002376991	0.0003380547	0.0004525076	0.0005775361	0.0007110239
死亡	0	0	0	0.0000139324	0.0000338314	0.0000760637	0.0001484143	0.0002481493	0.0003872117	0.0005556741

表１１　今後 10 年間の直接医療費

項　　目	今後 10 年間の医療費（円）
HCV 医療費総計	2,214,000
HBV 医療費総計	193,851,458
HIV 医療費総計	11,883,782
細菌感染医療費総計	6,489,941
HPV-B19 医療費総計	7,462,582
HEV 医療費総計	10,793,511
総計	**243,488,785**

２．休業損失

今後 10 年間の休業損失総計は、4,201,504 円で 1 年当たり 420,150 円となる。数が多い HBV による損失が、この過半（2,751,410 円）を占めていた。

３．早世による遺失利益

過去に死亡例があったり、死亡を想定したものとして細菌感染と HCV があるが、これらの結果を表１２に示す。

表１２　遺失利益

項　　目	遺失利益（円）
HCV による遺失利益総計	57,768
細菌感染による遺失利益総計	10,778,922
総計	**10,836,690**

４．便益

以上より、不活化技術導入により得られる 1 年当たりの「直接医療費」「休業損失」「早世による遺失利益」を併せた便益は、**25,852,698 円**となる（表１３）。

表１３　不活化技術導入による便益

項　　目	便益（円）
直接医療費総計	243,488,785
休業損失総計	4,201,504
遺失利益総計	10,836,690
総合計（今後 10 年間）	258,526,979
総合計（1 年当たり）	25,852,698

考察

わが国では HBV 感染者が多いが、これは「直接医療費」と「休業損失」の大半が HBV を原因としていることにも表れている。成人の HBV 感染の場合、その約 98%が急性肝炎で推移し、ほとんど慢性化しないことから 1 年目の医療費等の出費が増大するが、以後ほとんど影響を及ぼさない。但し、近年の海外に起源を持つ HBV は慢性化すると言われているがここでは考慮しなかった。

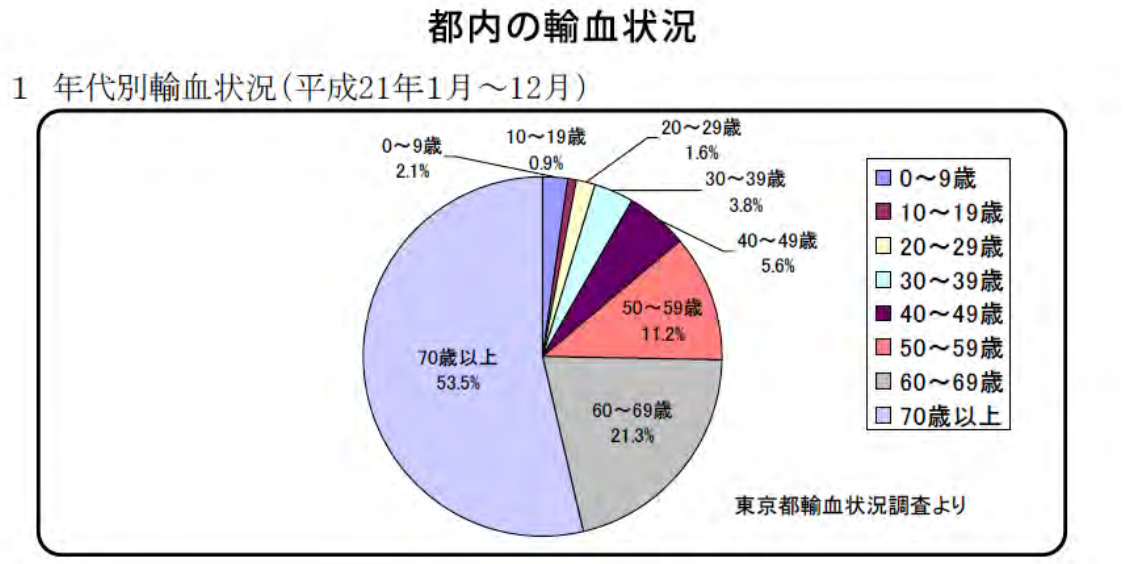
HCV については、慢性化する割合が高いものの、HBV に比べると数が少ないことにより、同様に経済的影響は少ないものとなっている。

HIV についても HBV 及び HCV に比して感染者自体が少ないことから、経済的影響は同様に少ないものと考えられる。

休業損失や遺失利益は就業者を対象にしたものであり、今回は勤労者の平均年齢を用いて便益を算定した。東京都の調査によると、輸血を受けている者の平均年齢は 64.6 歳と推計されることから、この平均年齢を用いると「休業損失」と「遺失利益」はほとんど生じないことになる。加えて原疾患の予後が不明であるが、健常人の生存曲線より減衰率が高いものと考えられる（図１）。したがって、これらのことを加味すると実際の便益は算定したものより少ないものと思われる。加えて今回の計算では、輸血によらない原疾患による輸血後の死亡のデータがないため計算できなかったが、これらを考慮すれば一層便益は低

下するものと思われる。一方、今回の計算では「感染性因子低減化技術」を 1 年間実施した場合の HCV の予後について 10 年間のみしか考慮しなかった。HCV の自然史経過は全体で 30 年間程度に及ぶことから、厳密には 30 年間の経済計算を行う必要があったと考える。しかし、30 年間の計算を行ったとしても、もともとの感染予想者の数値が小さいためその増分は僅かであり、結果にはほとんど影響を及ぼさないことと思われる。

図 1　都内の輸血状況



＊　「東京都の血液事業（平成 21 年度）　東京都福祉保健局保健政策部　疾病対策課」によると、60 歳以上の患者に対する輸血が全体の 74.8%を占めている。そこで各年齢階級の中央値に年齢が集中していると仮定して、輸血を受けた者の平均年齢を求めると 64.6 歳と推計される。

まとめ

不活化導入コストについては、本稿で示した便益と比較して議論する必要もあろう。NAT はウイルスを検出することに主眼を置いているが、ウイルス等の病原微生物そのものの不活化が各国で行われつつある。S/D 処理による感染性因子低減化技術の経済性については A. Pereria[7]により行われたが、その結果は経済性が低いものであった。

また、本稿では新興・再興感染症の流行の問題を考慮していない。いかなる感染症まで対象を広げて経済計算を行うべきか、そして血液の検査や製造工程にどの程度の経済資源を投入すべきかについても議論が必要であろう。

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