The PROTON study

Profiles of transfusion recipients in the Netherlands

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The PROTON study: profiles of transfusion recipients in the Netherlands

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De PROTON-studie

Profielen van transfusie-ontvangers in Nederland

(met een samenvatting in het Nederlands)

Proefschrift

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General introduction

Blood supply in the Netherlands

Blood transfusion is a medical intervention that is often life-saving. This motivates people to donate blood voluntarily. Despite its overall benefit, blood transfusion is also associated with several (small) risks, for example transfusion of a blood component of the wrong blood group due to a logistic error, allergic reactions or transmission of an infectious disease.[1,2] Therefore, blood transfusion is a special medical intervention, surrounded with emotions: donors get a good feeling because they help other people, recipients are thankful to receive blood components from volunteer donors, but recipients may also be very angry if they contract an infectious disease (for example AIDS) through blood transfusion.

In total, 906,113 blood components were transfused in the Netherlands in 2009.[3] This included 544,238 red blood cell concentrates (RBC), 273,663 units of fresh frozen plasma (FFP) and 88,212 platelet concentrates (PLT).[3] These blood components were made from blood donations of 393,201 donors who voluntarily donated 575,050 whole blood donations and 331,717 plasma donations.[3] The adverse risks for recipients of blood transfusion are small. The probability of getting a known infectious disease through blood transfusion is very low. In the Netherlands in 2008, a viral infection through blood transfusion was reported 7 times, one of which was highly imputable to transfusion.[4] Other adverse events after transfusion occur more often, but are still rare: anaphylactic reactions were reported 59 times, of which 27 were highly imputable, volume overload was reported 38 times (16 highly imputable) and TRALI (transfusion-related lung injury) was reported 19 times (17 highly imputable). Also, a wrong blood product was transfused 57 times. Despite its low share in the already rare side effects, transmission of infectious diseases is feared most. This forces blood banks to pay considerable attention to this adverse event.

Reducing the risk of viral infections through blood transfusion

To reduce the risk of viral infection through blood transfusion, a number of interventions are currently routinely performed in the Netherlands, as in many other countries.[5,6] First, before donating blood, persons have to fill out a standardized questionnaire to investigate whether their risk of infectious diseases is elevated. There are a.o. questions about risky sexual behavior, about (recent) traveling to countries where certain diseases are endemic and about ever having received a blood transfusion. Based on these questions, persons can be temporarily or permanently excluded from donation. Second, all blood donations are screened for the presence of antibodies against particular viruses and/or for the presence of viral DNA or RNA.[7] If a test turns out positive, the donations involved are destroyed and donors are deferred (usually for life) from donation. Currently, in the Netherlands all blood donations are screened for antibodies for hepatitis C virus (HCV), human immunodeficiency virus type 1 and 2 (HIV-1/2), human T-cell lymphotropic virus type

I and II (HTLV-I/II) and Treponema bacteria, that causes syphilis. The donations are also screened for HBsAg, the antigen of hepatitis B virus (HBV). Additional to antibody testing, a Triplex NAT test for HBV, HCV and HIV is performed in minipools of 6 donations (MP-6-NAT). Plasma units are further tested for hepatitis A virus (HAV) and Parvovirus B19. Introduction of these tests has reduced the probability of viral infections through blood transfusion tremendously.[2] Third, techniques are applied to remove or reduce pathogens from the blood components. For example, leukocytes (white blood cells) are removed from cellular blood components (RBC and PLT) to reduce the risk of transmission of cell-related viruses. Another example is that PLT can undergo pathogen reduction by photochemical inactivation.[8] This technique, that is not yet available for RBC, can further reduce contamination with any nucleic acid containing agent, including viruses.[9] An alternative to pathogen reduction is bacterial culturing to detect bacteria in finished blood components.[8] Besides these blood bank interventions on the supply side, clinicians aim at decreasing the use of blood products. To do this, new medical techniques are developed to reduce the loss of blood and to re-use blood that is lost during surgery. Strategies aiming to restrict the demand of blood products are generally referred to as 'optimal blood use'.[10-13]

Despite these safety interventions, an infectious blood component may enter the blood transfusion chain. This can occur for example when a new virus enters the donor population or when a test is not 100% sensitive. New blood safety interventions are invented to further reduce the risk of adverse events. Measured or estimated effects have to be balanced with costs o decide which interventions are worthwhile to be performed.[14] The resulting cost-effectiveness ratio of blood tests informs decision makers about the value for money. One may disagree on framing the issue of blood safety measures as an economic trade-off. Nevertheless, this way of supporting decision-making by a value for money expression has been gradually accepted in health care. In many countries, including the Netherlands, cost-effectiveness analyses (CEAs) are increasingly performed. The Dutch minister of health requires CEAs for new blood safety measures.

Cost-effectiveness of blood safety interventions

A CEA of any blood safety intervention starts with building a mathematical model of the transfusion chain from donor to recipient. Here, we restrict the framework to safety interventions dedicated to reducing the risk of transmission of infectious diseases. Several parameters have to be estimated, for example the prevalence and/or incidence of viral infection among donors, the testing costs and the number of transmissions that will be avoided by the test. The second part of the CEA is modeling the disease progression in the recipient after transmission, to estimate the effect of avoiding the disease in one transfusion recipient. To model the disease, information is required on the kinds of health condition involved in the disease and

the yearly probability to end up in such condition or to decease. The result of this part of the model is twofold: the effects, expressed in terms of quality-adjusted life-years (QALYs) gained, and the avoided treatment costs. These results depend strongly on the age and life expectancy of this recipient. For example, infection of a little baby with HIV will have a large impact on its life expectancy and quality of life. On the other hand, an HIV-infected blood product will not affect life prospect at all when transfused to a woman with progressive breast cancer who will die within weeks. So, information on transfusion recipient age and survival is essential to perform cost-effectiveness analyses of blood screening.

CEAs of blood screening tests already have some history. In 1988, Eisenstaedt and Getzen presented a CEA of HIV antibody testing for blood donations.[15] For their calculations, they used the age distribution of the first 194 possible transfusion-associated AIDS cases that were reported to the Centers for Disease Control in the USA. HIV antibody testing appeared to be cost-saving. Thanks to serological testing, the risk of transfusion-associated transmission of known viruses like HBV, HCV and HIV has become so small that mathematical modeling is needed to estimate the expected effect of avoiding one transmission.[2,16] Recipient age distribution and survival after transmission of a virus must be obtained by analyzing data on all blood product recipients, assuming that the probability of transmission of a virus does not depend on recipient characteristics. However, no national registry concerning blood product transfusion recipients exists in the Netherlands, although in 1999 blood bankers already noted that 'it is somewhat paradoxical that the Netherlands is self-sufficient [in blood supply], without a well-documented overview of the use including the associated indication.'[17] The lack of data may well explain the stepwise building of an impressive defence against infectious transmission without explicit trade-off of the costs of any additional measure against its assumed benefits. The PROTON study (PROfiles of TransfusiON recipients), as described in this thesis, was initiated to fill in this gap. The aim was to collect data on blood product transfusion recipients in the Netherlands, with retrospection as far as possible. These data can be used for improving evaluation of blood safety interventions and for many other applications.

Other applications of blood product recipient data

Combined with demographic information, data on blood transfusion recipients are very useful for estimating future blood use. As most blood components are transfused to elderly patients and as the general population ages, it is important to predict the future need of blood components to enable anticipatory strategies in donor recruitment. Modeling scenarios on possible future medical or policy changes towards optimal blood use can further refine such forecasts.

Another application is that hospitals can compare the PROTON results with their own data for benchmarking purposes. For this aim, each hospital participating in the PROTON study was sent a short report with the analysis results of the provided data.

Thesis outline

Chapter 1 presents a cost-effectiveness analysis of HBV-NAT (nucleic acid amplification testing), that was performed at the beginning of the project. At that time, only old recipient data from a small study and one-hospital survival data were available. Nevertheless, it was shown that the age distribution of blood transfusion recipients had a large impact on the resulting cost-effectiveness ratio. Chapter 2 describes the process of collecting data from 20 hospitals, creating the PROTON dataset and estimating national distributions of blood components over recipients, with respect to age, gender and diagnosis. Linking the data to the national mortality registry allows studying survival after transfusion. The methodological aspects of estimating survival after transfusion are described in Chapter 3. In Chapter 4, survival after transfusion in the Netherlands is presented, as estimated from the PROTON dataset. In Chapter 5, all PROTON data are used to perform cost-effectiveness analyses of three blood screening tests: Triplex nucleic amplification testing (NAT) for HBV, HCV and HIV, antibody screening for HTLV-I/II and NAT for HAV and Parvovirus B19. Finally, Chapter 6 shows how combining PROTON data with demographic prognoses resulted in prediction models for future blood supply and demand.

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Chapter 1

Cost-effectiveness of additional hepatitis B virus nucleic acid testing of individual donations or minipools of six donations in the Netherlands

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Abstract

Background To further reduce the risk of hepatitis B virus (HBV) transmission by blood transfusion, nucleic acid testing (NAT) can be employed. The aim of this study is to estimate the incremental cost-effectiveness ratio (ICER) in the Netherlands of employing a triplex NAT assay aimed at HBV nucleic acid detection in individual donations (ID-NAT) or in minipools of 6 donations (MP-6-NAT), compared to a triplex NAT assay in minipools of 24 donations (MP-24-NAT).

Study design and methods A mathematical model was made of the whole transfusion chain from donors to recipients of blood in the Netherlands. The annual number of avoided HBV transmissions was estimated with the window-period incidence model. The natural history of a HBV infection in recipients is described by a Markov model.

Results The ICER of adding HBV MP-6-NAT or HBV ID-NAT in the Netherlands is €303,218 (95% confidence interval [CI], €233,001-€408,388) and €518,995 (95% CI, €399,359-€699,120) per quality-adjusted life year, respectively. The ICER strongly correlates with the age of transfusion recipients.

Conclusion The cost-effectiveness of additional HBV NAT is limited by the limited loss of life caused by HBV transmission. Despite a higher effectiveness, HBV ID-NAT is less cost-effective than MP-6-NAT due to higher costs. A future equivalent participation of immigrants from HBV-endemic countries in the donor base renders HBV NAT only slightly more cost-effective.

Introduction

Although all blood transfusions are associated with a residual risk, over the past decades the risk of transmission of viruses has decreased considerably.[1] Nevertheless public concern about transmission of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) keeps up the pressure to implement extra interventions making blood transfusions even safer.[2] To spend health care budgets efficiently, Dutch public health policies aim at optimal instead of maximum blood safety.[3] This implicates that costs and effects of new screening methods for blood products should be taken into account when deciding whether or not to introduce new (screening) methods.

Additional to serologic screening of all blood donations for anti-HIV-1/2, anti-HCV, hepatitis B surface antigen (HBsAg), anti-HTLV-1/2, and treponemal antibody, HCV nucleic acid testing (NAT) and HIV NAT in minipools of 48 donations were implemented in the Netherlands in 1999 and 2000, respectively. The introduction of HCV NAT and HIV NAT was not based on cost-effectiveness analyses, but it was a result of regulatory requirements for plasma pools for fractionation.

Owing to CE certification requirements for in vitro diagnostics for blood screening the previously published platform for NAT minipool screening, which forms the base of the current program, needs replacement.[4] In Europe only two triplex NAT platforms, both designed for simultaneous NAT of HIV, HBV, and HCV are CE certified. This certification is mandatory for blood donor testing.[5] One platform (Procleix Tigris, Chiron, Emeryville, CA) is primarily designed and CE marked for triplex NAT on individual donations (ID-NAT). The other platform (cobas s 201, Roche, Indianapolis, IN) is primarily designed and CE marked for triplex NAT in minipools of 24 donations (MP-24-NAT) or minipools of 6 donations (MP-6-NAT). This implies that NAT will be performed in pools of at most 24 donations. The MP-24-NAT format is not likely to detect HBV infections in addition to those already detected by present serologic screening with a highly sensitive HBsAg test (Prism, Abbott, Abbott Park, IL).[6] ID-NAT has a higher effectiveness, but is also more expensive than MP-NAT. In the light of cost containment in health care, a cost-effectiveness analysis of installing triplex NAT in a pool size sufficiently small to detect additional HBV infections is performed, either in the MP-6-NAT or ID-NAT format.

Some European countries also screen for antibodies to hepatitis B core antigen (anti-HBc), previously implemented in the United States as a surrogate marker for non-A, non-B hepatitis and more recently as an additional test for the detection of cryptogenic HBV infections. In the Netherlands the request for anti-HBc testing was declined by the minister of health given the poor cost-effectiveness estimates and

considerable loss of donors. Therefore, anti-HBc testing is not included in this analysis.

The incremental cost-effectiveness ratio (ICER) can be used as a tool to support the decision on whether newly developed safety measures should be introduced. The ICER reflects the ratio of the additional effects (life-years saved) of a new blood test to its additional costs.[7] This number can be used as an objective measure to compare safety measures. The aim of this study is to estimate the ICER of HBV MP-6-NAT and ID-NAT compared to triplex MP-24-NAT in the Netherlands, a country of low endemicity for hepatitis B.

Materials and methods

Costs and effects

The additional costs are the costs of testing subtracted by the expected costs related to HBV infection that are avoided as a result of the additional screening. The incremental testing costs for both MP-6-NAT and ID-NAT versus the reference of MP-24-NAT were calculated by Sanquin for the formal annual budget proposals to the Ministry of Health. These encompass all incremental costs within Sanquin, including a.o. reagents, disposables, personnel, and investments. The costs of an HBV infection include direct medical costs and indirect costs due to inability to work.

The effects of implementing MP-6-NAT or ID-NAT are measured in quality-adjusted life-years (QALYs) gained by prevented HBV transmissions to transfusion recipients. QALYs are calculated as the product of life-years experienced after an intervention (here blood transfusion) and the quality of life (QoL) of the recipient during every subsequent year, expressed as a figure between 0 (death) and 1 (normal QoL). Hence, life-years are weighted or indexed. The main reason to incorporate QALYs instead of life-years is that an improvement of QoL is also relevant when calculating the effect of avoiding an infection. Because mortality due to HBV transmission is not 100 percent, consequently, it is possible that the number of QALYs lost due to infection will be larger than the number of life-years lost. We do not take into account the existing QoL of transfusion recipients, being aware that in some recipients the contraction of HBV infection only further reduces already compromised QoL. We assume that the resulting overestimation of QoL effects of avoiding HBV infections is counterbalanced by the observation that part of the existing diseases for which blood donations are given progress worse if a coinfection with HBV is present.

Note that we do not consider other causes of HBV infections, but only the incremental infections due to blood transfusion. The low number of HBV infections possibly transmitted by blood transfusion prohibits a clinical experiment measuring

the efficacy of the intervention; therefore, a modeling approach is used. A mathematical model of the transfusion chain from donor to recipient is developed to estimate the number of infections avoided by MP-6-NAT or ID-NAT. A Markov model is used to calculate the expected medical costs and the expected number of QALYs lost by one HBV infection.

The number of avoided infections

During early infection, the viral load may be lower than the detection limit of the screening test. The period during which this occurs is called the window period (WP). The effect of MP-6-NAT or ID-NAT is based on the number of infected donations that fall in the WP of the serologic HBsAg test, but not in the WP of the NAT test. This number can be determined using the "window period incidence model."[8] The length of the WP multiplied with the incidence rate among repeat blood donors and the number of donations per year yields the number of window donations per year.

In the Netherlands, donors do not give blood for transfusion at their first attendance. At first visit they are only interviewed and tested. The measured incidence rate must be corrected for the estimated number of incidents not detected by donor screening, which depends on the interdonation intervals among Dutch donors.[9,10]

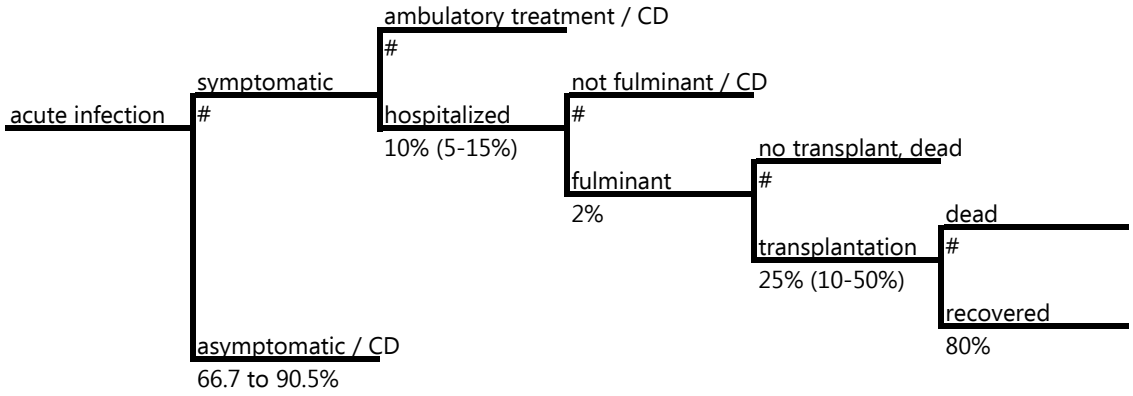
Two WPs need to be considered in the case of HBV: in the ramp-up phase just after infection and in the early reconvalescence when HBsAg disappears and anti-HBs does not yet neutralize the virus. The length of the WP is determined by two variables: sensitivity of the test and doubling time of the virus during the acute phase and half-life of the virus during reconvalescence. The sensitivity for the current Prism HBsAg test is estimated 3000 IU per mL, which corresponds to the WP reduction experimentally found for this test.[6] The cutoff ratio of HBV NAT is 22.2 IU per mL for MP-6-NAT and 10.9 IU per mL for ID-NAT (H.T.M. Cuijpers, personal communication, 2006). The doubling time of HBV in the acute initial phase of the infection is 2.6 days and the half-life in the recovering phase is 1.6 days.[11] It is assumed that transfusing a blood component containing 30 to 200 mL of plasma and donated during the WP of the serologic HBsAg test, but positive for NAT (either MP-6-NAT or ID-NAT, i.e., containing respectively more than 22.2 or 10.9 IU/mL,) results in a HBV transmission to the recipient.

Description of the disease model

After calculating the number of avoided infections, the costs and effects of one HBV infection caused by blood transfusion are estimated. This is done by use of a Markov model, being an update of the model used to study the cost-effectiveness of HBV vaccination in the Netherlands.[12] Updates concern treatment costs, the possibility of children from 0 to 15 years old being infected by horizontal transmission and the

inclusion of QoL. The Markov model describes the natural history of an HBV infection with dependence on age at infection. It consists of five health states for each of which mortality, costs, and QoL are estimated. The transition probabilities indicate the annual probability to move from one health state to another. These probabilities differ according to age. The outcomes of the model are the expected number of QALYs gained by avoiding one infection and the expected costs due to one HBV infection. A lifelong time horizon is used. The costs are expressed in 2005 euros. The model starts with an event tree for the first 6 months of the infection: the acute phase, which is shown in Figure 1. The fraction of asymptomatic patients is estimated at 90.5 percent when the patient is infected at age lower than 5 years of age, 90.2 percent when the infection occurs at ages 5 to 10, 89.7 percent for ages 11 to 15, and 66.7 percent for patients older than 15 years.[13]

Figure 1 Event tree of the acute phase of HBV infection A probability indicated with "#" equals 1 minus the other branch probability. Some probabilities can have different values according to the age of the person concerned (ranges are given between brackets). It is assumed that transplantation is not performed in patients younger than 5 years of age. CD = chronic disease



It is assumed that a liver transplantation is not performed for patients younger than 5 years of age. It is assumed that, in case the virus is not cleared from the blood after 6 months, the patient becomes a chronic HBV carrier. The higher the age of the infected patient, the lower the probability to become a chronic carrier. This relationship can be described as:

$$P_{chronic}(age)=\exp(-0.645 * (age + 0.5) \wedge 0.455).^{14}$$

In the chronic stage of infection, two basic states are described by the model: there is either active viral replication (AVR) or there is no AVR, but the virus is still present in the patient's blood ("healthy" carrier). The probability of having AVR is 65 percent (range, 55%-75%) for chronic carriers. In the subsequent years, a chronic HBV carrier can reside in one of the following states: healthy carrier without active AVR, AVR, compensated cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma

(HCC). The costs and loss of QoL associated with these infection states are given in Table 1.

Table 1 Costs and loss of quality of life during HBV infection Costs are given in 2005 Euro's and corrected for inflation (inflation factor 1.183; currency exchange rate €1 = $1.45 in March 2008). Quality of life is given on a scale of 0 to 1, where 1 is perfect health.

State	Costs[15]	Quality of life
ambulatory treatment in acute phase	€373	0.70[16]
acute clinical infection, non fulminant, hospitalized	€2,679	0.60
acute clinical infection, fulminant, hospitalized	€3,779	0.20[16]
immune	€0*	1
healthy, no AVR	€113*	0.97
AVR	€1,284*	0.95[17]
compensated cirrhosis	€1,784*	0.74[18]
decompensated cirrhosis	€9,924*	0.66[18]
HCC	€13,717*	0.65[18]
interferon treatment	€5,825*	0.91
transplantation	€79,058	
after transplantation (first six months)	€7,025*	0.69[18]
after transplantation (subsequent years)	€17,025*	0.86[17]

* treatment costs per year

The uncertainty in costs per disease state is assumed to range from 0.5 to 3 times the point estimate. The transition probabilities for the chronic phase and their ranges are given in Table 2.

In the model it is assumed that transitions from one state to another take place halfway through a year. The treatment costs for a particular year therefore depend on the state of the patient at the start and at the end of the year. All future costs are discounted at a rate of 4 percent per year and the life-years at a rate of 1.5 percent per year, as recommended for health economic evaluations in the Netherlands.[19] The age distribution of transfusion recipients is obtained in a pilot study performed in 1997 in the region of the Utrecht blood bank.[20] This study encompassed a random sample of 1000 whole blood donations being traced back to all recipients of the thereof derived components: for example, red blood cells (RBCs), platelets (PLTs), and fresh-frozen plasma. This study only included recipient age profiles per transfused blood product. It did not include mortality rates or disease variables. Given that short-term mortality of recipients of blood[21] may be influential to the model, we included preliminary recipient survival data from a pilot of the PROTON study on transfusion recipient profiles. From this pilot mortality rates of recipients of blood components in the University Medical Center Utrecht are available, stratified to age. The pilot study includes transfusion recipient information between 1995 and 2003, linked to mortality databases from Statistics Netherlands, which maintains the national mortality registry. Given the availability of these survival data of transfusion

recipients, these were incorporated into the model for the first 5 years after transfusion. The survival rates were calculated for the transfusion recipient of age 0 and furthermore for age groups of 5 years. For subsequent years general mortality rates from Statistics Netherlands are used. The weighted mean of the survival rate in the first 5 years after transfusion is given in Table 3, together with overall survival rates from various other articles.

Table 2 Annual probabilities used in the Markov model for the chronic phase of HBV infection It is assumed that transition from one state to another takes place halfway the year.

From	To	Prob.	Range	Note
State transition probabilities				
healthy, no AVR	HCC	2.5%		
AVR	healthy, no AVR	9%	1-15%	
AVR	compensated cirrhosis	5.5%	1-8.5%	from year 6*
compensated cirrhosis	decompensated cirrhosis	3.75%	1.5-5%	from year 11
compensated cirrhosis	HCC	1.75%	1-2.5%	from year 11
compensated cirrhosis	dead	5.5%	3-7.5%	from year 16
decompensated cirrhosis	HCC	7.75%	5-10%	from year 11
decompensated cirrhosis	dead	22%	17-60%	
HCC	dead	65%	40-80%	
Other probabilities				
AVR-patient gets interferon		30%	20-50%	from year 2 to 5
interferon is succesful		35%	25-40%	
decomp. patient gets transplantation		12.5%	5-40%	
recovery after transplantation		60%		

* since infection

Table 3 Weighted average of the survival rate after transfusion

	time since transfusion				
	1 year	**2 years**	**3 years**	**4 years**	**5 years**
UMC Utrecht	67%	58%	53%	48%	45%
Tynell[22]	66%		52%		
Kleinman[23]	69%	60%	53%	50%	46%
Wallis[21]		59%			47%
Kamper-Jorgensen[24]	74%				53%

Survival rates for different age groups were comparable to those reported by Kleinman and colleagues.[23] Recipients are assumed not to be vaccinated nor to be immune for HBV infection by resolved previous infection. There is no universal vaccination for HBV for the general public,[25] and data regarding prevalence of protective anti-HBs in hospital patient populations is unknown.

Immigrant donors

Immigration from HBV-endemic countries to the Netherlands is accompanied by elevated HBV incidences,[26] while participation of immigrants as blood donors is being encouraged. This is the reason for studying the change of incidence and ICERs when the fraction of immigrants among donors becomes identical to the general Dutch population, which at present is not yet the case. Information about reported HBV cases in the Netherlands in 2005 is used.[26] Acute HBV infections have to be notified to public health authorities. The National Institute for Public Health and the Environment (RIVM) administers these reports. The country of birth of the HBV-infected persons is registered as well. In 2005, 20 percent of the incidence was registered in immigrants from HBV-endemic countries. It is assumed that this proportion is equivalent to the proportion of immigrant donors among HBV-infected donors, should the fraction of immigrant donors from endemic countries become similar to that of the general population. From 1995 to 2003, there were 57 notified cases of HBV among repeat donors in the Netherlands, of which 5 were immigrants from endemic countries.[27] This information can be used to estimate the incidence among repeat donors in case the fraction of immigrant donors becomes similar to that of the general population. Variations in the proportion of immigrants in the general population and in the donor population are modeled using suitable beta distributions.

Computational issues

The cost-effectiveness model is implemented in a computer worksheet (Microsoft Excel, MS-Excel 2002, Microsoft Corp., Redmond, WA). Simulations and sensitivity analysis are performed with an add-in for MS-Excel (@Risk Professional Version 4.5.2, Palisade Corp., Ithaca, NY).

Results

Incidence and WP

The main numerical results are summarized in Table 4. The measured incidence rate of HBV in the Dutch repeat donor population is 1.43 per 100,000 donor-years. This number must be increased with a factor 3.0 for the estimated number of incidents not detected by donor screening, which results in a corrected incidence rate of 4.3×10^{-5} per donor-year. This incidence rate is based on donations in the period 1989 to 2006 in the Netherlands. The number of donor expositions of blood recipients is based on the number of units supplied by Sanquin in 2006 and is estimated at 890,069 donor expositions from RBCs, PLT, and plasma transfusions per year. With the use of the sensitivities of the Prism HBsAg test, ID-NAT, and MP-6-NAT, the doubling time of HBV in the acute initial phase of the infection and the half-life of the virus in the reconvalescent phase, the length of the reduction of the WPs are computed. For MP-6-NAT the mean reduction of the WP compared to the Prism

HBsAg test is 18.4 days for the acute phase and 11.3 days for reconvalescence, in total 29.7 days. For ID-NAT the mean reduction of the WP compared to the Prism HBsAg test is 21.1 days for the acute phase and 13.0 days for reconvalescence, in total 34.0 days. Thus, the probability of detecting a MP-6-NAT-positive blood donation that is given during one of the serologic WPs is 3.5 per 1,000,000 donations, preventing 3.12 (95% confidence interval [CI], 2.62-3.66) HBV cases per year. The probability of finding an ID-NAT-positive blood donation that is given during one of the serologic WPs is 4.0 per 1,000,000 donations, preventing 3.57 (95% CI, 3.01-4.19) cases per year.

Table 4 Summary of main quantitative results

	MP-6-NAT	**ID-NAT**	**MP-6-NAT; immigrants included**	**ID-NAT; immigrants included**
cut-off per donation IU/ml	22.2	10.9	22.2	10.9
first window period reduction	18.4	21.1	18.4	21.1
second window period reduction	11.3	13.0	11.3	13.0
window period reduction (compared to HBsAg)	29.7	34.0	29.7	34.0
incidence of HBV among donors	4.3E-05	4.3E-05	4.6E-05	4.6E-05
number of cases prevented	3.12	3.57	3.36	3.85
cost per case prevented	€308,001	€526,383	€285,348	€487,669
Incremental Cost-effectiveness Ratio (ICER) in €/QALY	€303,218	€518,995	€280,835	€480,742

The ICERs

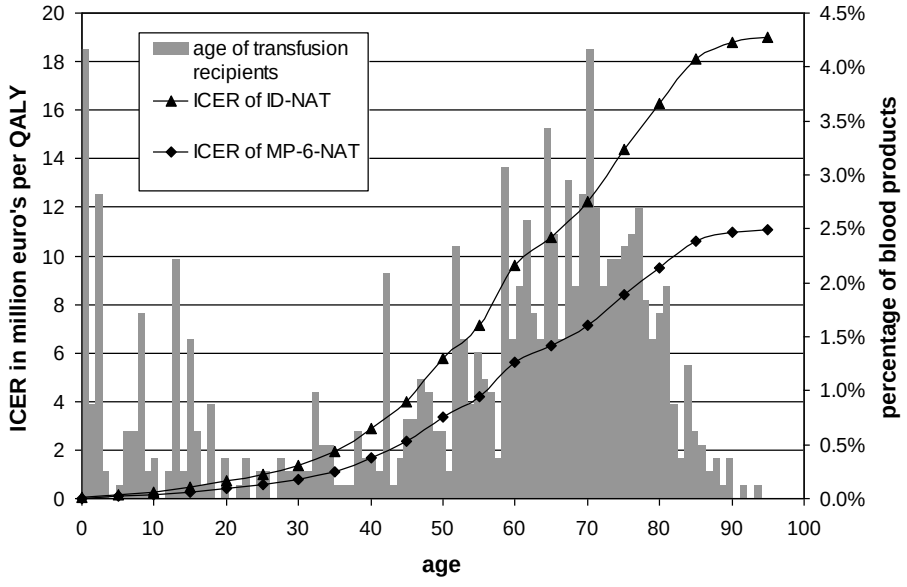
The estimated incremental annual costs for implementing triplex MP-6-NAT or ID-NAT in the Netherlands compared to triplex MP-24-NAT are calculated by Sanquin at €959,600 and €1,877,785 respectively (H. Bos, personal communication, 2006). The Markov model in combination with the age distribution of the recipients of blood components yields expected treatment costs of €1122 (95% CI, €532-€2320) per HBV infection. The mean number of QALYs that are lost as a result of one HBV infection is estimated at 1.01 (95% CI, 0.80-1.22). The ICER of HBV NAT in the Netherlands is estimated at €303,218 (95% CI, €233,001-€408,388) per QALY for MP-6-NAT and €518,995 (95% CI, €399,359-€699,120) for ID-NAT. The ICER is also calculated for the future scenario where the fraction of immigrants from endemic countries becomes identical to the fraction of these immigrants in the general Dutch population. In the Netherlands 299 incident cases of hepatitis B were reported in 2005.[26] Of all HBV patients 20 percent are born in a country where hepatitis B is endemic, whereas 8.69 percent of all inhabitants are born in these countries.[28] It can be calculated that for the future situation the incidence of HBV among donors will increase by 8 percent and will become 4.6 per 100,000 donor-years. Therefore, if immigrant donors are participating proportionally in the donor base in the Netherlands, the ICER becomes

€280,835 (95% CI, €216,015-€379,793) per QALY for MP-6-NAT and €480,742 (95% CI, €370,067-€650,374) per QALY for ID-NAT.

Sensitivity analysis

Model sensitivity is analyzed by regression analyses of output variables on model input variables. The model sensitivity is expressed in standardized regression coefficients (SRCs). These show that the uncertainty in costs prevented per case is primarily related to the uncertainty in cost of treatment (SRC, 89%; R^2 = 93%) and second by the recovery rate of patients who contracted an HBV infection (SRC, -25%). The uncertainty in QALYs lost is primarily determined by the transition probability from AVR to compensated cirrhosis (SRC, 26%; R^2 = 85%). The uncertainty in cost-effectiveness is primarily caused by the HBV incidence rate (SRC, -87%; R^2 = 75%) to which it is roughly inversely proportional: double the incidence rate would halve the ICER. Approximately 20 percent of the variance in the ICER is induced by the limited sample size of the transfusion recipient population (817 samples). Because the costs of treatment are negligible compared to the screening costs, the ICER is insensitive to the discount rate for cost (4% used in this analysis) and the ICER increases almost linearly with increasing screening costs. The ICERs reduce with approximately 50 percent when health outcomes are not discounted. When discount rates of 3 percent are used, like in similar studies, the ICERs grow to €550,344 per QALY for MP-6-NAT and €942,249 per QALY for ID-NAT.

Figure 2 Sensitivity analysis of ICERs of HBV NAT to patient age at constant testing costs



Recipient age is an important variable in the cost-effectiveness of screening. To illustrate this, the ICER for both NATs is calculated per patient age (Figure 2). The ICER for MP-6-NAT ranges from approximately €21,000 in neonates to €11 million in

patients 95 years of age. The ICER for ID-NAT ranges from approximately €37,000 for neonates to €19 million in patients 95 years of age. The QALYs gained in the current results are mainly due to avoiding infections in children. They have both a high life expectancy and a high probability of becoming a chronic HBV carrier, which results in cost-effective screening.

Discussion

Application of the results

It is shown that in the Netherlands, implementation of triplex MP-6-NAT is more cost-effective for prevention of HBV transmission by blood components than triplex ID-NAT, even though the latter is more sensitive. The additional risk reduction achieved by the ID-NAT compared to MP-6-NAT comes at relatively too high a price. The ICER of prevention of HBV transmission by MP-6-NAT or ID-NAT compared to MP-24-NAT, the latter not being designed for additional HBV detection, amounts to €303,218 (95% CI, €233,001-€408,388) and €518,995 (95% CI, €399,359-€699,120) per QALY, respectively. This ICER can become €280,835 (95% CI, €216,015-€379,793) per QALY for MP-6-NAT and €480,742 (95% CI, €370,067-€650,374) per QALY for ID-NAT when immigrants from HBV-endemic countries join the donor population on an equivalent demographic basis. The influx of immigrants only slightly affects the ICER of the HBV NAT tests.

For application to preventive and/or curative health care interventions, several threshold values for the ICER are suggested, ranging from €20,000 to more than €100,000 per QALY.[29] In these policy views, however, producer's risks such as liability and public concern, resulting in public enquiries where blood safety is scrutinized,[2] are not accounted for. Neither are the costs thereof. An alternative, but not widely used, policy view could be analogous with the requirements for sterility testing in pharmaceutical products, for example, a probability of less than 10^{-6} of the end product being contaminated with one detectable infectious unit would be considered a "sterile" intravenous pharmaceutical. At present there is no consensus on an acceptable cost-effectiveness threshold value for blood safety measures. When we compare our ICERs of HBV NAT with the cost-effectiveness of other blood safety measures, such as HCV NAT and HIV NAT, it appears that in the past ICERs of millions of euros per QALY did not deter decision makers from introducing such screening.[30,31] Thus, among NATs, HBV NAT is relatively more cost-effective, even in a low-endemic country such as the Netherlands. In general, interventions that are directed at the avoidance of risks, rather than the reduction of mortality or morbidity, are associated with higher ICERs. Society is willing to pay more for risk avoidance.[32]

Strengths and weaknesses of the model

In this analysis the WP incidence model for donors was used to calculate the number of avoided HBV infections. Besides during the two mentioned WPs, the HBV NAT test can also be positive for donations that are negative for the presence of HBsAg when there is still replication at low level after recovery or in case of an escape mutant of the virus. This is called an occult hepatitis B virus infection. The frequency of occult hepatitis B virus infections in the Netherlands donor population is unknown, but the number of averted contaminated blood products might be higher than estimated here. On the other hand, the level of infectivity of these products is unclear, while donations given during the WP of acute hepatitis B are known to be highly infectious.[33]

Possible secondary transmission of HBV from blood recipients to their partners is not included in this model. The incorporation of such secondary transmissions would improve the cost-effectiveness as estimated in our study. However, as the mean age of blood recipients is rather high and the recipients are sick patients, secondary transmission can be expected to be lower than secondary transmission in the general population and this risk is essentially not known.

The likelihood of chronic HBV carriership may be higher in immune-compromised transfusion recipients. This might increase the costs of treatment for HBV and loss of QALYs and could reduce the ICER of HBV NAT.

The model for age distribution and survival of blood recipients in the Netherlands is the subject of ongoing research (PROTON study). Life expectancies of patients as available for one academic hospital are used here. The life expectancy of blood recipients in the Netherlands in general might be higher, because the patient population in university hospitals is more severely ill than in general hospitals. Assigning patient categories to the health economic effects of HBV NAT, for instance, limiting the application of HBV NAT to transfusion products for pediatric transfusions only, introduces another policy view. Note that the costs per donation are likely to increase when the number of tested donations is reduced; this is not further elaborated in our model because it does not seem to be a likely scenario in the Netherlands.

Comparison with other studies

The ICER depends on the reference scenario, which is a very sensitive test for HBsAg plus triplex MP-24-NAT in the Netherlands. In countries with a less sensitive - previous generation - HBsAg test, the yield of the HBV NAT might be higher. The effectiveness of the additional HBV screening is largely dependent on the incidence rate. In regions with a high incidence, like Mediterranean European countries, the

yield of the additional HBV screening will be higher. Other ICERs for HBV NAT are in the literature.[16,34-36] The ICERs presented in four referenced articles range from €4.9 million to €66 million per QALY. These articles compare individual donor HBV NAT to HBsAg testing either by Prism or other assays. In addition, the three articles by Busch, Jackson, and Marshall compare HBV NAT in minipools of 16 to 24 donors to the HBsAg test. However, none of the studies is similar to our study design: the change from triplex MP-24-NAT (not detecting HBV) to either triplex MP-6-NAT or to triplex ID-NAT. Jackson, Marshall, and Pereira describe details on their Markov models. There are some slight differences between the models. One model contains fewer health states for HBV infection than our model[34] and one of the models yields some lower transmission probabilities.[16] Further, our analysis is based on an age distribution of transfusion recipients. Age distributions appear to be a very sensitive parameter in the model. Only the study of Pereira employs an age distribution for the recipients.[16] In the article of Pereira a similar length of WP reduction is computed.[16] The Busch, Marshall, and Jackson models yield smaller WP reductions, rendering higher ICERs.[34-36] This may explain the difference between the Busch and Pereira studies. From these studies it can be concluded that HBV MP-24-NAT in comparison to the HBsAg test is not cost-effective. Nevertheless, when triplex MP-24-NAT is already introduced due to EC regulations, the ICER of reducing the pool size to six or one appears to be more cost-effective than previously taken blood safety measures.

In conclusion, in the Netherlands, reducing the minipool size of a CE-marked triplex NAT assay from 24 into 6 donations yields a relatively cost-effective prevention of HBV transmission compared to other blood safety measures that have already been implemented. Furthermore, triplex MP-6-NAT is more cost-effective for prevention of HBV transmission than triplex ID-NAT, despite the fact that the latter assay is more sensitive. A future equivalent participation of immigrants from HBV-endemic countries in the donor base renders HBV NAT only slightly more cost-effective.

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Chapter 2

The PROTON study: profiles of transfusion recipients in the Netherlands

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Abstract

Background Transfusion recipient data are needed for correct estimation of cost-effectiveness in terms of recipient outcomes after transfusion. Also, such data are essential for monitoring blood use, estimation of future blood use and benchmarking.

Study design and methods A sample of 20 of 93 Dutch hospitals was selected. Datasets containing all blood product transfusions between 1996 and 2006 were extracted from hospital blood bank computer systems, containing transfusion date, blood product type and recipient characteristics such as gender, address, date of birth. The datasets were appended and matched to national hospitalization datasets including primary discharge diagnoses (ICD-9). Using these data, we estimated distributions of blood recipient characteristics in the Netherlands.

Results The dataset contains information on 290,043 patients who received 2,405,012 blood products (1,720,075 RBC, 443,697 FFP, 241,240 PLT) from 1996 to 2006. This is 28% of total blood use in the Netherlands during this period. Comparable diagnosis and age distributions of all hospitalizations indicate included hospitals to be representative, per hospital category, for the Netherlands. Of all red blood cells (RBC), fresh-frozen plasma (FFP) and platelets (PLT), respectively 1.7%, 2.5% and 4.5% were transfused to neonates. Recipients of 65 years or older received 57.6% of RBC, 41.4% of FFP and 29.0% of PLT. Most of the blood products were transfused to patients with diseases of the circulatory system (25.1%) or neoplasms (22.0%).

Conclusion Transfusion data from a limited sample of hospitals can be used to estimate national distributions of blood recipient characteristics.

Introduction

Quantitative information on the fate of blood products issued (BPI) to hospitals is needed to analyse the cost-effectiveness of blood safety interventions such as nucleic acid amplification testing (NAT), leucocyte depletion or pathogen reduction. To know 'where the blood goes' is necessary for estimating the beneficial effects of safety interventions in terms of health gain in the recipients. Information on blood donors, donations and BPI is carefully registered by blood establishments in many countries, as in the Netherlands. Additionally, hospitals must register personal and clinical information on recipients of the blood products, in line with EU regulations. In this article, we report on the PROfiles of TransfusiON recipients (PROTON) study that resulted in the first national dataset including characteristics of blood product recipients in the Netherlands. Apart from restricting privacy regulations on matching individualized datasets, the absence of a national personal identification number in health care datasets (as in Scandinavian countries[1]) is prohibitive. We show alternative methods to match data. The resulting dataset enables answering several relevant questions on today's blood supply and its future. One application is to assess the effects of envisioned or already implemented blood safety measures. Economic evaluations, such as cost-effectiveness analyses, are increasingly considered mandatory by governmental and regulatory bodies.[2,3] Costs can be calculated from blood establishment data, but the effects of avoiding transfusion complications depend on age, morbidity and survival of the blood product recipients.[4] In this article, the current distribution of blood products over age, gender and diagnosis of recipients is estimated. These data can be directly incorporated in models for cost-effectiveness analysis of blood safety measures.

Methods

Definitions

For the aim of this study, we define a blood product transfusion (BPT) as the event at which one blood product is actually transfused. Pooled platelet transfusions (from five buffy coats) as well as split product (neonatal) transfusions are counted as one BPT. The blood product recipient profile consists of recipient gender, age at time of the BPT and primary discharge diagnosis code (ICD-9) of the hospitalization during which the BPT took place.

Primary data collection

From included hospitals, approval and commitment of the boards and professionals were obtained, as well as approval of Medical Ethical Committees. The sampled hospitals (for sampling procedure, see below) extracted microdata on all BPTs between January 1st 1996 and December 31st 2006 from their hospital blood bank computer systems, as far as data were available. All types of blood products were

included, both apheresis and whole-blood derived. Participating hospitals were requested to provide the following data: type of blood product (RBC, FFP or PLT), date of transfusion, recipient gender and date of birth and address of the recipient.

Discharge diagnosis (ICD-9) microdata were obtained from the National Medical Registry (in Dutch: Landelijke Medische Registratie) that contains records of all hospitalizations in the Netherlands from 1996 to 2005 (coverage 99% in 1998). These data are stored at Statistics Netherlands (in Dutch: Centraal Bureau voor de Statistiek), the national governmental bureau of statistics of the Netherlands. The hospitalization data include unique person identification numbers. Full personal identification data of all Dutch citizens are also stored at Statistics Netherlands, including personal identification number, postal code, house number, gender and date of birth.

Sanquin, the only national public blood component provider, provided the total annual numbers of BPIs for the years 1996 to 2006, categorized into RBC, FFP and PLT, and the annual number of BPIs for specific hospitals.

Hospital selection

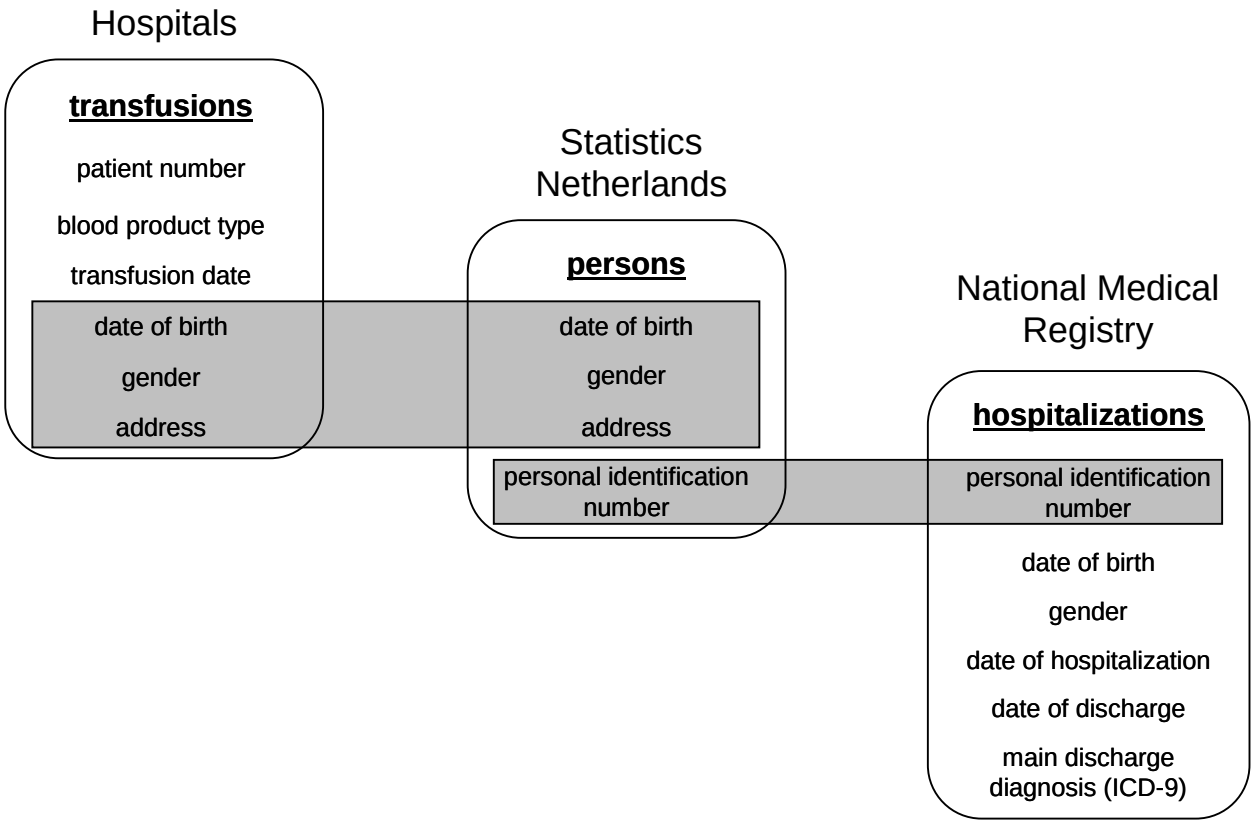
Given the time and budget constraints of the study, it was decided to base the national estimates of recipient profiles on a sample of hospitals rather than all 93 hospitals in the Netherlands. A hospital sample covering about 30% of the total blood use in the Netherlands was aimed at. For all hospitals, the number of hospital beds in 2006 was known.[5] The number of BPI (categorized into RBC, FFP and PLT) in 2006 was provided by Sanquin. Analysing the average blood use per hospital bed revealed significant differences between three principal hospital categories: academic, general and specialized cancer hospitals. From these categories, we drew a random sample: five out of eight academic hospitals and 14 out of 85 general hospitals. As there are only two specialized cancer hospitals, we aimed at including both these cancer hospitals in the study. Selected hospitals were invited to provide data for the study. If a hospital appeared to be unable to provide the requested data, another hospital from the same category was selected at random.

Dataset matching procedure

BPT data obtained from hospital blood bank laboratories were encrypted within the hospital and personally transported to Statistics Netherlands, to ensure patient privacy protection. In a protected environment, the data were decrypted, matched and analysed, following the strict privacy regulations in the Netherlands. Data needed conversion into a general format, as a result of differences in the various laboratory computer systems that are used in the hospitals. Next, a two-stage matching procedure was performed. First, the BPT data were matched to personal identification

numbers by postal code, house number, gender and date of birth. Second, BPTs were matched to a hospitalization with a diagnosis code (ICD-9), if the personal identification number matched and the date of transfusion was between the hospital intake and discharge dates. Figure 1 shows the scheme of matching the datasets. Some BPTs were not matched to a diagnosis, but an earlier BPT in the dataset of the same recipient was available. In such cases, it was assumed that the latter BPT was given during a hospitalization with the same diagnosis as the previous one.

Figure 1 The PROTON recipients approach of matching existing datasets The two matching steps are marked by the grey rectangles. Blood product transfusion datasets are downloaded from hospital bloodbank information systems, encrypted and brought to Statistics Netherlands, the national governmental statistics office that includes governance of the National Medical Registry.



Validation of sampling and matching procedures

Nationwide hospitalization data from the National Medical Registry were used to compare the distribution of patient age and diagnosis (ICD-9) of all hospitalizations (whether or not transfused) in the included hospitals and in the remaining hospitals, categorized into general and academical hospitals. When comparing these distributions, hospitalizations were counted as 'included' from the date that the transfusions of the hospital were included in the PROTON dataset. Specialized cancer hospitals were not taken into consideration here. Diagnosis (ICD-9) and age distributions of all hospitalizations in the Netherlands were compared, to evaluate whether the patient populations in the included academic and general hospital

samples respectively can be considered representative for all academic and general hospitals in the Netherlands. Distributions of age, gender and type of blood product in completely matched records were compared to distributions of incomplete records to investigate whether unmatched records caused any bias.

Data analysis

To describe the profile of Dutch BPT recipients, we extrapolated the data from the included hospitals to the national level. We created weights for each BPT in the PROTON dataset by dividing the total numbers of BPIs (provided by Sanquin) per hospital category, product type and year by the corresponding numbers of BPTs in the PROTON dataset. As both cancer hospitals were included, the BPTs in those hospitals were weighted as 1. All distributions shown in this article are created using these weights.

The weights were used to estimate distributions of number of BPTs per recipient per blood product type. Furthermore, weighted counts were made of BPTs over age and gender, main diagnosis groups and main diagnosis groups according to age, all categorized per blood product type. To improve readability of the plots concerning the relationship between recipient age and diagnosis, the graphs were smoothed using a kernel density estimator.[6]

Software

Random numbers for hospital sampling were generated using Excel (version 2003; Microsoft Corporation, Redmond, WA, USA). Data matching with the hospitalizations in the National Medical Registry was performed using SAS Enterprise Guide (version 4.1; SAS Institute Inc., Cary, NC, USA). All other data management and analysis was performed using STATA / SE (version 9.2 for Windows; StataCorp LP, College Station, TX, USA). Graphs were created using R (version 2.8.1, 2008, The R Foundation for Statistical Computing, Vienna, Austria).

Results

Collected data

Initially, 20 selected hospitals were invited to participate in the PROTON study. Of these hospitals, seven could not participate because of hospital staff time constraints and/or limitations of the computer systems. Every time a hospital appeared to be unable to join the study, another hospital from the same category was selected at random and invited. In total, five of eight academic hospitals, 14 of 85 general hospitals and two of two cancer hospitals provided data on blood products transfused between 1996 and 2006. One cancer hospital became part of an included academic hospital because of merger. Some hospitals were unable to extract data

covering the whole study period, mostly as a result of IT changes. The resulting coverage by the PROTON dataset of all BPI from Sanquin is given in Table 1. In the dataset of one hospital, no distinction could be made between FFP and PLT, so only its RBC data were included. In addition to the nationwide ICD-9 diagnoses from the National Medical Registry, six hospitals provided their own diagnosis data by ICD-9 code.

Table 1 Coverage of blood product transfusions (BPTs) in the PROTON dataset as compared to annual blood products issued (BPI) by Sanquin[a]

year	# BPTs in PROTON database			# BPI by Sanquin in the Netherlands			fraction of BPI covered by PROTON database		
	RBC	FFP	PLT	RBC	FFP	PLT	RBC	FFP	PLT
1996	141,675	37,204	18,251	715,366	106,972	46,519	20%	35%	39%
1997	148,859	41,328	20,106	718,785	121,316	48,449	21%	34%	41%
1998	159,075	47,397	22,124	713,896	111,215	49,242	22%	43%	45%
1999	151,129	40,595	20,665	680,000	105,000	47,600	22%	39%	43%
2000	161,466	40,883	21,317	635,731	99,576	42,797	25%	41%	50%
2001	154,326	41,399	22,217	602,098	100,793	43,329	26%	41%	51%
2002	161,212	42,527	23,380	626,661	104,683	43,167	26%	41%	54%
2003	169,129	42,834	23,843	617,015	111,600	47,620	27%	38%	50%
2004	170,229	39,341	24,007	595,090	97,200	52,680	29%	40%	46%
2005	157,641	38,102	23,008	569,879	93,838	47,831	28%	41%	48%
2006	145,334	32,087	22,322	556,509	92,380	51,869	26%	35%	43%
Total	*1,720,075*	*443,697*	*241,240*	*7,031,030*	*1,144,573*	*521,103*	*24%*	*39%*	*46%*

[a]An unknown fraction of the BPIs in the Netherlands is not transfused to patients, among others because of outdating.

The total PROTON dataset contains information on 290,043 patients who received 2,405,012 blood products (1,720,075 RBC, 443,697 FFP, 241,240 PLT) during the study period 1996–2006. For the whole study period, 28% of the total BPI in the Netherlands is covered by the PROTON dataset. Data from the National Medical Registry concerning hospitalizations in 2006 were not yet available. Of the BPTs in the PROTON dataset over the period 1996–2005, 87% could be matched to a diagnosis. Table 2 gives the matching percentages to diagnoses and the retrospective years of follow-up allowed by data provided by the included hospitals.

Table 2 Hospital data and matching to ICD-9 primary discharge diagnosis of blood product transfusions (BPTs) in the PROTON dataset

hospital number	category	years of follow-up	# patients in database in 1996-2006	# BPT in database in 1996-2006	mean # BPT per recipient in 1996-2006	% BPT linked to diagnosis in 1996-2005
1	cancer	11.0	6,651	55,020	8.3	94%
2	academic/cancer	11.0	39,935	414,542	10.4	93%
3	academic	11.0	30,291	289,695	9.6	94%
4	academic	11.0	28,342	285,189	10.1	87%
5	academic	11.0	27,514	333,606	12.1	94%
6	academic	9.3	21,898	174,562	8.0	93%
subtotal	academic/cancer		154,631	1,552,614	10.0	
7	general	11.0	18,519	135,689	7.3	97%
8	general	8.2	14,409	90,215	6.3	93%
9	general	11.0	13,061	72,355	5.5	96%
10	general	8.7	12,233	90,731	7.4	89%
11	general	11.0	13,485	80,873	6.0	92%
12	general	11.0	22,644	158,985	7.0	92%
13	general	11.0	6,601	31,510	4.8	92%
14	general	11.0	7,667	46,605	6.1	85%
15	general	2.5	1,743	7,403	4.2	93%
16	general	11.0	10,864	61,171	5.6	88%
17	general	7.9	4,349	23,115	5.3	94%
18	general	11.0	6,661	37,482	5.6	94%
19	general	4.6	2,458	12,393	5.0	95%
20	general	1.7	718	3,871	5.4	97%
subtotal	general		135,412	852,398	6.3	
total			290,043	2,405,012	8.3	87%

Validation of sampling and matching procedures

Overall patient age and diagnosis distributions (with or without transfusions) in the included academic and general hospitals were compared to the distributions in the remaining academic and general hospitals of the Netherlands. Data were derived directly from the National Medical Registry, including all 25 million hospitalizations of patients in the observation period. The mean age of patients was 49.1 in the included and 48.2 in the remaining general hospitals, and 44.3 in the included and 42.9 in the remaining academic hospitals. The distribution of patients over four age groups and seven largest diagnosis groups is given in Table 3. As the distributions are quite similar, the sample is regarded to be representative for all hospitals in the Netherlands, while distinguishing between academic and general hospitals. Distributions of age, gender and type of blood product in completely matched records were similar to the distributions in incomplete records. This indicates that matching was unbiased with respect to age, gender and type of blood product.

Table 3 Baseline characteristics of included (n = 20) and remaining (n = 73) hospitals in the Netherlands in 1996–2005 Data were derived directly from the National Medical Registry, including all 25 million hospitalizations of patients in the observation period, whether transfused or not.

	academic hospitals		general hospitals	
	PROTON hospitals included in	% hospitalizations in	remaining hospitals	% hospitalizations in
age				
0 years	6%	7%	6%	6%
1-16 years	13%	15%	8%	10%
17-40 years	22%	22%	21%	21%
41-64 years	34%	33%	31%	30%
65 years or older	25%	24%	34%	33%
primary discharge diagnosis (ICD-9)				
neoplasms	19%	20%	12%	11%
circulatory system	16%	17%	15%	14%
nervous system and sense organs	10%	11%	11%	11%
musculoskeletal system and connective tissue	8%	6%	12%	13%
digestive system	8%	7%	9%	9%
injury and poisoning	7%	9%	6%	7%
pregnancy, childbirth and puerperium	6%	7%	8%	8%

Distributions of BPT dose Figure 2 shows the annual transfusion dose for each product type per specific recipient. On average, blood recipients received 5.8 BPTs per calendar year. RBC recipients received 4.8 RBC units on average per calendar year. FFP recipients and PLT recipients received on average 5.2 units of FFP and 3.6 units of PLT respectively per calendar year.

Distributions of BPT characteristics

Figure 3 shows recipient age and gender distributions for the three blood product types. Of all RBC, 50% were transfused to men. Of all FFP and PLT, respectively 59% and 60% were transfused to men. Furthermore, 1.7% of RBC, 2.5% of FFP and 4.5% of PLT were transfused to children of age 0. Children between 1 and 16 years of age received 1.9% of RBC, 4.3% of FFP and 10.1% of PLT. Recipients between 17 and 40 years of age received 11.3% of RBC, 18.9% of FFP and 17.6% of PLT. Recipients between 41 and 64 years received 27.6% of RBC, 33.0% of FFP and 38.7% of PLT. Recipients of 65 years or older received 57.6% of RBC, 41.4% of FFP and 29.0% of PLT.

Figure 2 Distribution of annual transfusion dose per recipient for each blood product type in 1996–2006

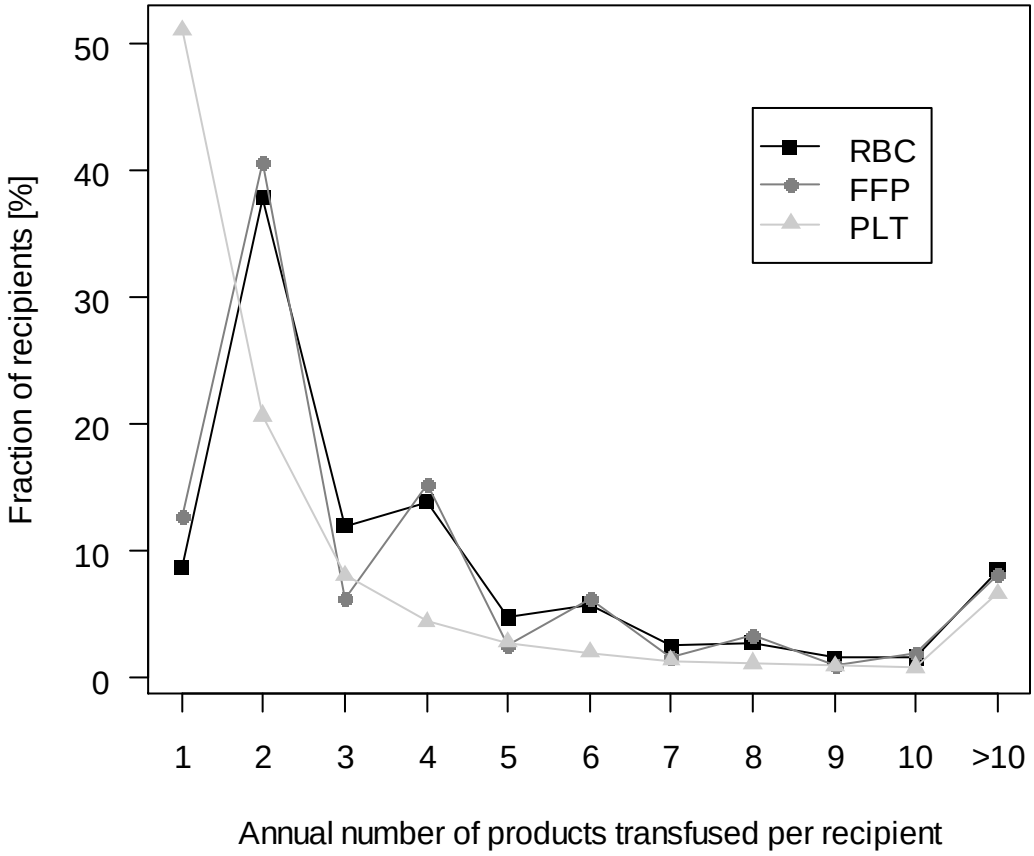


Figure 3 Age distributions of blood product recipients during the years 1996 to 2006 For the graph of FFP, recipients who received over 100 products were left out. The table from which these graphs were created can be obtained by contacting the authors.

Figure 3a Age distribution of RBC recipients

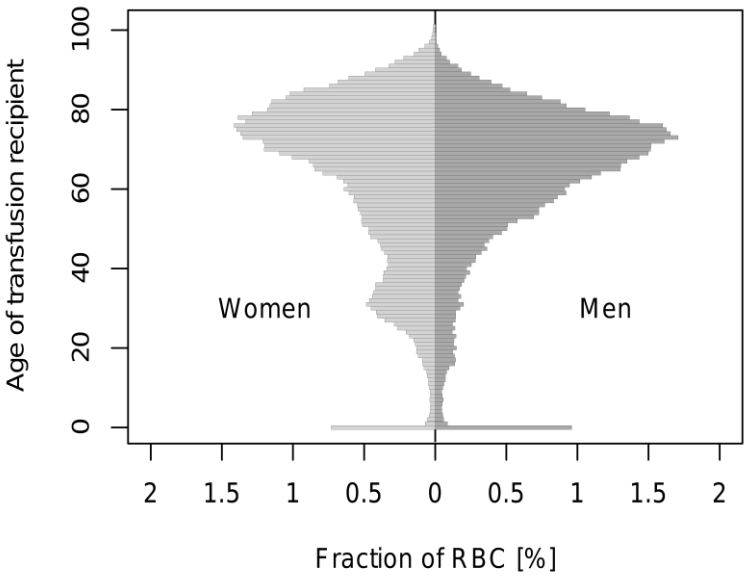


Figure 3b Age distribution of FFP recipients

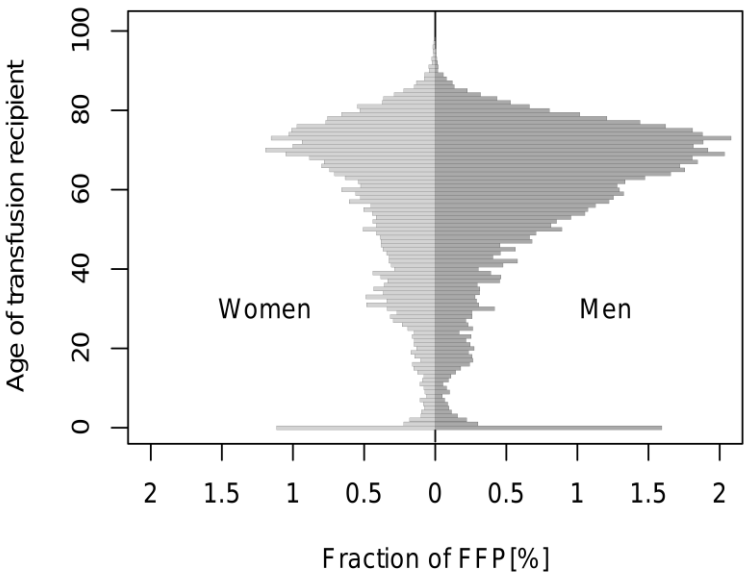


Figure 3c Age distribution of PLT recipients

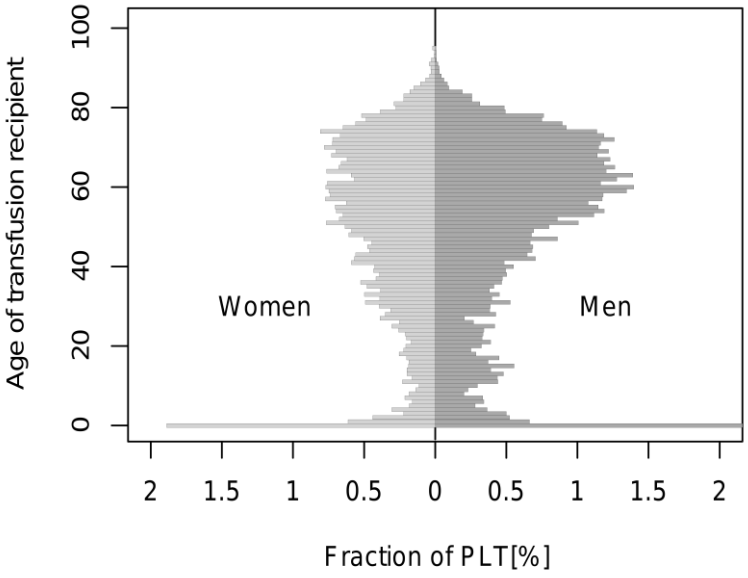


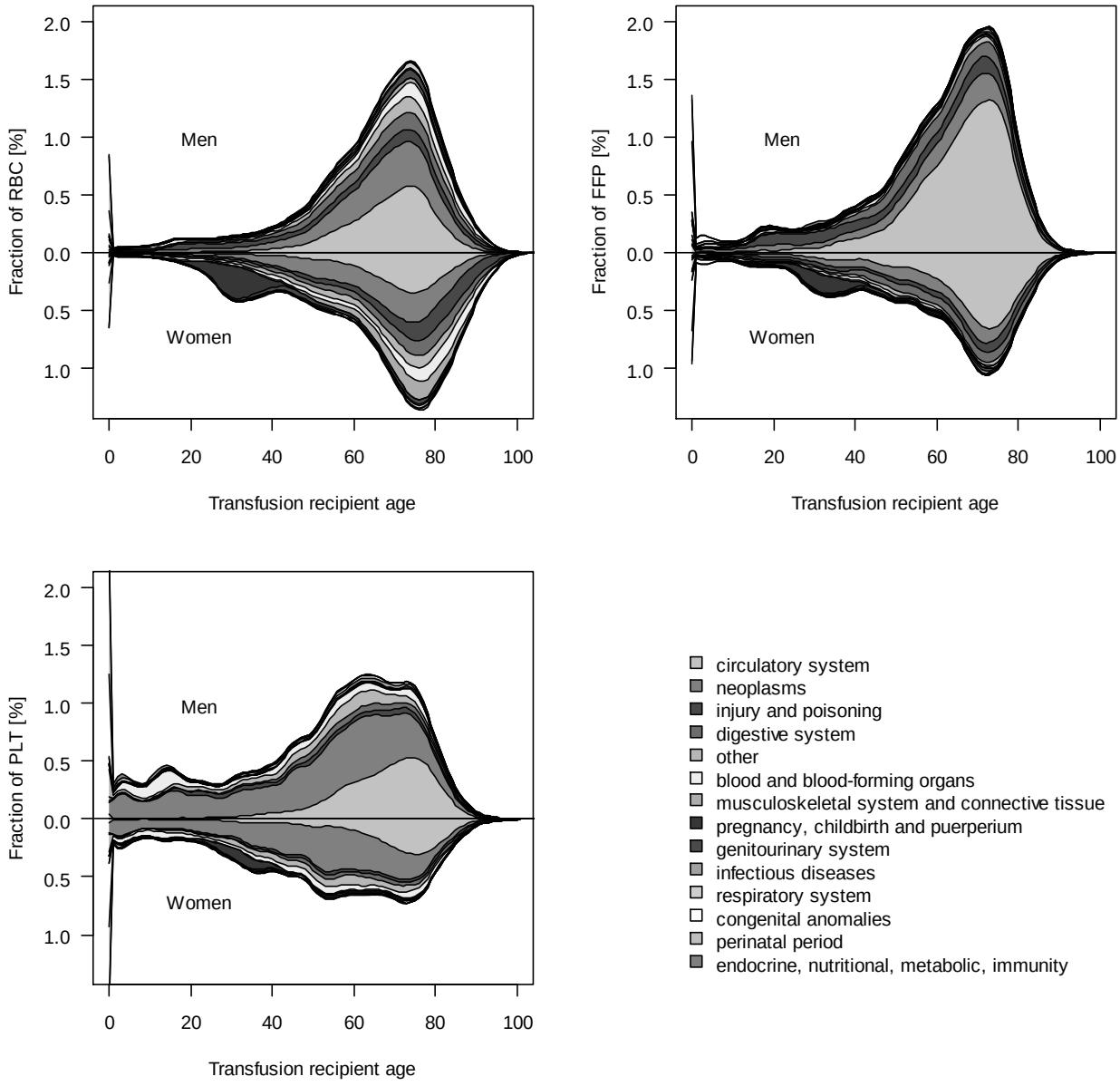
Table 4 shows the distributions of BPTs over the main diagnosis (ICD-9) groups. For all three blood product types, the diagnosis group that used most blood products was the group of patients with diseases of the circulatory system (ICD-9 codes 390–459) or with neoplasms (ICD-9 codes 140–239), including haemato-oncological diseases. The ICD-9 diagnosis group called 'blood and blood-forming organs' includes patients with anaemia, coagulation defects or purpura.

Table 4 Diagnosis distributions of blood product transfusion recipients during the years 1996 to 2005

ICD-9 discharge diagnosis, main group	% of transfused products			
	RBC	FFP	PLT	Total
circulatory system	21.5%	47.8%	21.0%	25.1%
neoplasms	22.2%	12.7%	41.2%	22.0%
injury and poisoning	10.5%	9.4%	4.3%	9.9%
digestive system	9.8%	9.0%	4.4%	9.4%
blood and blood-forming organs	8.6%	4.8%	8.7%	8.0%
musculoskeletal system and connective tissue	5.3%	1.2%	0.6%	4.4%
genitourinary system	3.8%	2.2%	1.0%	3.4%
pregnancy, childbirth and puerperium	3.7%	2.3%	1.4%	3.3%
symptoms, signs and ill-defined conditions	3.3%	2.2%	3.5%	3.1%
respiratory system	2.4%	1.1%	1.5%	2.1%
infectious diseases	1.3%	2.1%	2.4%	1.5%
endocrine, nutritional, metabolic, immunity	1.1%	0.7%	1.0%	1.1%
congenital anomalies	0.8%	2.1%	2.0%	1.0%
perinatal period	0.9%	0.6%	1.9%	0.9%
nervous system and sense organs	0.3%	0.6%	0.5%	0.4%
skin and subcutaneous tissue	0.4%	0.1%	0.1%	0.3%
mental disorders	0.1%	0.1%	0.0%	0.1%
other	4.2%	1.2%	4.5%	3.8%

Figure 4 shows the relationship between age and ICD-9 diagnosis of recipients of RBC, FFP and PLT respectively. In all categories, most blood products were transfused to elderly patients with circulatory system diseases or with neoplasms. It appears that PLT recipients, mostly allocated to neoplasms (including haemato-oncological diseases), are more equally distributed over age. Elderly men received more blood products than women of the same age, especially far more plasma products were transfused to men than to women. This is mainly caused by men having a higher probability of being hospitalized for circulatory diseases (in the National Medical Registry, they have 1.5 times more hospitalizations than women). On the other hand, 72% of the RBC with a recipient age between 25 and 35 years was transfused to women, mainly related to childbirth. Detailed data on the age and diagnosis distribution of RBC, FFP and PLT are given in the Appendix.

Figure 4 The relationship between age and diagnosis The graphs are smoothed to improve readability.



Discussion

Applications of the PROTON dataset

We describe a method for collating nationally representative data on the distribution of BPT to recipients, including recipient diagnosis, age and gender. The dataset was created without the presence of a nationally governed personal identification number system for all inhabitants in the Netherlands, as is the case in Scandinavia.[1] BPT data are required for the correct analyses of cost-effectiveness of blood safety measures in terms of recipient outcomes after BPT. For such analyses, survival of blood product recipients after transfusion is essential. This survival can now be studied by matching the PROTON dataset to national mortality data as governed by Statistics Netherlands. The PROTON data are also useful for monitoring blood use and, in combination with demographic data, for estimating future blood use. With an ageing population, it is important to predict future need of blood products to enable anticipatory strategies in donor recruitment, as most blood is given to elder patients. Modelling scenario's on possible future medical or policy changes towards 'optimal blood use' can further refine such forecasts. In addition, participating hospitals can use the PROTON data for comparisons with their own data for benchmarking purposes on optimal blood use.

Considerations on the results

RBC (in the Netherlands 270–290 ml) and FFP (in the Netherlands 300 ml) are most often transfused in doses of 2 or 4 or 6 units. Apparently, clinicians often consider one unit to be insufficient as an adult therapeutic dose. As compared to platelets, where one adult therapeutic dose represents five whole-blood donations (buffy-coat method), RBC and FFP units are derived from one whole-blood donation (500 ml). One whole-blood donation, representing about 10–13% of total blood volume of the donor, may therefore not yield enough substitution in case of a bleeding or anaemic patient.

A considerable fraction of blood products (2%) are transfused to neonates. This group yields the highest positive effects of blood safety interventions, in terms of life years gained, because of their relatively long life expectancy. Thus, transfusion recipients with a very good prognosis positively influence the cost-effectiveness of new blood safety measures.[4]

Comparison with other studies

The only comparable dataset that contains more BPT data than ours is the Scandinavian Donations and Transfusions database (SCANDAT) dataset, which includes 11.7 million transfusions given between 1966 and 2002 in Sweden and Denmark.[1] The researchers of SCANDAT published an article about post-transfusion survival rates, but not about the distribution of blood products over age or diagnosis

of transfusion recipients.[7,8] It would be interesting to compare the distributions described in this article with those from SCANDAT, especially because there is a large difference in RBC use: 50.5 RBC were used per 1000 inhabitants in Sweden in 2004 and 72.9 per 1000 in Denmark (2000–2002) against 36.6 per 1000 inhabitants in the Netherlands in 2004.[8,9]

Other studies on recipient distributions resulted in smaller and more regional datasets than ours. Regan shows age distributions of recipients in five hospitals in Oxford, UK, in which recipients of FFP and PLT are relatively older than in the Netherlands.[10] Greinacher et al. shows the age distribution of RBC recipients in a region of Germany.[11] There, 52% of RBC is transfused to patients of 60–74 years of age, against 34% of RBC transfused in the Netherlands, while 16% of RBC is transfused to recipients above 74 years of age against 32% in the Netherlands. Cobain et al. published a review in which recipient data from four countries are shown: England, USA, Australia and Denmark.[12] In this study, age distributions are reported for RBC, FFP and PLT transfused in the North of England, where the FFP recipients are older than those in our study. Blood use in the USA is summarized for three age groups. The FFP recipients and PLT recipients in our study appear to be younger than FFP and PLT recipients in the USA during 1989–1992. Cobain et al. also show three age groups for Western Australia, and these distributions are similar to ours. Only the FFP recipients in the Netherlands are somewhat younger. Age and diagnosis distributions are reported for a county in Denmark. The Danish RBC and PLT recipients are relatively old compared to ours. Apparently, age distributions of blood product recipients vary across countries. Comparing the diagnoses, in the Netherlands a smaller fraction of RBC and FFP is transfused to patients with diseases of the digestive system: 10% of RBC and 9% of FFP against 16% and 21% respectively in Denmark. Further, it is reported that 66% of the PLT are transfused to patients with neoplasms, while in the Netherlands only 41% of the PLT are transfused to that patient group. On the other hand, 9% of the PLT in the Netherlands are transfused to patients with diseases of blood or blood-forming organs against 5% of the PLT in Denmark.

These comparisons show that there are considerable differences in the profile of blood product recipients in different countries, probably reflecting differences in clinical practice. The PROTON and SCANDAT datasets may therefore not be representative for other countries, as the clinical blood use and the allocation of BPT to different patient categories may differ considerably, as is also illustrated with the Council of Europe survey data. Comparing data from different countries in a benchmark could highlight potential areas where further optimization of blood use might be possible. During our collaboration with the 20 participating hospitals, it

appeared that they appreciate to compare the PROTON data to their own for benchmarking purposes towards optimal blood use.

Conclusion

The PROTON approach provides a practicable way to obtain national data without nationwide coverage, using a sample of hospitals to estimate national distributions of blood recipient characteristics. Using these distributions will improve future cost-effectiveness analyses of blood safety interventions in the Netherlands, as their effects are achieved in recipients of BPTs.

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Appendix

Table A Distribution of RBC over age and diagnosis of recipients

	age												
	0	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	>=91	total
neoplasms	0.0%	0.2%	0.3%	0.5%	1.0%	2.1%	3.9%	5.7%	5.9%	2.3%	0.2%	22.2%
circulatory system	0.0%	0.0%	0.0%	0.2%	0.4%	1.1%	2.9%	6.4%	8.3%	2.1%	0.1%	21.5%
injury and poisoning	0.0%	0.1%	0.4%	0.6%	0.6%	0.7%	1.0%	1.7%	2.7%	2.2%	0.5%	10.5%
digestive system	0.0%	0.0%	0.1%	0.2%	0.5%	0.9%	1.5%	2.0%	2.7%	1.6%	0.2%	9.8%
blood and blood-forming organs	0.0%	0.2%	0.4%	0.3%	0.4%	0.6%	0.8%	1.2%	2.5%	1.9%	0.3%	8.6%
musculoskeletal system and connective tissue	0.0%	0.0%	0.1%	0.1%	0.1%	0.3%	0.7%	1.3%	1.9%	0.7%	0.0%	5.3%
other codes	0.1%	0.1%	0.1%	0.1%	0.2%	0.3%	0.6%	0.9%	1.1%	0.5%	0.1%	4.2%
genitourinary system	0.0%	0.0%	0.0%	0.1%	0.3%	0.5%	0.5%	0.8%	1.0%	0.4%	0.0%	3.8%
pregnancy, childbirth and puerperium	0.0%	0.0%	0.1%	1.6%	1.8%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	3.7%
symptoms, signs and ill-defined conditions	0.0%	0.0%	0.0%	0.1%	0.1%	0.3%	0.5%	0.8%	0.9%	0.4%	0.0%	3.3%
respiratory system	0.0%	0.0%	0.0%	0.0%	0.1%	0.2%	0.4%	0.5%	0.7%	0.3%	0.0%	2.4%
infectious diseases	0.0%	0.0%	0.0%	0.1%	0.1%	0.2%	0.2%	0.3%	0.2%	0.1%	0.0%	1.3%
endocrine, nutritional, metabolic, immunity	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.2%	0.2%	0.3%	0.2%	0.0%	1.1%
perinatal period	0.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%
congenital anomalies	0.4%	0.1%	0.1%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.8%
skin and subcutaneous tissue	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%	0.0%	0.4%
nervous system and sense organs	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.0%	0.0%	0.3%
mental disorders	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
total	1.5%	1.0%	1.9%	4.0%	5.9%	7.4%	13.2%	22.0%	28.6%	12.9%	1.5%	100.0%

Table B Distribution of FFP over age and diagnosis of recipients

	age												
	0	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	>=91	total	
circulatory system	0.1%	0.1%	0.2%	0.6%	1.5%	3.0%	7.5%	15.3%	16.4%	2.5%	0.0%	47.2%	
neoplasms	0.0%	0.4%	0.5%	0.7%	1.1%	1.7%	2.8%	3.6%	2.5%	0.6%	0.0%	14.0%	
injury and poisoning	0.1%	0.2%	0.9%	1.2%	1.3%	1.1%	1.4%	1.9%	1.9%	0.5%	0.0%	10.3%	
digestive system	0.0%	0.1%	0.2%	0.2%	0.6%	1.7%	2.2%	2.2%	2.0%	0.7%	0.1%	9.9%	
congenital anomalies	1.1%	0.6%	0.2%	0.1%	0.1%	0.1%	0.1%	0.1%	0.0%	0.0%	0.0%	2.4%	
infectious diseases	0.1%	0.3%	0.2%	0.2%	0.2%	0.3%	0.3%	0.4%	0.2%	0.1%	0.0%	2.3%	
symptoms, signs and ill-defined conditions	0.1%	0.1%	0.0%	0.1%	0.1%	0.3%	0.3%	0.6%	0.4%	0.2%	0.0%	2.2%	
genitourinary system	0.0%	0.1%	0.1%	0.1%	0.2%	0.4%	0.3%	0.4%	0.5%	0.1%	0.0%	2.1%	
blood and blood-forming organs	0.0%	0.3%	0.3%	0.1%	0.3%	0.5%	0.2%	0.2%	0.2%	0.0%	0.0%	2.1%	
pregnancy, childbirth and puerperium	0.0%	0.0%	0.0%	0.8%	1.2%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.0%	
respiratory system	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.3%	0.2%	0.3%	0.1%	0.0%	1.2%	
musculoskeletal system and connective tissue	0.0%	0.0%	0.2%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.0%	0.0%	1.2%	
other codes	0.1%	0.0%	0.1%	0.1%	0.1%	0.1%	0.2%	0.2%	0.1%	0.0%	0.0%	1.0%	
endocrine, nutritional, metabolic, immunity	0.1%	0.0%	0.0%	0.2%	0.1%	0.1%	0.1%	0.0%	0.1%	0.0%	0.0%	0.7%	
perinatal period	0.6%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.7%	
nervous system and sense organs	0.0%	0.0%	0.1%	0.1%	0.0%	0.1%	0.1%	0.1%	0.1%	0.0%	0.0%	0.6%	
skin and subcutaneous tissue	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	
mental disorders	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	
total	2.4%	2.3%	3.1%	4.5%	7.0%	9.6%	15.9%	25.3%	25.1%	4.8%	0.2%	100.0%	

Table C Distribution of PLT over age and diagnosis of recipients

age	age												
	0	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	>=91	total
neoplasms	0.2%	3.2%	3.0%	3.1%	4.4%	6.3%	9.0%	7.5%	4.0%	0.5%	0.0%	41.2%
circulatory system	0.1%	0.1%	0.1%	0.3%	0.7%	1.4%	3.5%	6.5%	7.2%	1.0%	0.0%	21.0%
blood and blood-forming organs	0.1%	1.1%	1.6%	0.6%	0.6%	1.2%	1.3%	0.8%	1.1%	0.2%	0.0%	8.7%
other codes	0.2%	0.2%	0.3%	0.3%	0.5%	0.7%	1.1%	0.8%	0.3%	0.1%	0.0%	4.5%
digestive system	0.1%	0.1%	0.1%	0.1%	0.3%	0.8%	0.9%	0.9%	0.7%	0.3%	0.0%	4.4%
injury and poisoning	0.0%	0.1%	0.3%	0.4%	0.5%	0.6%	0.6%	0.7%	0.7%	0.2%	0.0%	4.3%
symptoms, signs and ill-defined conditions	0.1%	0.1%	0.2%	0.2%	0.3%	0.6%	0.8%	0.6%	0.4%	0.1%	0.0%	3.5%
infectious diseases	0.1%	0.2%	0.2%	0.2%	0.3%	0.3%	0.4%	0.4%	0.2%	0.0%	0.0%	2.4%
congenital anomalies	1.3%	0.4%	0.1%	0.1%	0.1%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	2.0%
perinatal period	1.9%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.9%
respiratory system	0.0%	0.1%	0.1%	0.1%	0.1%	0.2%	0.4%	0.3%	0.2%	0.0%	0.0%	1.5%
pregnancy, childbirth and puerperium	0.0%	0.0%	0.0%	0.5%	0.8%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.4%
endocrine, nutritional, metabolic, immunity	0.1%	0.3%	0.2%	0.0%	0.0%	0.0%	0.1%	0.1%	0.0%	0.0%	0.0%	1.0%
genitourinary system	0.0%	0.0%	0.0%	0.0%	0.1%	0.1%	0.2%	0.2%	0.2%	0.1%	0.0%	1.0%
musculoskeletal system and connective tissue	0.0%	0.0%	0.1%	0.0%	0.1%	0.0%	0.2%	0.1%	0.1%	0.0%	0.0%	0.6%
nervous system and sense organs	0.1%	0.1%	0.1%	0.0%	0.0%	0.1%	0.1%	0.1%	0.0%	0.0%	0.0%	0.5%
skin and subcutaneous tissue	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
mental disorders	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
total	4.4%	6.1%	6.3%	6.1%	9.0%	12.4%	18.7%	19.1%	15.3%	2.7%	0.1%	100.0%

Chapter 3

Estimating survival after transfusion for the cost-effectiveness evaluation of blood safety interventions

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Abstract

Background For some medical interventions, like blood transfusion, patients are exposed repeatedly to low risks of transmission of infectious diseases. Survival after transfusion (SAT) is required to assess the cost-effectiveness of safety interventions reducing these risks. SAT differs from normal survival analysis as patients usually obtain multiple transfusions and therefore patients' survival is counted multiple times: once for each transfusion. Because of this dependency the commonly used Kaplan-Meier (KM) method for survival estimation might not be appropriate. The aim of this study is to compare patient survival (after first transfusion) and SAT and to evaluate whether the KM estimator is suitable for estimating SAT.

Study design and methods Two different methods for SAT estimation are evaluated and applied to estimate SAT of red blood cells, platelets, plasma transfused to patients of the University Medical Center of Utrecht (UMCU). The methods used are direct estimation and estimation using the KM method. Transfusions given in the UMCU between 1995 and 2003 were collected allowing SAT estimation over 13.6 years. In addition, a simulation study was performed to compare the performance of the two methods.

Results Both methods provide comparable estimates for SAT. However, as a result of a change in patient survival over time, differences in SAT for plasma were found when applying different methods. Also, confidence intervals obtained by the standard KM procedure deliver overly optimistic confidence intervals.

Conclusion There is a marked difference between patient survival (after first transfusion) and SAT for each of the blood components considered. In general the KM method provides a correct estimate for SAT itself, but the confidence intervals obtained with standard procedures are incorrect.

Introduction

Blood safety has been a major issue in the 1980's and 1990's. Blood safety policy has largely been driven by liability issues and the wish to render blood products as safe as possible.[1] More recently, cost constraints triggered the wish for more rational decision making in blood safety. It may be argued that other health care can be financed alternatively using the same resources.[2,3] In the Netherlands the government strives towards optimal instead of maximum blood safety.[4] Such policy decisions require outcomes from cost-effectiveness analyses (CEA) of blood safety interventions. In such analyses the impact of adverse events on the transfusion recipients in terms of costs and effects are assessed and balanced against the costs and effects of the (to be) implemented safety intervention(s). The effect on the transfusion recipient is expressed in terms of (quality adjusted) life years lost. Therefore, transfusion recipient survival is critical when assessing CEA of blood safety interventions.

Patient survival is the probability of a patient being alive at a specified time since a marked event. There is a simple relation between a patients' survival probability and his life expectancy: the latter is the area below the survival probability curve. The higher the survival probability, the higher the life expectancy. In the blood transfusion literature patient survival is most commonly reported as the survival of a particular patient after his or her first transfusion (SFT). For CEAs however, the life years lost after any of the patients' transfusions are relevant. The life years lost due to an adverse – let's presume lethal – transfusion to a patient is equal to the life expectancy of that patient at the time of the transfusion. If that patient would receive multiple transfusions at different time points, the average number of life years lost (given that one of these transfusions would indeed be lethal) would be the average of the life expectancies of that particular patient at the times he received these transfusions. We define survival after transfusion (SAT) as the survival of a transfusion recipient since transfusion, without referring to any specific transfusion. This survival could also be interpreted as the survival of the transfused product instead of that of the patient. With SAT we can adequately describe the effect of adverse transfusion events on patients.

For the estimation of SAT we can use observed time intervals from transfusion until death (or censoring). When data is (right) censored, survival is most commonly estimated using the Kaplan-Meier (KM) product limit estimator.[5] Censoring occurs when follow-up of a patient is incomplete and it remains unknown whether a patient has died or not. However, this method requires observed time intervals considered to be independent.[6] The question that arises is whether the KM method can be applied to estimate SAT. This is questionable, as the observed time intervals often concern

transfusions that were given to the same individuals, and are therefore connected by an identical endpoint (the time of patients' death or censoring).
To answer this question, we simulated a transfusion recipient population and applied two different methods for SAT estimation. In addition, we applied both methods to estimate SAT of transfusions given in the UMCU hospital between 1995 and 2003.

Methods

Estimating survival after transfusion (SAT)

Survival is commonly calculated using the product limit estimate proposed by Kaplan and Meier.[7] As discussed in the introduction, this method is invalid when there is a dependency between the observed follow-up times. For such circumstances, Kaplan and Meier propose direct estimation of the survival probability.[6] The survival probability is in that case is calculated as the fraction of observed deaths amongst all observations that might have survived until that time point. The advantage of the direct estimation (DE) method is that it provides an unbiased estimator of survival.[6] The drawback is that as a result of the diminishing amount of data used for estimating survival for longer survival times, its variance will generally be bigger than that of the KM estimator. Another drawback is that that the estimated survival will not necessarily be decreasing over time: one might find that is more likely to survive until time $t+\delta$ than it is to survive until time t. To overcome this problem the direct survival curve can be monotonized. This is a mathematical procedure that forces continuous decline of a function and can be shown to provide a better survival estimate.[8] Confidence intervals for the estimated survival probabilities are obtained by bootstrapping.[9] The DE confidence intervals are derived from the monotonized DE estimate. A formal description of both estimators is given in the Appendix A.

Simulation of a transfusion recipient cohort

A number of fictive cohorts of transfusion recipients with a known survival probability and transfusion regime were simulated. For such cohorts the theoretical SAT can be determined. This allows comparing accuracy and variation of both estimation methods. For instance, for a cohort of transfusion recipients with a SFT of $(1-t/T)^{\alpha}$ (where $t<=T$) which is subject to a constant transfusion rate per unit time, it can be derived that the SAT is equal to $(1-t/T)^{(1+1/\alpha)}$. Also, more complex cohorts were simulated where there was an associated between the transfusion intensity and patient survival to mimic transfusion practice more realistically. The simulations performed are described in detail in Appendix B.

Assessing SAT of blood components

All blood transfusions in the Netherlands are recorded such that identification of the donor who provided blood to any specific transfusion recipient is possible, and *vice*

versa. This is a legal requirement in the Netherlands which allows notification of recipients who have in the past received blood from a donor that is found to be infected with an infectious disease. In such cases previous donations might also have transmitted infections. For each transfused product, component type, date of transfusion and a unique hospital patient identification number (PID) are recorded. The hospital registration system therefore allows retrieval of past transfusions. Transfusion recipient data was extracted from the hospital databases from the period January 1st 1991 to December 31st 2003. At the CBS (Statistics Netherlands) a death register of all Dutch citizens is available from 1995 onwards. Transfusion and death register data were matched using the patients' date of birth, sex and address. This information allows unique identification of the patient (in most cases). This enables retrieval of either the date of death in case the patient is deceased, or a last date for follow-up in case the patient was alive at the time data retrieval (August 4, 2008). To ensure the privacy of the patients, all identifying information was encrypted before being transferred to the CBS. In addition, all analyses were performed in a secure environment and the results checked by CBS staff to make sure there was no risk of disclosure of individual patients' information.
SAT of various blood components admitted to patients in the UMCU was estimated with both the KM and the DE methods.

Software used

Data management was performed using SAS Enterprise Guide (Version 4.1, SAS, Cary, NC, USA; Statistical analyses were performed with Stata/SE (Version 9.2 for Windows, StataCorp LP, College Station, TX, USA); Derivation of the theoretical SAT was performed with Mathematica (Version 7, Wolfram Research, Champaign, IL, USA); Survival graphs were produced with Excel (Version 2002, Microsoft Corporation, Redmond, WA, USA); The simulations were performed in *R* (Version 2.10.2, The *R* Foundation for Statistical Computing, Vienna, Austria).

Results

UMCU transfusion recipient population

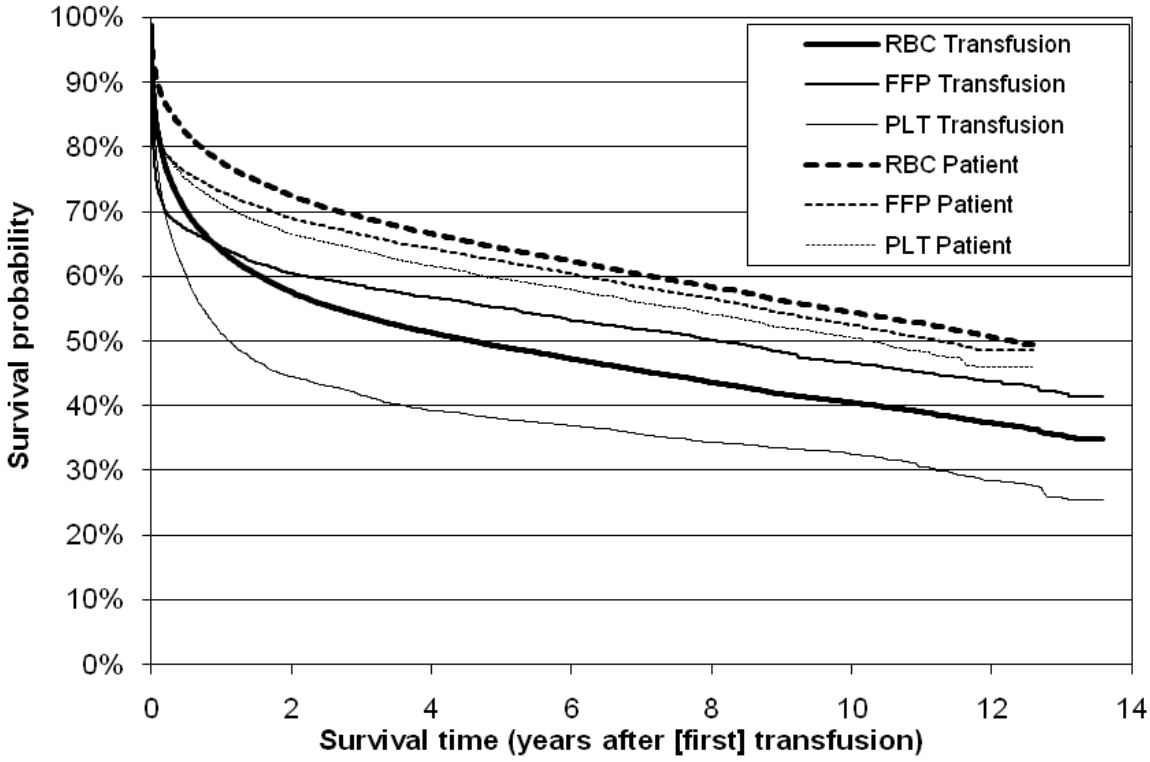
From 1995 through 2003, 24,859 patients received 252,339 transfusions during 39,893 hospitalization periods. The numbers of components transfused in this period were 158,969 red blood cell (RBC) units, 60,153 fresh frozen plasma (FFP) and 33,217 platelet (PLT) units. Male patients received 58% of all components. The male-female distribution is about the same for RBC units (57% male), FFP units (58% male) and PLT units (60% male). A total of 23,115 (93%) patients were matched using sex, address and date of birth. By August 4, 2008, the date at which the deceased status was obtained from the death register, 10,348 of these patients were deceased. There were no dependencies on age, sex and number transfusions received between the

matched and non-matched individuals. Both 93% of males and females were matched and both of matched and unmatched patients 52% were males.

Transfusion recipient survival

In Figure 1 both SAT and SFT is given for patients receiving RBCs, FFPs and PLTs respectively. Note that the SFT is provided for one year less than this SAT. This is because for the estimation of SFT we discarded patients that were transfused in 1995. As most patients receive all transfusions within one year, discarding transfusion recipients from this first year ensures that almost all remaining first transfusions in actual fact are first transfusions.

Figure 1 Patient survival after first transfusion (SFT, indicated as 'Patient') and survival after transfusion (SAT, indicated as 'Transfusion') per type of blood component.

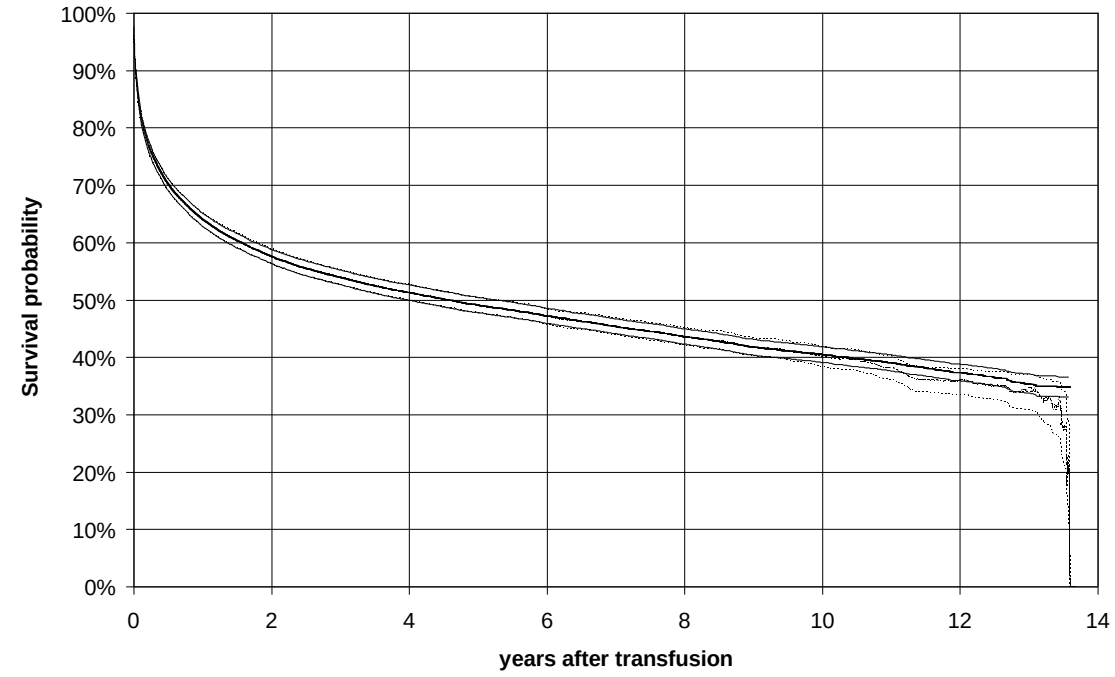


SAT is less than SFT for all products. There is an average (over time declining) difference of about 15% in survival probability between SAT and SFT for RBCs, a difference around 7% for FFPs, and a difference around 20% for PLTs.

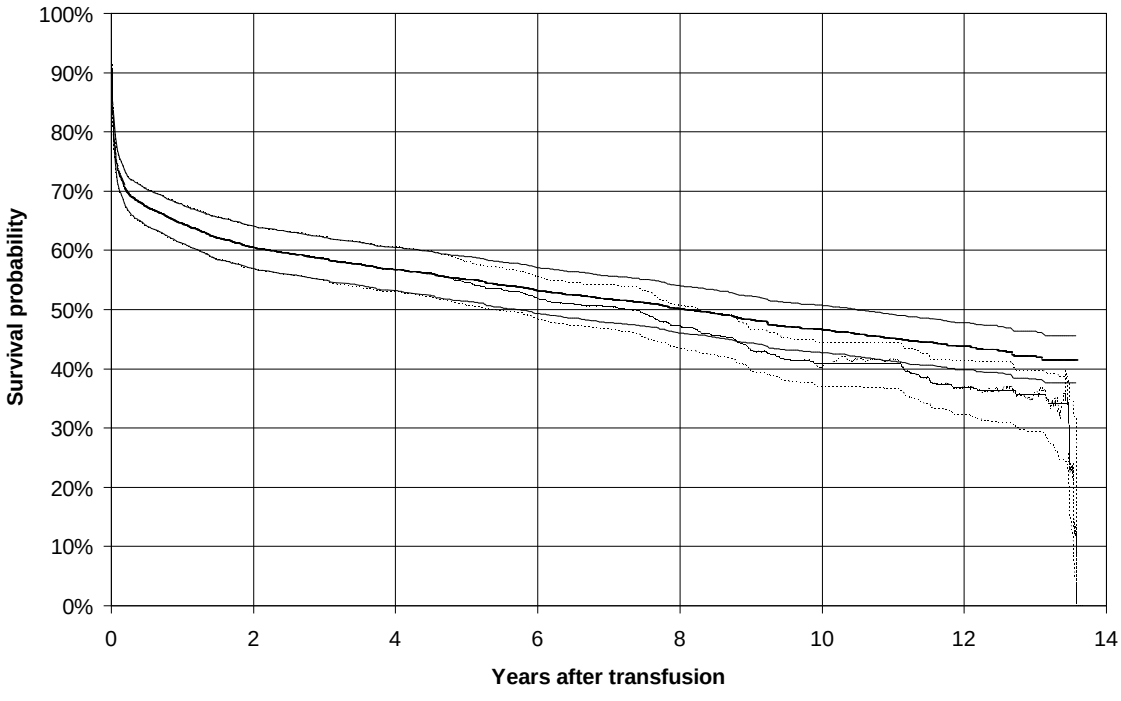
In Figure 2 SAT estimates for RBCs, FFPs and PLTs are given using KM and DE methods for survival estimation. The indicated 95% CIs are obtained by bootstrapping. Figure 2 shows that the KM and DE methods provide comparable estimates for the first six years of follow-up for all transfused components. For RBCs (Figure 2a) the results are almost identical for the first ten years follow-up (both the

estimate itself and the CI). For the last four years follow-up, the estimates remain (almost completely) within each others 95% CIs.

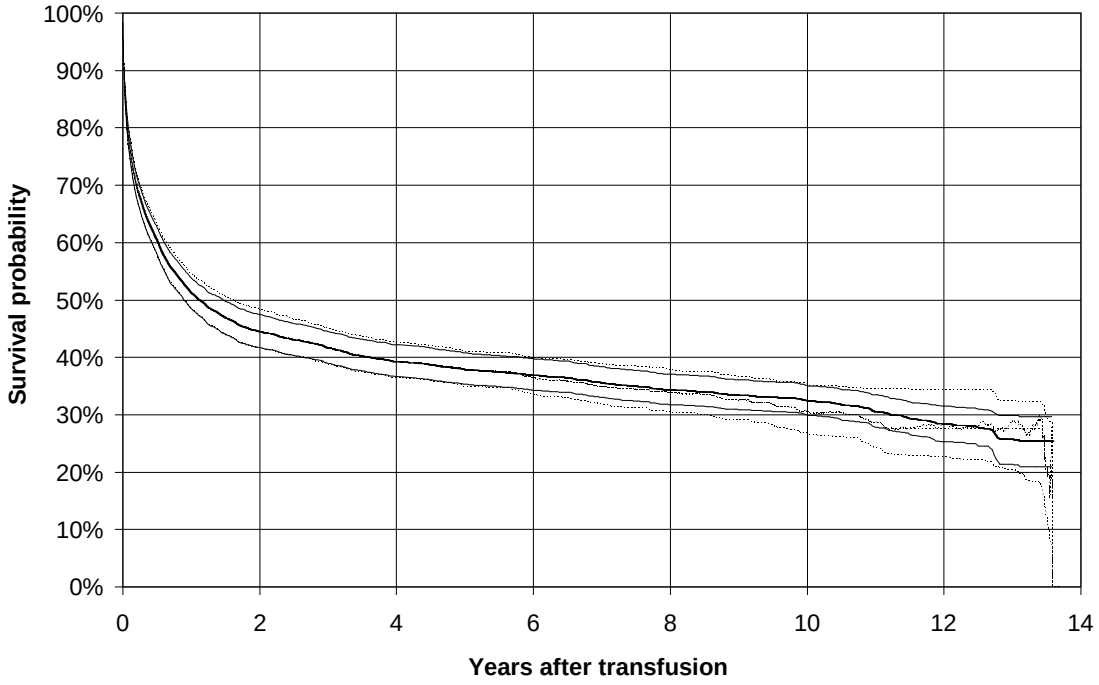
Figure 2 Survival after transfusion (SAT) of RBCs (a), FFPs (b) and PLTs (c) with 95% CI using the KM (—) and DE (---) methods. Both the raw and monotonized DE estimates are given.



(a)



(b)



(c)

For FFP the similarity between estimation methods remains up until 5 years follow-up. From thereon there is an increasing difference between both survival estimates, with a lower survival for the DE method. From twelve years follow-up onwards the 95% CIs are almost non-overlapping, suggesting a statistically significant difference in survival estimation. Another thing that becomes clearly visible here is the effect of the monotonizing procedure on the survival estimate just after 10 years follow-up: the monotonized estimate does not follow the inclination of the directly estimated survival probability.

The survival estimates for PLT are again in good agreement for the first eight years of follow-up. From there on there is a small deviation, but the survival probability estimates remain in each other's 95% CIs. For the PLT estimates the difference between the raw and monotonized DE estimates becomes apparent for long-term follow-up.

All Figure 2 graphs clearly illustrate the larger CIs for long-term follow-up for the DE method as compared to the KM method.

Simulating transfusion recipient survival

Simulations were performed to study differences between the KM and DE estimates. In the simulations both patient survival and transfusion characteristics were varied. The simulations show that both estimators provide similar results even for a limited number of observations, and even in case of a dependency between patient survival and transfusion intensity. In case there are many observations both estimates provide

near identical results. SAT confidence intervals were obtained by a bootstrapping procedure.[9] When bootstrapping observations, resampling of patients with their associated transfusions and not directly resampling of transfusions is required to obtain correct SAT CIs. This is required to maintain the dependence between transfusions given to a single patient. As standard KM CI estimation occurs without accounting for this dependence, such CI estimates will generally deliver overconfident results.

The simulation and results are described in Appendix B. The source code for the simulations is available from the authors upon request.

Discussion

There is a substantial difference between SFT and SAT for all types of blood components transfused. One would expect SAT to be less than SFT as all observed survival intervals of transfusions after the first transfusion will be less than that of the first transfusion. However, as most transfusions are given within one year after the first transfusion, this does not account for the eminent difference between SFT and SAT. From the literature it is known that SFT decreases with the number of components received.[10] As SAT can (roughly) be interpreted as survival weighted by the number of components received, it is clear that this effect will be the source of the difference between SAT and SFT. From Figure 1 it is clear that the difference between SFT and SAT is the strongest for PLTs, and the weakest for FFPs. This indicates that the association between the number of transfusions and death rate is the strongest for PLTs and the weakest for FFPs.

Survival analysis is used for a wide range of problems with many different applications. In most cases when repetitive treatment is involved one is interested in the effect of treatment. In such cases a multi-state modeling approach is appropriate.[11] However, in our specific application we are not interested in the effectiveness of treatment but purely in the survival of the patient after (any given) transfusion. Various survival models can be used to obtain different transfusion survival characteristics. For instance, an analysis of patient survival after the first, second, third, fourth, etcetera (n^{th}) transfusion. This information in combination with for instance age and clinical indication could be used for establishing a prognosis of patient survival. A description of such modeling exercise is outside the scope of this paper.

The results show that both the KM and DE estimation methods provide similar survival curves for the SAT of both RBCs and PLTs. This result was confirmed by various simulation studies. For FFP units however, there is a marked difference

between the results from these two methods. Further analysis of the FFP data showed that the distribution of the number of units transfused changed over time, but, more importantly, that patient survival increased over the years. Especially the differences found in long-term survival using different methods are caused by the change in short-term patient survival over time. Where the KM estimate at a particular follow-up time is based on the average hazard rate of earlier follow-up times, the DE method is based on the survival of all patients that (potentially) survived for the duration of the follow-up time considered. As such, the use of the KM method is to be preferred over the DE method.

Our simulation studies demonstrated what was confirmed by the analyses of the transfusion data: both methods are valid for estimating SAT. Mathematical proof of the fact that both estimation methods provide similar results was derived, but is not provided here. The simulation studies illustrate that despite the fact that transfusions are grouped per patient, SAT can be correctly estimated using the KM method. However, this grouping of transfusions does affect the estimation of its associated CIs: for a proper estimation of the SAT CIs bootstrapping of patients (with associated transfusions) is required. Standard KM CI estimates will generally deliver overly optimistic CIs.

In our paper we illustrate that SAT can be estimated using both the DE and KM methods, with each method having its own (dis)advantages. For both methods CIs can be obtained by bootstrapping patients. The necessity of determining SAT was revealed when performing cost-effectiveness analyses of for blood safety interventions, but in fact SAT is in fact relevant when analyzing the cost-effectiveness of *any* safety intervention. The only prerequisite is that patients have multiple exposures over a prolonged period of time and that each exposure is associated with a controllable (small) risk.

Acknowledgments

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Appendix A: Description of the KM, DE and monotonized DE estimators

Suppose we have observed X transfusions, given at times $(d1_1, d1_2, ..., d1_X)$ in an interval $[0; D]$, to N patients (in general it is possible that one patient receives several transfusions). The time at which the patient who received the transfusion either died or was censored is given by $(d2_1, d2_2, ..., d2_X)$. Whether the patient died or was censored is given by outcomes $(o_1, o_2, ..., o_X)$, where $o_i = 1$ means that the patient receiving transfusion i died. There exists $D_1 \geq D$ such that for all patients, we know whether they have died or not before time D_1.

Let $S(t)$ be the probability that a patient will have a lifetime exceeding t after obtaining a transfusion. The survival function $S(t)$ can be obtained by either the Kaplan-Meier (KM) method or by direct estimation of the survival (DE).

Define for each $i \in \{1, ..., X\}$, the observed time until death or censoring as $t_i = d2_i - d1_i$. Let the ordered subset $T_d \subset \{t_1, t_2, ..., t_X\}$ denote all the observed times of transfusions of patients who died. Note that if two transfusions have the same observed time, this time is included only once in the set T_d. The Kaplan-Meier survival estimate is calculated by the following formula:

$$\hat{S}(t) = \prod_{s \in T_d : s<t} \left(1 - \frac{\sum_{i=1}^{X} 1_{\{o_i=1\}} 1_{\{t_i=s\}}}{\sum_{i=1}^{X} 1_{\{t_i \geq s\}}} \right) \quad (1)$$

Here $1_{\{B\}}$ is the indicator function which takes the value 1 if condition B is true, and 0 otherwise.

The direct survival estimate is calculated by the following formula:

$$\hat{S}(t) = \frac{\sum_{i=1}^{X} 1_{\{t_i \geq t\}} 1_{\{d1_i \leq D_1 - t\}}}{\sum_{i=1}^{X} 1_{\{d1_i \leq D_1 - t\}}} \quad (2)$$

Here we use the fact that for all transfusions that took place before D_1 - t, it is known whether or not the patient survived longer than t.

By definition, a survival function has to be a monotonic decreasing function of time. The Kaplan-Meier estimate is such that monotonicity is implicit. However, for the direct estimator this is not the case, which means that the estimate may increase over time. To correct for this, a monotonization step can be added that transforms the survival estimator to a strictly decreasing function. In the monotonization step the integral of $\hat{S}(t)$ is taken. Of this integral the least concave majorant is taken, which is the smallest concave shape that fits over the integrated function. This majorant

function is subsequently differentiated to produce the updated estimate $\hat{S}_m(t)$, the monotonized version of $\hat{S}(t)$.

Appendix B: Description of simulation of patient cohorts

Survival after transfusion (SAT)

Consider a patient population with survival probability $S(t)$, indicating the probability of an individual being alive at time t. Suppose this population had a probability $B(t)$ of obtaining a transfusion at time t. The probability of a transfusion actually occurring at time t requires the patient to be alive at time t, and would therefore be equal to $B(t)S(t)$. The survival probability of a patient at time t after having received a transfusion at time x would be $S(x+t)/S(x)$. The survival after transfusion (SAT) of a cohort of patients from this population will be equal to the survival after any timepoint x, weighted by the probability of transfusion at timepoint x:

$$SAT(t) = \frac{\int_{x=0}^{T_{\max}} B(x)S(x)\frac{S(x+t)}{S(x)}dx}{\int_{x=0}^{T_{\max}} B(x)S(x)dx} = \frac{\int_{x=0}^{T_{\max}} B(x)S(x+t)dx}{\int_{x=0}^{T_{\max}} B(x)S(x)dx} \quad (1)$$

Where:

$S(0) = 1$ and $S(t) = 0$ for $t \geq T_{\max}$

Theoretical SAT for two example patient populations

With Equation (1) for any patient population and transfusion regime the SAT can be calculated. This was done for the patient population mentioned in the paper with a probability of survival of $S(t) = (1 - t/T_{\max})^{\alpha}$ (where $0 \leq t \leq T_{\max}$) which is subject to a constant transfusion rate per unit time (transfusion intensity) c. For such a population it can be derived that the $SAT(t) = (1 - t/T_{\max})^{(1+1/\alpha)}$. For this population the average number of transfusions per patient (the denominator of equation (1)) is equal to $E(n) = \alpha c T_{\max}/(1+\alpha)$.

A more complex patient population is one where patient survival is equal to $e^{-\alpha t}$ for $0 \leq t \leq T_{\max}$ and 0 for $t > T_{\max}$ and where the patient hazard rate (α) is a stochastic variable. In our example population α varies between α_{min} and α_{max} with a linear diminishing probability density. The probability density function for α is then equal to $P(\alpha) = 2(\alpha_{\max} - \alpha)/(\alpha_{\max} - \alpha_{\min})^2$. For a patient from this population with hazard rate α, subject to a constant transfusion intensity c-α, can be derived that $SAT_{\alpha}(t) = (1 - e^{-\alpha(T_{\max} - t)})/(1 - e^{-\alpha T_{\max}})$. The expected number of transfusion given to this patient is $E_{\alpha}(n) = c(1 - e^{-\alpha T_{\max}})$.

Now with the known distribution of α and the known SAT and expected number of transfusions for any patient with a known α, $S(t)$ and $SAT(t)$ of the population as a whole can also be calculated:

$$S(t) = \int_{\alpha=\alpha_{\min}}^{\alpha_{\max}} S_\alpha(t)P(\alpha)d\alpha = \frac{2e^{-(\alpha_{\max}+\alpha_{\min})T_{\max}}\left(e^{\alpha_{\min}t} + e^{\alpha_{\max}t}\left((\alpha_{\max}-\alpha_{\min})t-1\right)\right)}{t^2(\alpha_{\max}-\alpha_{\min})^2} \quad (2)$$

$$SAT(t) = \frac{\int_{\alpha=\alpha_{\min}}^{\alpha_{\max}} SAT_\alpha(t)E_\alpha(n)P(\alpha)d\alpha}{\int_{\alpha=\alpha_{\min}}^{\alpha_{\max}} E_\alpha(n)P(\alpha)d\alpha} = \frac{\int_{\alpha=\alpha_{\min}}^{\alpha_{\max}} (1-e^{-\alpha(T_{\max}-t)})(\alpha_{\max}-\alpha)d\alpha}{\int_{\alpha=\alpha_{\min}}^{\alpha_{\max}} (1-e^{-\alpha T_{\max}})(\alpha_{\max}-\alpha)d\alpha} =$$
$$= \frac{2T_{\max}^2\left(e^{-\alpha_{\max}t} - e^{-\alpha_{\min}t}\left((\alpha_{\max}-\alpha_{\min})t-1\right)\right) - 2t^2\left(e^{-\alpha_{\max}T_{\max}} + e^{-\alpha_{\min}T_{\max}}\left((\alpha_{\max}-\alpha_{\min})T_{\max}-1\right)\right)}{t^2T_{\max}^2(\alpha_{\max}-\alpha_{\min})^2 - 2t^2e^{-(\alpha_{\max}+\alpha_{\min})T_{\max}}\left(e^{-\alpha_{\min}T_{\max}} + e^{-\alpha_{\max}T_{\max}}\left((\alpha_{\max}-\alpha_{\min})T_{\max}-1\right)\right)} \quad (3)$$

Simulation of survival after transfusion

A simulation of a cohort of patients as described above with an exponential survival and a stochastic hazard rate was performed. There was a continuous inflow of 20 new patients per year in the patient population which appear at Poisson distributed intervals. The constant transfusion intensity (c) was equal to 3. The patient hazard rate (α) varied between 0.05 and 1.5 per year. The maximum survival of the patients ($T_{\max}$) was 10 years. We observe transfusions and deaths in this population over a period of five years.

In Figure B1 the mean patient survival in the cohort is shown as well as the distribution of the individual patient survival. The curves for the distribution of individual patient survival are equally spaced on the cumulative density function of the hazard rate α. The average patient receives 2.8 transfusions. On average only 83% of the patients receive 3 transfusions, 14% receive 2 transfusions, and only 3% of the patients receive 1 transfusion.

Figure B2 shows various characteristics of one thousand cohort simulations. On average there are 100 patients in the cohort who receive on average 277 transfusions. The proportion of observations that is censored is 38%, which refers to the proportion of times since transfusion. In Figure B2 also the distribution of the number transfusions per patient in the simulated cohort is given. Note that the proportion of patients that receive only 1 transfusion is much higher than the theoretical proportion. This is caused by the fact that in the simulation
37% of the patients are already in the cohort when the interval of observation is started. Also, a part of the 37% of the patients in the cohort that are censored will obtain subsequent transfusions beyond the end of the observation interval. This limitation of the observation window will bias the distribution of the number of transfusions per patient strongly to the left.

Figure B1 Mean patient survival in the simulated cohort and the distribution of individual patient survival.

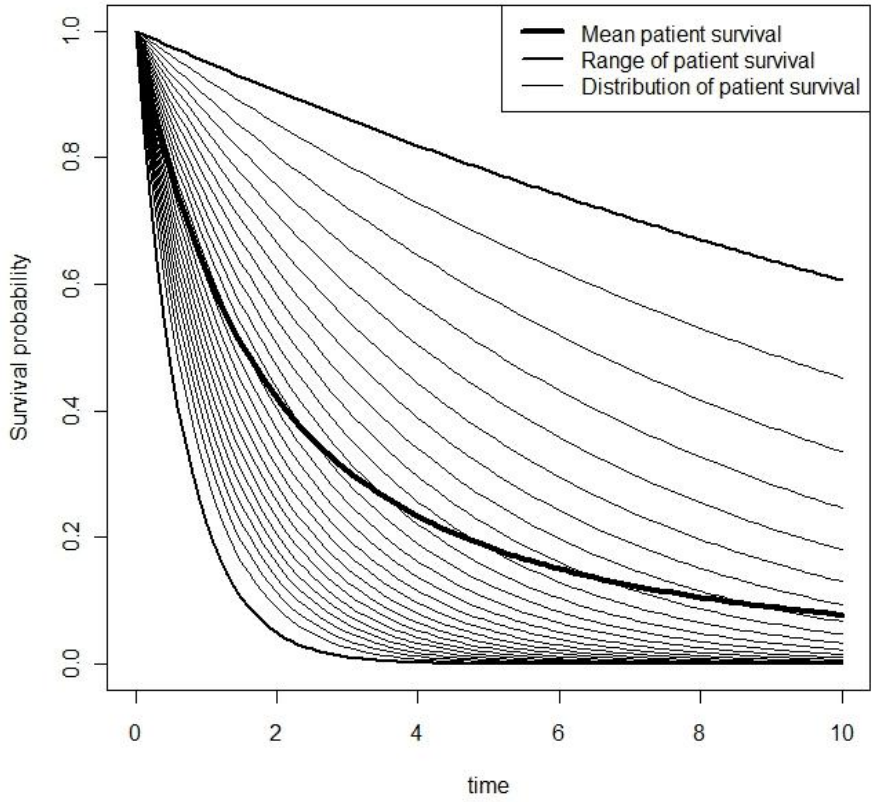
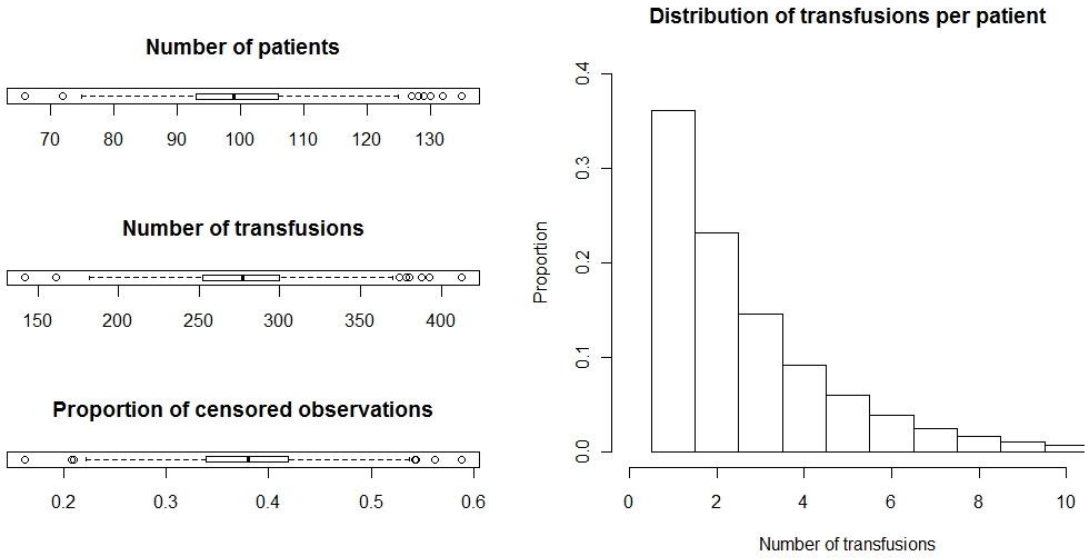


Figure B2 Various simulation characteristics: distribution of number of observed patients and transfusions, the proportion of censored observations (transfusions for which the patient was still alive at the end of the observation period) and the distribution of number of transfusions per patient.



For each of the simulated cohorts SAT was estimated by means of the KM method, the DE method and the monotonized DE method. Figure B3 shows the 2.5, 50 and 97.5 percentiles of the estimated survival probability at various times after transfusion. In addition, the theoretical SAT for the patient cohort (Formula 3) is provided. The results show that the median estimates for all three estimates coincide with the theoretical SAT, at least for the first 4 years. Also, the 95% CIs are similar for all three methods, although those for the KM estimates seem to be the smallest and those for the non-monotonized the largest.

For each of the simulated patient cohorts the following characteristics were determined:

(1) the survival probability, estimated by the KM method;
(2) the 95% CI of the KM estimate using greenwoods formula;
(3) the 95% CI by bootstrapping transfusion intervals: for each bootstrap the whole set of observed time-intervals from transfusion to patients' death or censoring were resampled, and
(4) the 95% CI by bootstrapping transfused patients: for each bootstrap the whole set of observed patients were resampled. For each resampled patient all associated transfusion time-intervals and outcomes (censoring or death) are added to the collection of bootstrapped time-intervals and outcomes.

In Figure B4 the 2.5, 50 and 97.5 percentiles of the simulated KM estimators are shown. In addition, the median values for each of the CI estimates over the 1000 simulated cohorts given. These were calculated for 100 equally spaced times after transfusion on the interval 0 to 5 years. Figure B4 shows that, as expected, the 95% CI of the bootstrap on transfusions is similar to the 95% CI of the KM estimator by greenwoods formula. However, the 95% CI of the simulated cohort is much wider and is very well represented by the 95% CI obtained by the patient bootstrap. This illustrates the fact that with bootstrapping patients the variability in the KM estimate related to the patient cohort is correctly represented. Also it shows that the CIs of SAT are incorrectly estimated when ignoring the effect of clustering of transfusions at patient level.

Figure B3 The 2.5, 50 and 97.5 percentiles of SAT for various survival estimation methods from a simulation of 1000 patient cohorts.

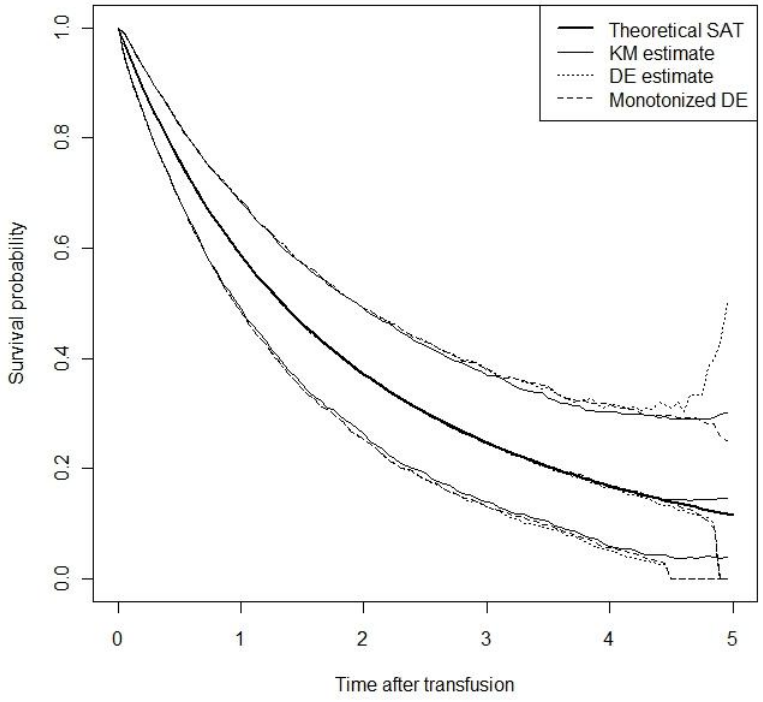
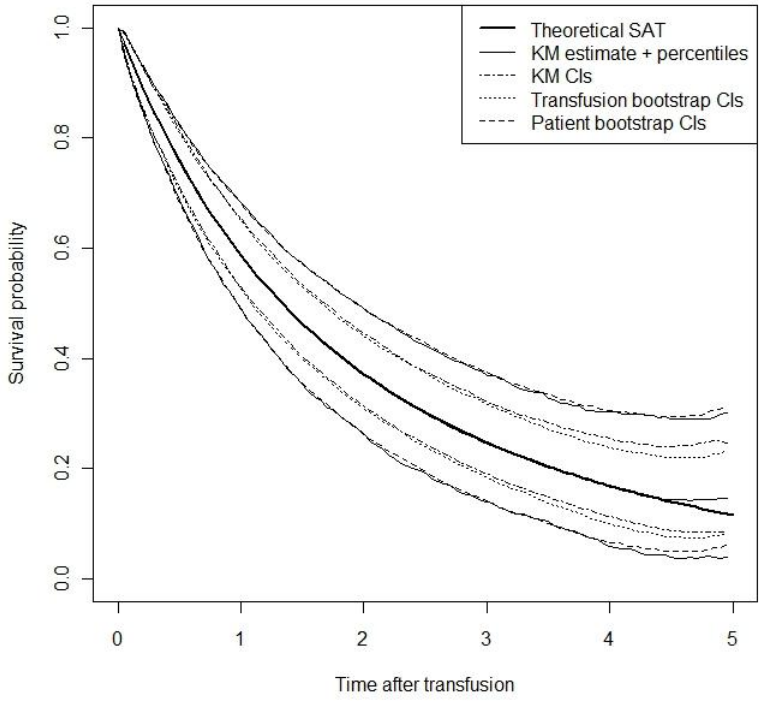


Figure B4 2.5, 50 and 97.5 percentiles of the KM survival estimator cohorts and the median value of various 95% CI estimates from 1000 simulated cohorts.



Chapter 4
Survival after transfusion in the Netherlands

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Abstract

Background Cost-effectiveness analyses of blood safety interventions require estimates of the life expectancy after blood product transfusion. These are best derived from survival after blood transfusion, per age group and blood component type.

Study design and methods The PROTON (PROfiles of TransfusiON recipients) study collects transfusion recipient data from a hospital sample covering 28% of the total blood use between 1996 and 2006 in the Netherlands. The dataset includes date of transfusion, blood component type transfused and recipient age. PROTON data were individually matched to mortality data of the Netherlands. Survival after first transfusion and after any transfusion was calculated, per blood component type and age group. PROTON mortality rates were compared to mortality rates in the general population. The results were used to estimate survival beyond the study period and to estimate life expectancy after transfusion.

Results Of all 2,405,012 blood product transfusions in the PROTON dataset, 92% was matched to the national Dutch Municipal Population Register, which registers all deaths. After 1 year, survival after any transfusion was 65.4%, 70.4% and 53.9% for RBC, FFP and PLT respectively. After 5 years, this was 46.6%, 58.8% and 39.3% for RBC, FFP and PLT respectively. Ten years after transfusion, mortality rates of recipients are still elevated in comparison to the general population.

Conclusion Mortality rates of transfusion recipients are higher than those of the general population, but the increase diminishes over time. The mortality rates found for the Netherlands are lower than those found in comparable studies for other countries.

Introduction

Various safety interventions are implemented to reduce the risk of various adverse events in recipients of blood product transfusions.[1] An example is the screening for infectious diseases to prevent transmission through blood transfusion.[2] Lately, discussions on the costs of blood components focus on the cost-effectiveness of new blood safety interventions. Cost-effectiveness analyses (CEAs) can support governments and blood banks in deciding where to allocate scarce health care resources.[3] Typically, CEAs estimate the costs of the safety intervention and the number of adverse events avoided. Next, the cost savings are estimated that are associated with one such adverse event in a transfusion recipient and it is estimated what preventing an adverse event means in terms of (quality-adjusted) life years gained. This is equal to the normal life expectancy after transfusion minus the life expectancy after an adverse event. While the life expectancy after an adverse event - such as after transmission of hepatitis B - is quite often well documented, little information is available on the average survival after blood transfusions without any adverse events.[4]

There are various ways one can determine survival for the use in CEA models for blood safety interventions. One way is to compute overall survival (for all blood component types simultaneously) and use this estimate to determine the health lost by contaminated blood products. However, in some cases this method is not applicable. For example, if the cost-effectiveness of screening of donor blood for infectious diseases is investigated. The natural history of the disease might depend on age at infection. This means that stratified survival probabilities are needed to calculate costs and health effects per age stratum.[4] Also, when interventions for particular recipient groups (e.g. pediatric recipients) are considered, survival for these specific groups are needed. When a safety intervention only applies to one or two blood component types, separate survival information for red blood cells (RBC), fresh frozen plasma (FFP) and platelets (PLT) is needed to analyze the cost-effectiveness. Survival per blood component type is also required when risks differ between products: e.g. in the Netherlands, PLT concentrates are usually produced from five donations, so these have a five times higher risk to be contaminated with an infectious disease than are RBC units, which are obtained from single donations.[5]

This article reports the survival analysis results of the PROTON (PROfiles of TransfusiON recipients) study. The aim of this study is to collect and analyze transfusion recipient data in order to improve the accuracy of CEAs of blood safety interventions. The distribution of transfusions of RBC, FFP and PLT over age, gender and discharge diagnosis was described earlier.[6] In this article, we present estimates for survival after transfusion in the Netherlands, stratified by age group and blood

component type, as these are essential elements for CEAs of blood safety interventions.

Methods

Data matching

The PROTON dataset contains information on 290,043 recipients who received 2,405,012 blood products (1,720,075 RBC, 443,697 FFP, 241,240 PLT) during the years 1996 to 2006.[6] Data were collected in 20 hospitals, covering 28% of total blood use in the Netherlands. Weight factors were applied to the observed transfusion records, to obtain estimates for the distribution of blood products over transfusion recipients in the Netherlands.[6] These weight factors were used to adjust for the proportion of transfusions in academic, general and cancer hospitals. The PROTON transfusion data were individually matched to mortality data from the Dutch Municipal Population Register (in Dutch: Gemeentelijke Basisadministratie, GBA) of the Netherlands. This dataset contains basic demographic data on all Dutch citizens, including the precise dates of death of people who deceased in the Netherlands after 1995. For a more detailed description of the data and matching procedure we refer to the description of the PROTON study.[6]

Survival analyses

The primary outcome of CEAs concerning blood screening tests for infectious diseases is the investment, expressed in money or otherwise, to prevent one (additional) infectious blood product transfusion. The subsequent effect, in terms of life years lost due to one infectious transfusion, starts from the moment of transfusion of the blood product that caused the transmission of the disease. Therefore, one has to determine patient survival considering all transfusions given to a patient, as any of these transfusions might be the contaminated one. Patient survival after any transfusion (SAT) instead of general patient survival (for instance measured after the date of first transfusion) must be used in CEAs for blood safety interventions. We used the conventional Kaplan-Meier estimator to estimate SAT of RBC, FFP or PLT. Confidence intervals around the resulting survival curves are determined by bootstrapping transfusion recipients.[7] Recipient survival after first transfusion (SFT) per blood component type was estimated as well. This is to highlight the difference between these two survival outcomes and to enable comparison with other studies, as to our knowledge most studies except two estimated SFT.[8,9] To reduce the bias introduced by recipients that possibly were transfused before the observation period of a hospital, recipients transfused in the first year of observation of each hospital were eliminated from the patient's SFT estimation.

Next, SAT was estimated for age strata of five years. We made two exceptions to this stratification: 1) A separate recipient age stratum was defined for the age of 0 (neonates), as this concerns a different distribution of diagnoses than in older transfused children[6]; 2) To obtain sufficient observations in the oldest recipient age strata, one collective recipient age group was defined respectively for all RBC recipients older than 90 years, for all FFP recipients older than 85 years and for all PLT recipients older than 80 years. We calculated annual mortality rates, which are the probabilities of dying in a particular year after transfusion, given that the recipient was alive at the beginning of that year.

Standardized mortality ratios

Statistics Netherlands provided survival data of the general population of the Netherlands, according to age and gender.[10] We used the distribution of blood product transfusions over recipients of particular age and gender to determine the aggregate survival of a matched cohort of the general population, for four age strata. These data were used to calculate mortality ratios for the general population. The ratio of the mortality rate of transfusion recipients and the mortality rate of the general population is the Standardized Mortality Ratio (SMR). When the SMR is larger than 1, mortality rates after transfusion are higher than in the general population.

Life expectancy after transfusion

To estimate the life expectancy after transfusion, according to recipient age, we need to extrapolate survival beyond the 12 years of retrospective data that is available. It appears invalid to assume that long term mortality rates are identical to those in the general Dutch population, as mortality rates of transfusion recipients are still elevated after 12 years. The additional risk appeared to be constant after 8 years. We calculated the average difference between mortality rates after transfusion and that of the general population over the years 8 to 12 after transfusion, per blood component type and age group. We assume that the increase in mortality rates remains constant beyond 10 years after transfusion to calculate the life expectancy after transfusion, stratified to age group and blood component type.

Computational issues

Data management and analysis was performed using Stata/SE (version 9.2 for Windows, StataCorp LP, College Station, TX, USA). Graphs were created using Excel (version 2007, Microsoft Corporation, Redmond, WA, USA).

Results

Data matching

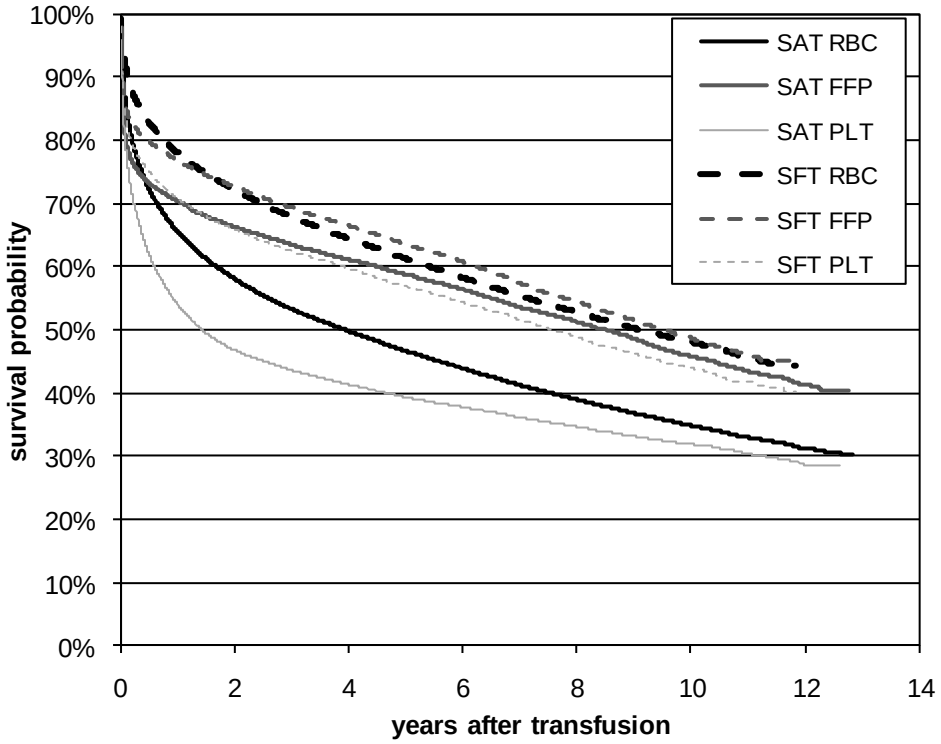
Of all 2,405,012 blood product transfusions in the PROTON dataset, 92% could be matched to the Dutch Municipal Population Register. A match implies that a date of

death is found or the recipient is known to be still alive at the day of performing the matching procedure. Matching was not performed at the same date for all hospitals. The last date of observed recipient deaths varied between 7th November 2007 and 6th November 2008. There is little variation in matching rate by age, and this is therefore not expected to affect the analysis results.

Survival analysis results

Figure 1 shows the overall SAT and SFT, for RBC, FFP and PLT. Of all RBC 65.4% (95% CI: 65.1-65.9) was transfused to a recipient that was still alive after 1 year. Of all FFP and PLT, respectively 70.4% (95% CI: 69.6-72.1) and 53.9% (95% CI: 52.9-55.1) was transfused to a recipient that was still alive after 1 year (note that this concerns SAT). After 5 years, SAT was 46.6% (95% CI: 46.1-47.0), 58.8% (95% CI: 57.4-60.8), and 39.3% (95% CI: 38.1-40.4) for RBC, FFP and PLT respectively. SFT of RBC, FFP and PLT are plotted in dashed lines. After 1 year, SAT and SFT for RBC differ 19%. This relative difference increases to 38% after 10 years. For FFP, this difference is 9% after 1 year, decreasing to 6% after 10 years. For PLT, the difference between SAT and SFT is 31% after 1 year, increasing to 45% after 5 years and then declining to 38% after 10 years.

Figure 1 Survival after transfusion (SAT) and survival after first transfusion (SFT) of RBC, FFP or PLT



At the time of transfusion, the mean age of recipients is 60.6 years and the median age is 66. The mean age of transfusion recipients at the time of their first transfusion

is 60.8 years, the median age is 67. Note that this implies that the mean number of transfusions is slightly higher in young recipients than in those above 70 years of age. In Figure 2 SAT is plotted for four age groups, for RBC, FFP and PLT transfusions respectively. For all defined age strata, survival data are tabulated in the Appendix, in order to be available for CEA models for blood safety interventions. Figure 2 indicates that survival after any RBC transfusion is similar for children and young adults. After FFP transfusion young adults survive longer and after PLT transfusion children survive longer.

Figure 2a Survival after any RBC transfusion according to age 1,580,018 transfusions in total: 105,618 for ages 0-16, 208,965 for ages 17-40, 513,038 for ages 41-64 and 752,397 for ages 65 and older

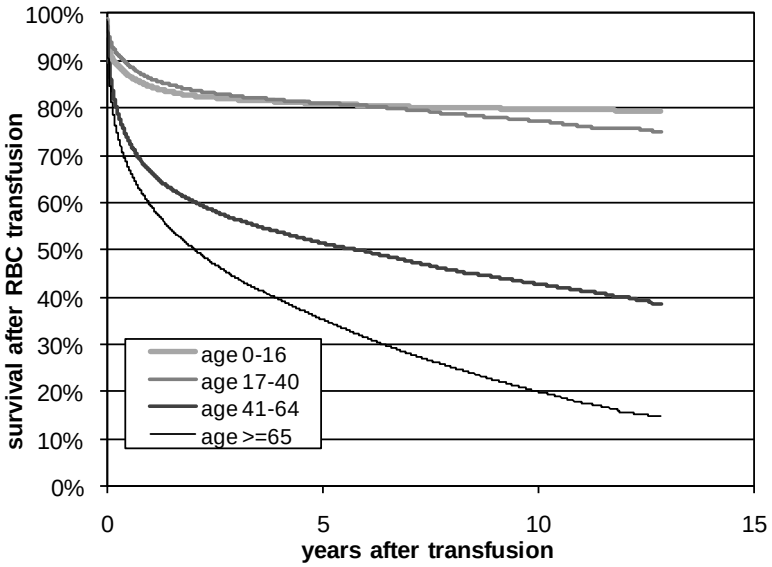


Figure 2b Survival after any FFP transfusion according to age 408,258 transfusions in total: 45,135 for ages 0-16, 83,703 for ages 17-40, 138,294 for ages 41-64 and 141,126 for ages 65 and older

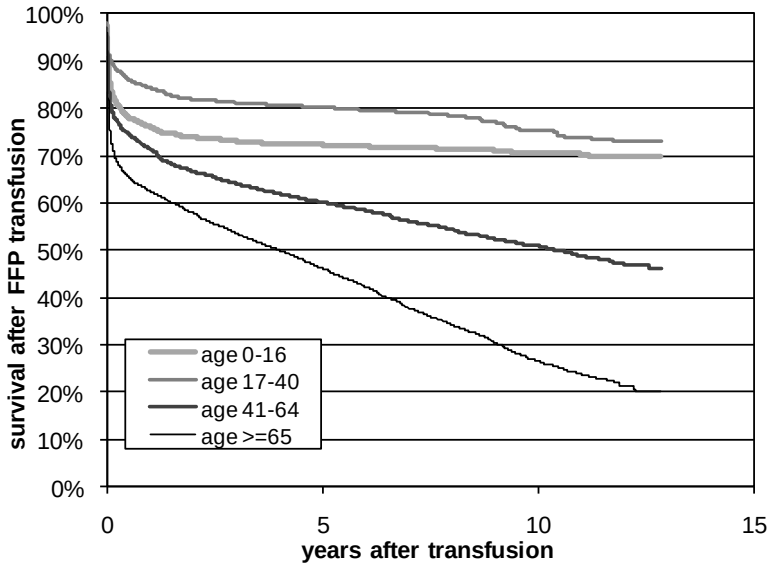
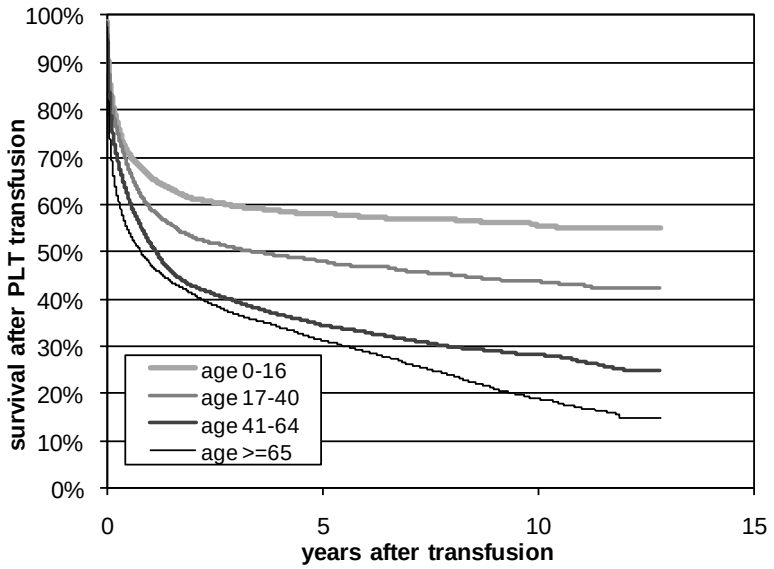


Figure 2c Survival after any PLT transfusion according to age 225,079 transfusions in total: 40,133 for ages 0-16, 44,364 for ages 17-40, 90,370 for ages 41-64 and 50,212 for ages 65 and older



Comparison with survival in the general population

SMRs after any transfusion for four age groups and for each blood component type are shown in Figure 3. There is a dip after 8 years in the SMRs for the group aged 0 to 16, due to one recipient who received a very large number of transfusions of all three component types and the small number of recipients with long follow-up in this age group. The mortality rates of transfusion recipients are much higher than those of the general population, adjusted for age and gender: the highest SMR is 579 for PLT recipients aged 17 to 40 years in the first year after transfusion.

However, for recipients older than 80 years the mortality rates become equal to those of the general population: for RBC recipients the difference disappears after five to eight years, for FFP and PLT only the first-year mortality rate is elevated. So for this age group survival of the general population can be used to estimate survival beyond 12 years after transfusion. For the other age groups, the difference between the mortality rate of the general population and the transfusion recipients seems to become constant after a few years. An illustration is given by the mortality rates after any RBC transfusion in the age group of 71 to 75 years, in Figure 4.

Figure 3 Standardized mortality ratios (SMRs) of transfusion recipients as function of time since any transfusion SMR is the ratio of the mortality rates of recipients after transfusion and mortality rates of the general population, adjusted for age and gender

Figure 3a Standardized mortality ratios of RBC transfusion recipients

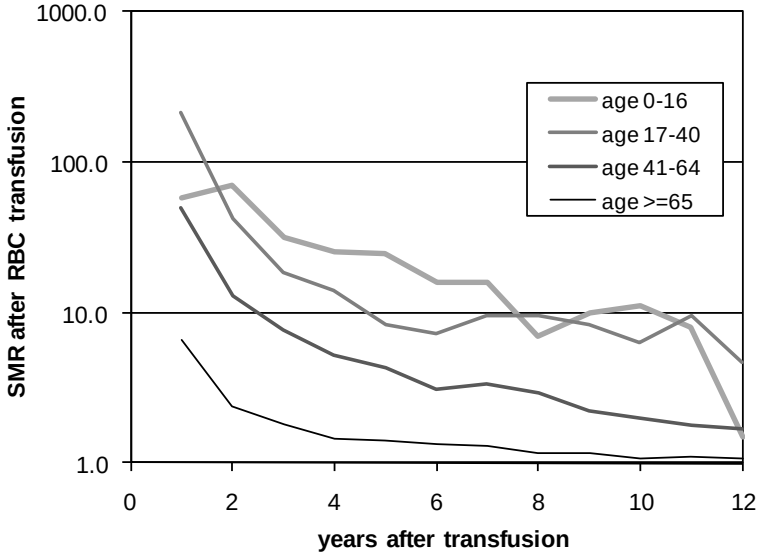


Figure 3b Standardized mortality ratios of FFP transfusion recipients

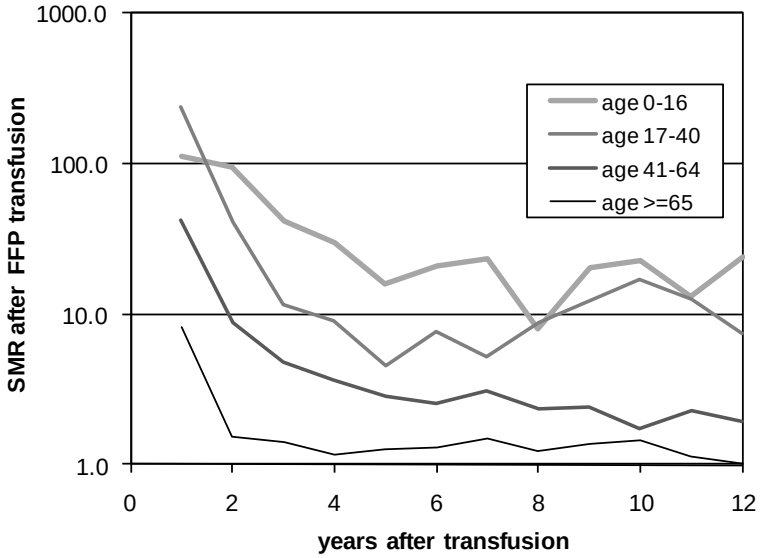


Figure 3c Standardized mortality ratios of PLT transfusion recipients

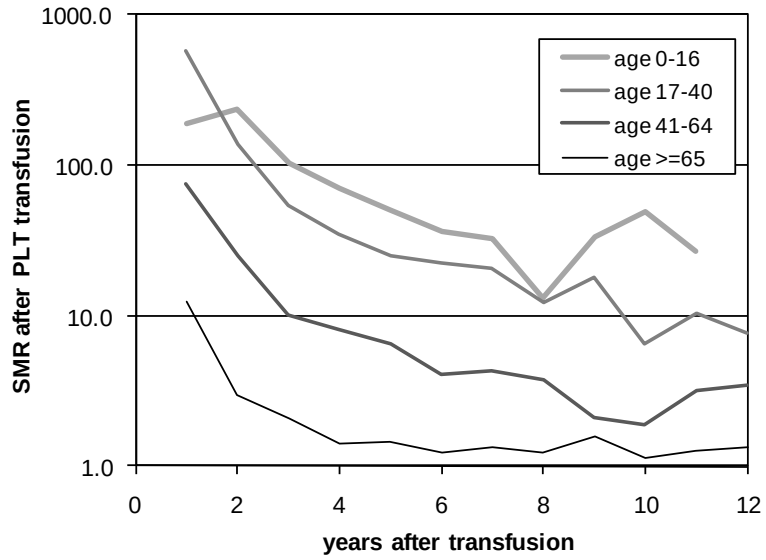
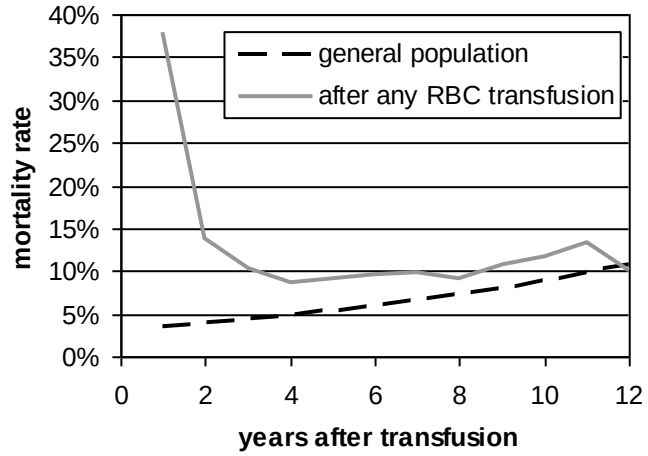


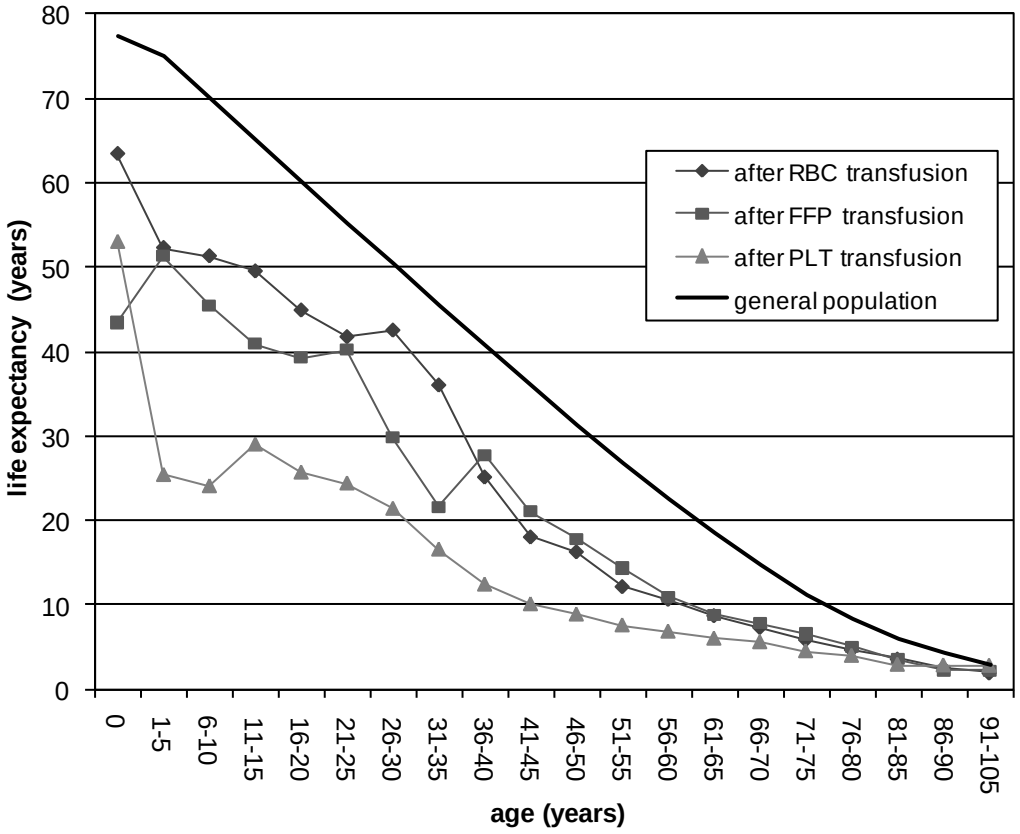
Figure 4 Example of stabilizing difference between the mortality ratio of RBC recipients and the general population (recipient age 71 to 75 years)



Hence, we calculated the mean differences between 8 and 12 years after transfusion, for each blood component type and age group. Assuming that the mortality rates beyond 10 years after transfusion remain increased by these constant levels, the life expectancy after any transfusion of RBC, FFP or PLT is calculated for each age group, as shown in Figure 5. The overall life expectancy after any transfusion is 12.9 years, while the overall life expectancy after first transfusion is 16.1 years. Adjusting general population control data for the gender ratio of transfusion recipients has no significant influence on the estimates of life expectancy, so this is effect neglected here. The life expectancy of the general population as a function of age is also shown. The assumption on the elevated mortality beyond 10 years after transfusion results in substantially lower life expectancies from that moment as compared to the life

expectancies in the general population: differences in estimated life expectancy up to 4 years are observed for RBC recipients, up to 10 years in FFP recipients and up to 15 years in PLT recipients. Note that the relative influence of this assumption diminishes over time, as mortality rates of an individual in the general population increases with age.

Figure 5 Life expectancy after any transfusion per type of blood component It is assumed that the mortality rates beyond 10 years after blood transfusion remain elevated by a constant rate (estimated per age group and blood component type)



Discussion

The difference between SFT and SAT

SAT is considerably lower than SFT, for all component types (Figure 1). This is caused by the fact that in general the number of transfusions per recipient is correlated with the severity of the disease and to patient mortality. This implies that the frailer recipients, who have lower survival rates, have a relatively large influence on the SAT, while all recipients have equal impact on the SFT. However, it should again be stressed that there is no causality between the number of transfusions given and the

higher mortality associated. Rather the reverse is true: more often patients who are severely ill, as a result of their severe illness require more transfusions.

The specific case of difference in survival of children and young adults after transfusion of FFP (Figure 2b) is a direct result of the diseases for which these recipients are transfused. Of all FFP transfusions in children aged 0 to 16, 28% is related to recipients with congenital anomalies (ICD-9 codes 740-759), while 23% of FFP units that are transfused to young adults between 16 and 40 years of age are given to injury patients (ICD-9 codes 800-999) and 15% to women due to childbirth complications (ICD-9 codes 630-679), who have high survival probabilities.[6]

Comparison with other studies

We found four studies that show overall SFT. Tynell et al. reported a lower SFT than we found in our recipient population in 2001.[11] This might be due to differences in the mean age at the time of first transfusion. In their study this was 66 years as compared to 60.6 years in our study. The SFT reported by Wallis et al. is also lower, for each component type considered.[8] In 2004 Kleinman et al. showed SFT for three age groups.[12] For all three groups the survival in the PROTON study is higher than in Kleinman's study. Also, results from the SCANDAT database showed a lower SFT than PROTON.[13] However, the median age at first transfusion was 69.9 in Denmark and 70.9 in Sweden (over the whole study period 1983-2002) and 62% of the recipients was 65 years or older at their first transfusion. The SCANDAT study shows survival for five age groups. We calculated the survival for the same age groups from the PROTON dataset, which resulted in similar survival after 1 year and after 5 years (data not shown). Therefore we consider the difference in survival to be due to the difference in age distribution of transfusion recipients in Scandinavia and in the Netherlands.

Only Wallis et al. presented SAT per blood component type, while SCANDAT showed SAT regardless of the type of blood component transfused.[8,9] For the UK region of Newcastle, Wallis et al. showed SAT that is significantly lower than our estimates, for each component type, while the age distribution of recipients at their first transfusion is similar to the recipient age distribution in the PROTON study (mean age 60.9 versus 60.6 years)[8] The association between the number of transfusions given and the decrease in survival probability described in the paper by Wallis was clearly confirmed by our data. From the SCANDAT database it was estimated that the overall life expectancy after transfusion in Denmark and Sweden is 10.4 years, versus 12.9 in our study.[9] This is most likely caused by the older recipient population in Denmark and Sweden.[13]

The reviewed studies all show higher mortality rates. These differences could be caused by differences in age of transfusion recipients, but in other cases remain unexplained. In these cases differences may be related to medical developments over time, as the PROTON study was performed more recently. In our relatively short observation period, we found that survival after transfusion (either SFT or SAT) improved over time. Also differences in clinical indication for transfusion, treatment protocols and clinical practice may underlie the differences found.

Strengths and limitations

The PROTON transfusion dataset allows reliable estimations of survival after blood transfusion. Even though not all studied hospitals provided data for the full observation period of 12 years, sufficient observations were available to create an accurate survival estimate. Nevertheless, it should be kept in mind that a minority of the recipients were followed for 12 years (yet still 14,319 RBC, 4,410 FFP and 1,985 PLT). Furthermore, blood use has changed over time and so has the survival of transfusion recipients. This renders it impossible to provide a suitable estimate of long-term survival for recipients that are transfused today, even when a dataset with a long time of retrospection is available. Still the data presented in this article are the best estimates currently available to support CEAs of blood safety interventions in the Netherlands. Despite possible differences in blood use and health care systems between countries, the data presented here may be used for health economic exercises in regions where detailed information on post-transfusion survival is lacking.[6]

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Appendix A

Table A1 RBC transfusion recipient age distribution and survival after any RBC transfusion according to recipient age

Age	% RBC	Time since RBC transfusion				
		1 year	2 years	3 years	5 years	10 years
0	1.7%	85%	84%	83%	83%	83%
1-5	0.5%	84%	80%	79%	78%	76%
6-10	0.4%	86%	83%	82%	80%	78%
11-15	0.7%	85%	81%	80%	79%	77%
16-20	1.3%	87%	85%	83%	82%	76%
21-25	1.6%	86%	84%	83%	81%	78%
26-30	2.6%	89%	87%	87%	86%	84%
31-35	3.1%	88%	86%	85%	84%	81%
36-40	2.9%	81%	77%	76%	73%	67%
41-45	3.2%	73%	68%	65%	61%	54%
46-50	4.3%	70%	65%	62%	58%	52%
51-55	5.8%	65%	59%	55%	51%	43%
56-60	7.2%	65%	58%	54%	48%	39%
61-65	9.1%	64%	57%	53%	47%	35%
66-70	12.1%	63%	56%	51%	44%	31%
71-75	14.6%	62%	54%	48%	40%	23%
76-80	13.3%	59%	50%	43%	34%	16%
81-85	9.0%	56%	46%	38%	26%	10%
86-90	4.6%	51%	37%	28%	17%	3%
91-105	1.7%	45%	31%	21%	9%	1%
all	100%	65%	58%	53%	47%	35%

Table A2 FFP transfusion recipient age distribution and survival after any FFP transfusion according to recipient age

Age	% FFP	Time since FFP transfusion				
		1 year	2 years	3 years	5 years	10 years
0	2.4%	73%	71%	71%	70%	69%
1-5	1.4%	79%	77%	76%	76%	74%
6-10	1.0%	80%	75%	74%	71%	69%
11-15	1.3%	77%	76%	75%	75%	71%
16-20	2.4%	83%	81%	80%	79%	76%
21-25	3.3%	88%	87%	87%	87%	83%
26-30	3.8%	83%	81%	80%	80%	76%
31-35	4.5%	82%	79%	78%	76%	69%
36-40	5.1%	85%	81%	80%	79%	75%
41-45	4.3%	74%	71%	69%	67%	60%
46-50	5.6%	74%	71%	69%	66%	61%
51-55	6.9%	74%	69%	66%	63%	56%
56-60	8.8%	68%	61%	58%	54%	43%
61-65	9.7%	69%	64%	60%	55%	39%
66-70	12.8%	66%	62%	59%	52%	35%
71-75	13.1%	65%	61%	56%	48%	28%
76-80	9.0%	60%	54%	50%	42%	19%
81-85	3.6%	48%	43%	39%	29%	11%
86-105	1.0%	43%	35%	28%	16%	0%
all	100%	70%	66%	63%	59%	46%

Table A3 PLT transfusion recipient age distribution and survival after any PLT transfusion according to recipient age

Age	% PLT	Time since PLT transfusion				
		1 year	2 years	3 years	5 years	10 years
0	4.5%	71%	70%	69%	68%	68%
1-5	4.1%	67%	61%	59%	58%	53%
6-10	2.2%	64%	58%	55%	51%	45%
11-15	3.3%	61%	54%	52%	51%	49%
16-20	2.8%	58%	55%	54%	52%	50%
21-25	3.0%	57%	51%	48%	46%	44%
26-30	3.4%	62%	54%	51%	48%	46%
31-35	4.4%	61%	53%	51%	50%	45%
36-40	4.7%	58%	52%	49%	44%	37%
41-45	5.9%	55%	44%	41%	35%	30%
46-50	6.5%	52%	42%	40%	35%	30%
51-55	8.8%	51%	42%	38%	34%	29%
56-60	9.8%	52%	44%	40%	35%	26%
61-65	9.7%	50%	42%	38%	34%	25%
66-70	9.4%	49%	42%	39%	34%	24%
71-75	9.2%	48%	42%	37%	32%	18%
76-80	5.6%	46%	40%	36%	30%	15%
81-105	2.8%	41%	35%	30%	21%	8%
all	100%	54%	47%	44%	39%	32%

Chapter 5

Cost-effectiveness of additional blood screening tests in the Netherlands

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Abstract

Background During the last decade, blood screening tests such as Triplex NAT and HTLV-I/II antibody testing were added to existing serological testing for HBV, HCV and HIV. In some low prevalence regions these additional tests yielded disputable benefits, that can be valuated by cost-effectiveness analyses (CEAs). CEAs are used to support decision making on implementation of new medical technology. We present CEAs of selected additional screening tests that are not uniformly implemented in the EU.

Study design and methods Cost-effectiveness was analyzed of: 1. HBV, HCV and HIV Triplex NAT in addition to serological testing, 2. HTLV-I/II antibody test for all donors, for first-time donors only and for pediatric patients only, and 3. HAV and Parvovirus B19 NAT for all donations. The disease progression of the studied viral infections was described in five Markov models.

Results The incremental cost-effectiveness ratio (ICER) of Triplex NAT is €5,199,220 per quality-adjusted life-year (QALY) for testing minipools of six donation samples and €4,647,062/QALY for individual donation testing. The ICER of testing all donations on HTLV-I/II is €45,182,666/QALY and the ICER of testing new donors only is €2,234,041/QALY. The ICER of HTLV-I/II testing of blood products for pediatric patients only is €26,984,140/QALY. The ICER of HAV NAT is €18,562,483/QALY.

Conclusion The resulting ICERs are very high, so these tests appear not to be cost-effective. Nevertheless they are implemented in the Netherlands and other EU member states. Policy makers could take ICERs into account more often before deciding on the implementation of additional blood screening tests.

Introduction

Apart from donor selection and exclusion, adding new screening tests to detect infectious diseases in blood donations is the most common strategy to improve the safety of blood product transfusions.[1] However, the rationale of additional testing has been debated, as the added health value may be relatively small, especially compared to the investments.[2] Cost-effectiveness analyses (CEAs) can support the decision process on candidate blood screening tests. Also, in theory, CEAs can be used to reconsider and eventually abandon particular blood safety tests if they are not cost-effective. In a CEA, the incremental cost-effectiveness ratio (ICER) is the principle outcome measure. The ICER is the ratio of the net incremental costs (intervention costs minus averted treatment costs) and the net effect of the intervention (usually expressed in terms of quality-adjusted life years gained: QALYs). The lower the ICER, the more effect is achieved per monetary unit spent. Thresholds for acceptable ICERs are usually made in a framework of a nation's public health policy and are subject to political processes.[3]

Currently, in the Netherlands all blood donations are subjected to a multi-stage screening protocol. All donations are screened for antibodies against hepatitis C virus (HCV), against human immunodeficiency virus type 1 and 2 (HIV-1/2) and against treponema bacteria. Also, all donations are screened on hepatitis B surface antigen (HBsAg). The new additional blood screening tests (ABST) performed in the Netherlands include 1. Triplex NAT assay for hepatitis B virus (HBV) DNA, HCV RNA and HIV RNA in minipools of six donation samples, 2. human T-cell lymphotropic virus type I and II (HTLV-I/II) antibody testing of each donation and 3. NAT for hepatitis A virus (HAV) DNA and Parvovirus B19 DNA in minipools of 480 donation samples. In addition, 100% leukodepletion of red blood cells (RBC), fresh-frozen plasma (FFP) and platelets (PLT) concentrates is performed, and all platelet concentrates are tested by bacterial culturing. The CEAs of leukodepletion and bacterial culturing were published elsewhere.[4,5]

In this article, the cost-effectiveness is analyzed of the following ABST:
1. Triplex NAT for HBV, HCV and HIV, in minipools of six donation samples (MP-6-NAT) or of individual donations (ID-NAT);
2. HTLV-I/II antibody testing for all donations (including plasma donations) as it is presently implemented, or alternative strategies: for first-time donors only or for pediatric patients only;
3. NAT for HAV and Parvovirus B19 in pools of 480 donations.

Methods

Costs calculations

The incremental costs for each ABST are defined as the additional testing costs minus the averted direct medical treatment costs, related to viral transmissions that are prevented by the studied interventions. ABST testing costs encompass the costs of additional testing as calculated within Sanquin financial department. Costs include those for reagents, disposables, personnel, overhead and investments [personal communication with H. Bos].

The number of recipient exposures to blood products

All analyses start with determining the annual number of exposures of recipients to transfused blood products. This number equals the total number of blood products distributed by Sanquin Blood Supply Foundation minus the estimated number of non-used blood products in the hospitals. Sanquin provided information on the number and types of blood products distributed to each Dutch hospital. To estimate the percentage of blood products that is distributed to hospitals but not transfused to patients, information from hospitals was needed. Therefore 20 Dutch hospitals (that participated in the PROTON study[6]) were sent a questionnaire concerning the proportion of RBC, FFP and PLT delivered by Sanquin that was not used in the year 2008, due to outdating, leakage or other reasons. The mean percentage of reported non-use per blood component type was calculated for academic and general hospitals separately. Combining these means, adjusting for the number of transfusions per hospital category, resulted in estimates of the proportion of non-used RBC, FFP and PLT in the Netherlands. The total blood use minus the resulting total number of non-used blood components gives the real annual number of blood product transfusions.

The numbers of possibly averted viral transmissions by ABST

In the following, we describe how the annual number of avoided infections was estimated for each ABST separately. Triplex NAT will reduce the length of the window period (WP) for HIV, HCV and HBV detection. The WP is a period during which donors are infected while their viral load and/or antibody level is too low to be detected. The WP incidence model can be used to estimate how many infected donations would be detected by Triplex NAT that are not found by classical serological testing.[7] The WP incidence model states that the WP as fraction of the year times the incidence of the virus among repeat donors provides an estimate for the annual probability that a blood product is infected but will not be found by the test. Multiplying this probability with the number of exposures yields the number of transmissions not avoided by the test. We applied the WP model both for NAT and for serological tests. The difference between the outcomes is the additional number of transmissions

avoided by NAT compared to serological testing only. For HIV, HCV and HBV infections it is assumed that transfusion of any Triplex NAT positive blood product will result in transmission of the given virus to the recipient. The effects per virus are assumed to be independent. This is plausible because the probability of viral transmission through blood transfusion is so small that the probability of acquiring multiple infections is negligible.

In the Netherlands, all blood products are currently screened for anti-HTLV-I/II antibodies. HTLV-I/II is a retrovirus mainly transmitted by RBC and PLT and it is generally considered not to be transmitted by FFP.[8,9] From the number of infections found in first-time donors in the years 2000 to 2008, the prevalence of HTLV-I/II among new donors is estimated. Multiplying the prevalence of HTLV-I/II in new donors with the total number of transfused RBCs plus five times the number of transfused PLTs (as PLTs are produced by pooling of 5 buffy-coats) gives the number of infected products that are prevented to enter the blood transfusion chain by testing new donors only, compared to no testing. This number is higher than the number of infections found, because untested donors may donate several times. HTLV-I/II has an incubation time of 10 to 20 years, so donors can be asymptomatic carriers for a long time, while continuing to donate blood. The mean number of new HTLV-I/II infections per year among repeat donors in the years 2000 to 2008 (the incidence) is used to estimate the effect of testing all donations. This number is multiplied by half the mean length of a whole blood donor career (because on average the infection will take place halfway) and by the mean number of donations per year. This gives the additional number of infected donations that will not enter the blood production process when testing all donations instead of new donors only. To estimate the number of transmissions avoided for both testing strategies, we used information on the number of RBC and PLT distributed to hospitals, outdating in hospitals (as described above) and estimates of the transmission probability of HTLV-I/II from a HTLV-I/II-positive blood product after leukodepletion.[10] The number of transmissions averted by testing blood products for pediatric patients (0 to 16 years of age) only is estimated by multiplying the effect of testing all donations with the fraction of RBC and PLT that is transfused to this age group, as estimated in the PROTON study.[6]

The incidence of HAV among donors is estimated using national reported HAV cases in 2008 [personal communication with Ingrid Friesema, National Institute for Public Health and the Environment]. Multiplying the annual HAV incidence with the period of viremia before the onset of symptoms and the total number of blood products transfused in 2008 yields an estimate of the number of HAV infected products that enters the blood supply chain when no testing would be performed. Here it is assumed that donors with symptoms of hepatitis do not donate and that other donor

selection procedures do not diminish the probability of HAV-infected persons to donate. Information on HAV immunity by age among the Dutch general population is used to estimate the number of infections in transfusion recipients that are averted by testing.[11] Human Parvovirus B19 can be transmitted by blood components and pooled products have been implicated in some transmissions in the past, generating the decision for producers of plasma products to screen.[12] However, transfusion transmission is a rare event and in general then does not cause disease.[13-17] Hence, in the absence of data showing clear systematic clinical benefits for recipients, which would allow us to include in mathematical modeling, we assume that the positive effect of a combined NAT test for HAV and Parvovirus B19 DNA consists of the health effects of avoiding HAV infections.

Modeling disease progression

The disease progression after an infection with HBV, HCV, HIV, HTLV-I/II or HAV is described in five independent Markov models. The outcome parameters are the expected number of QALYs gained by preventing one single infection in a recipient and the expected treatment costs due to one single infection. A lifelong time horizon is used. All models are dependent on age at infection. Consequently, expected QALYs gained and treatment costs are computed for each age stratum of one year separately. The mean expected QALYs gained and treatment costs are the sum of these outcomes per age stratum, weighted according to the distribution of blood products over recipient ages, as obtained in the PROTON study.[6] Multiplying the mean QALYs gained and treatment costs by the expected number of avoided infections yields the total QALY gain and avoided costs.

For the disease progression after HBV infection, we use the model described in our cost-effectiveness analysis of HBV-NAT.[18] It consists of two parts: an event tree for the acute phase of the infection and a Markov model with five health states, including liver cirrhosis and hepatocellular carcinoma. For each health state and for each year after transfusion, the model estimates mortality, health care costs and quality of life.

The acute phase of HCV infection after blood transfusion was modeled according to Pereira and Sanz.[19] The Markov model that describes the disease progression of chronic hepatitis C in the Netherlands was published earlier.[20] This model was an adapted and updated version of a model reported by Siebert et al.[21] It consists of nine health states, including liver cirrhosis, hepatic encephalopathy and hepatocellular carcinoma.

A two-state Markov model is used to describe the disease progression of an HIV infection.[22,23] First the patient is in the asymptomatic stage for 8.7 years on average. In the second stage the patient will receive antiretroviral therapy (ART) and the

annual probability of dying as a result of AIDS is 14% in the first year and 10% in subsequent years.

For HTLV-I/II, we use the model presented by Stigum et al.[24] In 5% of the cases, HTLV-I/II infection results in Adult T-cell Leukemia (ATL) after 25 years on average, which causes death within one year. Only 1% of the HTLV-I/II infections results in Tropical Spastic Paraparesis (TSP) 10 years after infection. Patients with this disease survive 20 years on average. Stigum et al. obtained the quality of life of patients suffering from TSP or ATL by interviewing chronically ill people, which gives a relatively low estimate of the quality of life lost. The model is run separately for RBC and PLT with their respective survival rates, as the HTLV-I/II transmission probability differs for each of these products.

The disease progression of HAV infection was modeled by Jacobs et al.[25] The model starts with an event tree for the acute phase, where immunity according to age is incorporated.[11] The probability that a HAV-infected person will have symptoms depends strongly on the age at infection and ranges from 7% for children below 5 years to 90% for infected persons over 70 years of age. Symptomatic patients of HAV are ill for 39 days on average, after which the virus is cleared. Only a very small proportion of the infected recipients will suffer from liver failure, for those patients a lower survival is modeled. We implemented the costs similar to the HBV model, as treatment costs from Belgium probably reflect the Dutch treatment costs better than cost estimates from the US do.

In all models, age distributions and recipient survival after transfusion derived from the PROTON study are implemented.[6,26] In the PROTON study, information was collected on 290,043 patients who received 2,405,012 blood products during the years 1996 to 2006 in 20 Dutch hospitals. Age distributions were estimated per blood component type and survival after transfusion was estimated per blood component type and age group of five years. Quality of life (QoL) after transfusion is approximated using the QoL of an individual in the general population with a similar mortality rate. For example, the mortality rate of a 28-year-old patient in the third year after RBC transfusion is 0.0091.[26] In the general Dutch population, this mortality rate is found in individuals of age 60.[27] We therefore presume the transfused patient has a QoL equivalent to that of a 60-year-old person from the general population. According to a study conducted in the UK, the QoL in the general population can be approximated by the formula 0.9397-0.0024*age.[28] QoL of an individual infected through transfusion is calculated by multiplying the QoL after transfusion with the QoL after infection. All treatment costs were updated to 2008 euro's using consumer price-indexes as provided by OECD.

All future QALYs are discounted at a rate of 1.5% per year and treatment costs at a rate of 4% per year, as recommended for health economic evaluations in the Netherlands.[29]

Sensitivity analysis

Monte Carlo simulations were performed for all models, to obtain confidence intervals for the outcome parameters and to investigate to which variables the model outcomes are most sensitive. This sensitivity is expressed in terms of standardized regression coefficients (SRCs). Pert distributions were used to model uncertainty of most parameters in the Markov models. Ranges given in the source articles of the models were used, as far as available. Treatment costs were assumed to vary between 0.5 and 2 times the point estimates. Incidences were assumed to follow Beta(a,b) distributions, where a is the number of cases and b the total number of observed donor years. Confidence intervals for survival rates after transfusion were obtained in the PROTON study.[26] Testing costs, discount rates and the age distribution of transfusion recipients were considered to be fixed. All models were evaluated without discount rates to investigate the influence of discounting. Also, all models were evaluated with the quality of life after transfusion set to 1, but still considering the QoL loss due to the transmitted virus. This allows comparing the results with other studies, as those did not correct for QALY loss after transfusion.

Computational issues

Data management and analysis was performed using Stata/SE (version 9.2 for Windows, StataCorp LP, College Station, TX, USA). Graphs were created using Excel (version 2003, Microsoft Corporation, Redmond, WA, USA). Simulations and sensitivity analysis are performed with an add-in for MS-Excel (@Risk Professional Version 5.5.0, Palisade Corp., Ithaca, NY).

Results

The main numerical results of this study are summarized in Table 1.

Table 1 Main results of cost-effectiveness analyses

Test		Cases prevented	QALYs gained per case	Cost per case prevented	ICER
Triplex NAT for HBV, HCV and HIV in minipools of 6 donation samples	HBV	2.55	0.29		€ 5,199,220
	HCV	0.51	0.25		
	HIV	0.16	4.32		
Triplex NAT for HBV, HCV and HIV for individual donations	HBV	2.92	0.29		€ 4,647,062
	HCV	0.53	0.25		
	HIV	0.21	4.32		
HTLV antibody test, new donors		2.22	0.005	€ 11,579	€ 2,234,041
HTLV antibody test, pediatric recipients		2.53	0.018	€ 480,542	€ 26,984,140
HTLV antibody test, all donors		0.24	0.005	€ 232,319	€ 45,182,666
HAV NAT		1.06	0.029	€ 544,698	€ 18,562,483

The number of transmissions avoided

The short questionnaire on non-use of blood products delivered to hospitals was filled out by 19 out of 20 hospitals. We estimate that 2.0% (95% CI: 1.3-2.6%) of RBC, 7.4% (95% CI: 4.0-11.7%) of FFP and 7.0% (95% CI: 5.4-9.9%) of PLT distributed to Dutch hospitals in 2008 was not transfused to a patient. In 2008, Sanquin Blood Supply Foundation distributed 545,222 RBC units, 92,568 FFP units and 50,784 units to hospitals in the Netherlands. PLT are produced by pooling of 5 buffy-coats. Hence, there were in total 856,314 donor-recipient exposures, through some of which infections might have been transmitted.

With Triplex MP-6-NAT as compared to serological testing, the WPs will be reduced with 29.7 days, 63.6 days and 11.4 days for HBV, HCV and HIV respectively. With Triplex ID-NAT as compared to serological testing, the WPs will be reduced with 34.0 days, 66.3 days and 14.9 days for HBV, HCV and HIV respectively.[18,30,31] The mean incidence rates of HBV, HCV and HIV among repeat donors in the years 1996 to 2008 were 1.22, 0.34 and 0.60 per 100,000 donor years, respectively.[32] Hence, it is estimated that MP-6-NAT will avoid 2.55 HBV, 0.51 HCV and 0.16 HIV infected products per year to be transfused. ID-NAT is estimated to avoid 2.92 HBV, 0.53 HCV and 0.21 HIV infected products per year to be transfused.

In the Netherlands, persons must be between 18 and 69 years old to be allowed to donate blood. In 2008, 110 cases of HAV were reported in the Netherlands in people between 18 and 69 years of age.[personal communication with Ingrid Friesema, National Institute for Public Health and the Environment] It is estimated that 30% of the clinical cases were reported. In 2009, the Netherlands had 11 million inhabitants

aged between 18 and 69 years.[33] From these numbers the incidence of HAV among donors is estimated at 4.3 per 100,000 donor years, assuming that the incidence of HAV among donating donors is similar to the incidence in the general population. An HAV-infected person can be viremic for 7 to 14 days before the onset of symptoms, so this is the period during which the silently infected person could donate blood.[34] Hence, it is estimated that 1.06 (95% CI: 0.91-1.21) HAV contaminated blood products per year will be averted to enter the blood supply chain by HAV NAT.

During the years 2000 to 2008, 17 HTLV-I/II infections were found in the Netherlands: 12 in repeat donors and 5 in new donors.[35] In total, 365,483 new blood donors were observed during these years, so the prevalence of HTLV-I/II among new donors is estimated at 3.28 per 100,000 donors. With these numbers, it is estimated that testing new donors only will avoid 17.9 RBC and 8.3 PLT containing HTLV-I/II to be distributed to hospitals. Of all WB donors in 2007, 11.6% was not a donor anymore in 2008, so the mean WB donor career is estimated to last 8.7 years.[36] The mean number of WB donations per donor was 1.69 in 2008. Hence, we estimate that another 2.6 infected RBC and 1.2 infected PLT per year will not enter the blood production process when testing all donations instead of new donors only. The computation behind these numbers is as follows: the probability for a repeat donor to get infected with HTLV-I/II is 5 infections per 9 years, so the annual probability is 5/9. This infection happens on average halfway the donor carrier, so there are 8.7/2 donation years left with 8.7/2*1.69=7.3 donations. This makes 7.3*5/9=4.07 infected donations per year, of which 63% results in a RBC product and 29% results in a PLT product. The transmission probability of HTLV-I/II after an infected RBC transfusion is 20% (range 13-28%) and after an infected PLT transfusion it is 50% (range 25-75%).[10] After leukodepletion these transmission probabilities are reduced with 70%. Thus, it is estimated that 2.22 HTLV-I/II transmissions per year are avoided by screening new donors only and 2.53 HTLV-I/II transmissions per year are avoided by screening all donations. In the Netherlands, 3.6% of all RBC and 14.7% of all PLT are transfused to recipients between 0 and 16 years of age.[6] Testing blood products for these patients only is estimated to avoid 0.24 HTLV-I/II transmissions per year (0.04 through RBC and 0.20 through PLT transfusion).

Cost and effects

For all five viruses, the QALYs gained are graphed in Figures 1 to 6, together with the corresponding age distribution of transfusion recipients.[6] For HTLV, two graphs show the results for the RBC and PLT models. These were run separately, because of the difference in transmission rate between these products.

Figure 1 QALYs lost after HBV transmission to recipients per age

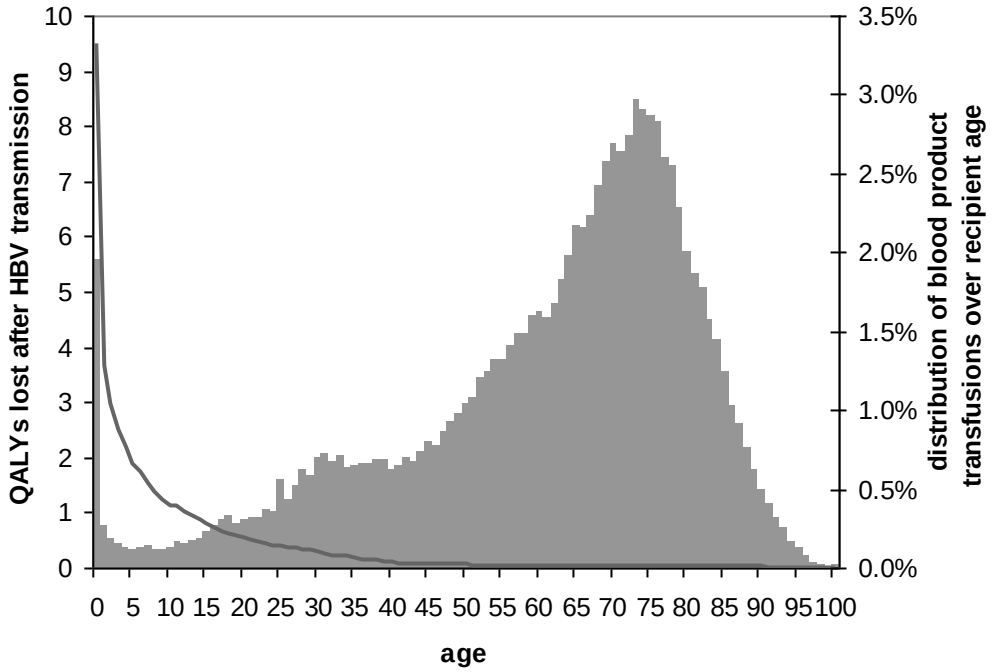


Figure 2 QALYs lost after HCV transmission to recipients per age

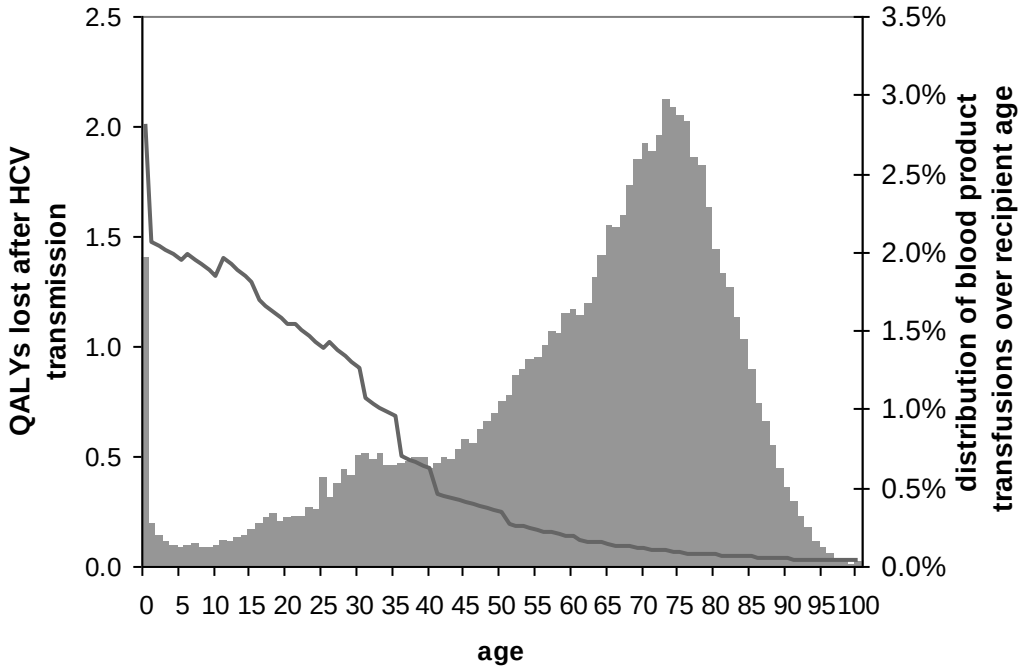


Figure 3 QALYs lost after HIV transmission to recipients per age

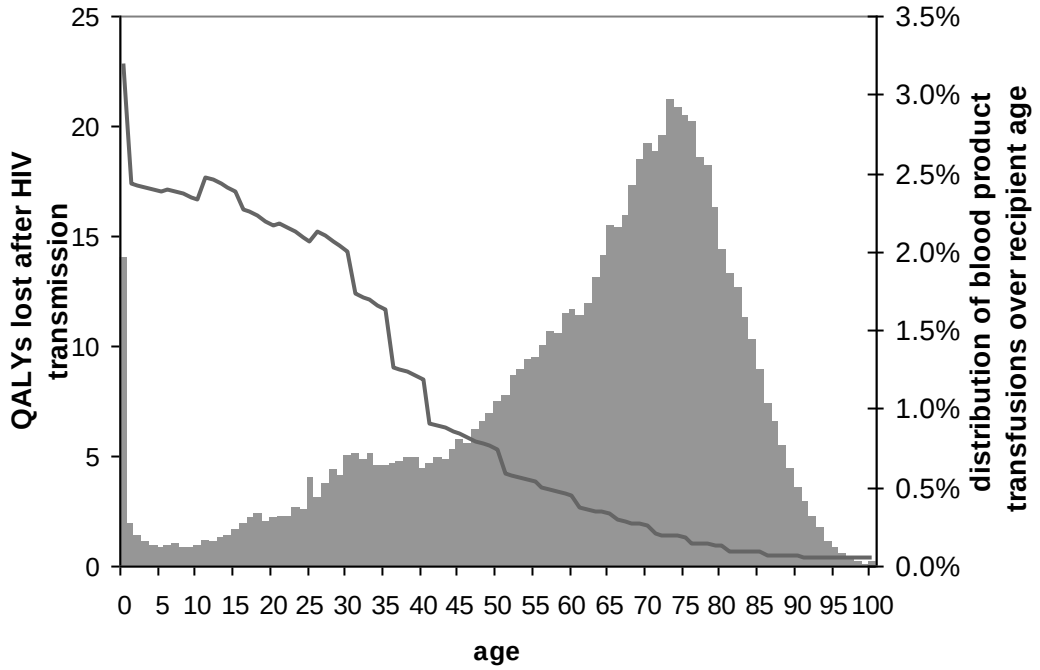


Figure 4 QALYs lost after HAV transmission to recipients per age

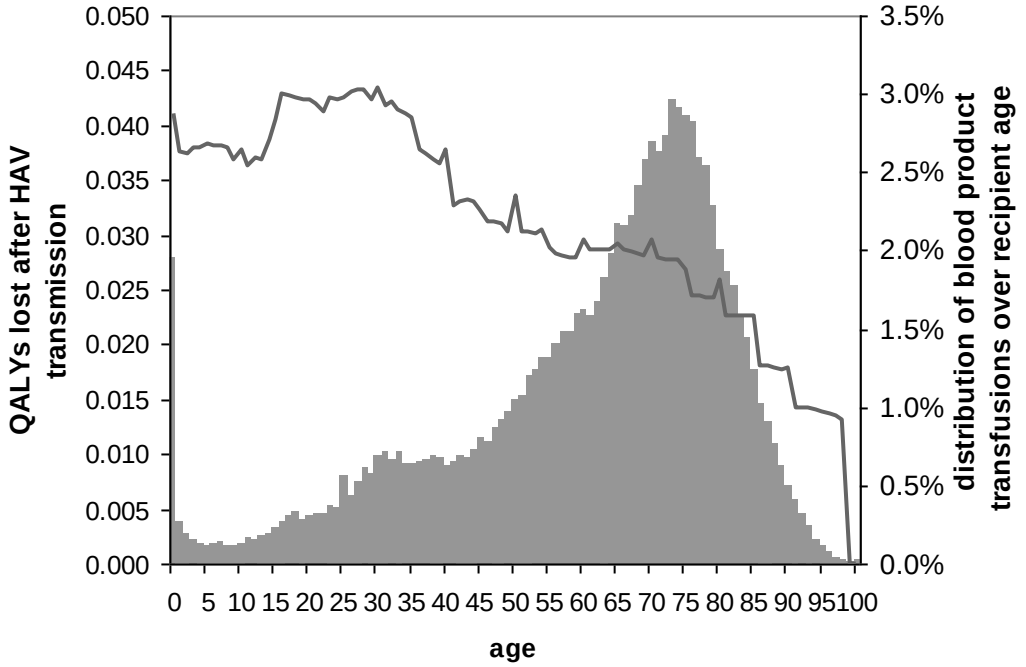


Figure 5 QALYs lost after HTLV transmission to RBC recipients per age

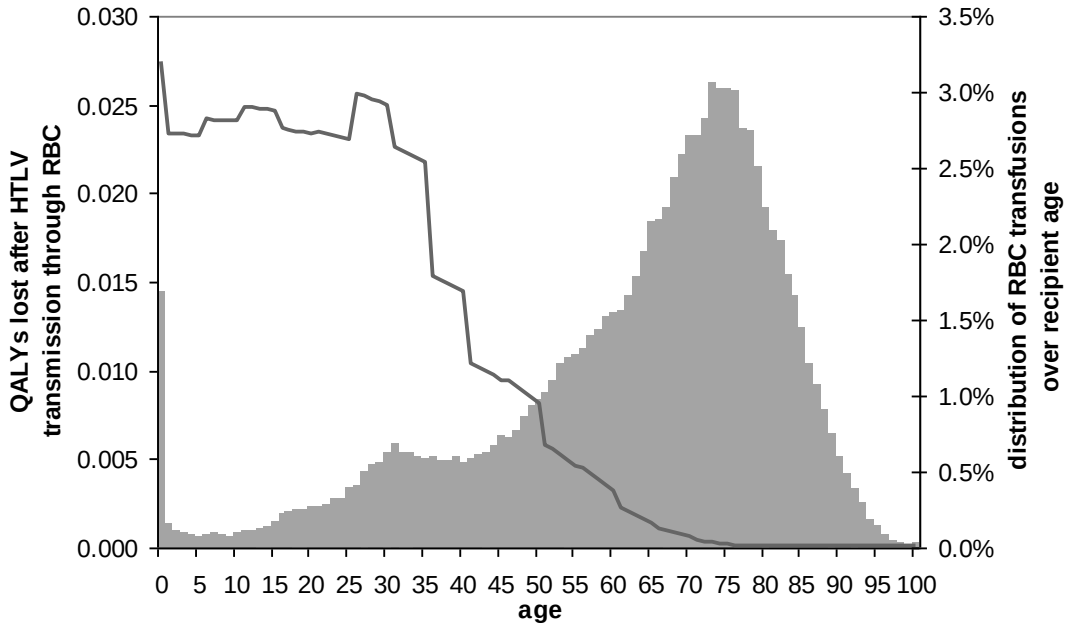
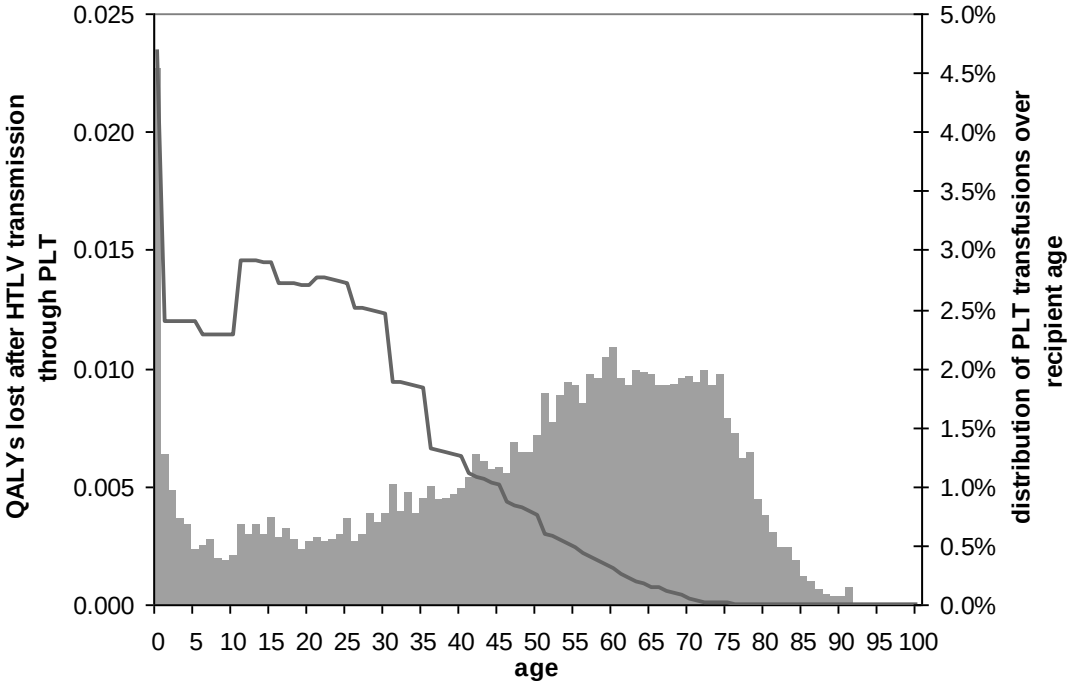


Figure 6 QALYs lost after HTLV transmission to PLT recipients per age



The estimated costs of the Triplex NAT test for HBV, HCV and HIV are €8,178,609 per year for testing minipools of six donation samples and €8,777,832 for individual donation testing. [derived from personal communication with H. Bos, Sanquin Blood Supply Foundation] The HBV model estimates that 0.29 (95% CI: 0.27-0.31) QALYs are gained and €530 treatment costs are averted per prevented HBV infection. Per

HCV infection prevented, 0.25 (95% CI: 0.18-0.32) QALYs are gained and €365 treatment costs are avoided. Per HIV infection prevented, 4.32 (95% CI: 4.18-4.46) QALYs are gained and €52,072 treatment costs are avoided. These numbers result in ICERs of €5,199,220 (95% CI: 4,401,529-6,354,062) per QALY for the Triplex NAT in minipools of six donation samples and €4,647,062 (95% CI: 3,914,104-5,694,730) per QALY for Triplex NAT of individual donations.

Screening for HAV and Parvovirus B19 costs €0.89 per donation.[personal communication with H. Bos, Sanquin Blood Supply Foundation] In total, there were 569,953 whole blood (WB) donations and 80,097 donations for quarantaine (donor-retested) plasma in the Netherlands in 2008, so the total testing costs are €578,367. The prevalence of anti-HAV in the Netherlands depends strongly on age and ranges from 2% in young children to 86% in people older than 75 years.[11] The reported fractions of immunity are incorporated in the Markov model. This results in 0.029 QALYs are gained and €347 treatment costs averted by avoiding one transfused HAV infected blood product. Thus, the ICER of screening all donations on HAV is €18,562,483 (95% CI: €16,322,800-€21,459,170) per QALY.

HTLV-I/II testing of all donations costs €0.68 per donation. When testing new donors only, this becomes €0.90 per donation. [personal communication with H. Bos, Sanquin Blood Supply Foundation] The HTLV-I/II model estimates that 0.0049 (95% CI: 0.0034-0.0069) QALYs will be gained by avoiding one transmission through RBC transfusion and 0.0053 (95% CI: 0.0037-0.0070) QALYs will be gained by avoiding one transmission through PLT. Discounted treatment costs of €95 and €98 will be avoided, respectively. This yields ICERs of €45,182,666 (95% CI: €23,666,430-104,352,200) per QALY for testing all donations and €2,234,041 (95% CI: €1,134,902-5,611,531) per QALY for testing new donors. In pediatric patients, avoiding one transmission through RBC leads to 0.026 (95% CI: 0.018-0.033) QALYs gained and avoiding one transmission through PLT leads to 0.016 (95% CI: 0.011-0.022) QALYs gained. Treatment costs in pediatric patients of €357 and €234 will be avoided, respectively. Testing blood products for pediatric patients only will also cost €0.90 per donation, so the testing costs for this group are €114,417. This results in an ICER of testing pediatric patients on HTLV-I/II of €26,984,140 (95% CI: €14,054,850-€63,909,720) per QALY.

Sensitivity analysis

The treatment costs avoided are negligible as compared to the costs of testing, so all ICERs are proportional to the QALYs gained by testing. The ICERs of Triplex MP-6-NAT and ID-NAT are primarily dependent on the incidence of HIV among donors (SRC -78% and -75% respectively), the incidence of HBV among donors (SRC -53% and -56%) and the incidence of HCV among donors (SRC -15% and -18%). The ICER

of HAV NAT is primarily dependent on the number of days the patient is infectious but not symptomatic (SRC -73%) and the estimated incidence among donors (SRC -65%). The ICERs of HTLV-I/II antibody testing are primarily dependent on the prevalence of HTLV-I/II among repeat donors (SRC around -64%), the probability on adult T-cell leukemia (SRC around -40%) and the probability of transmission of HTLV-I/II either through RBC or PLT.

If costs and QALYs are not discounted, the ICERs of the Triplex NAT tests become 40% lower and the ICERs of HTLV-I/II antibody testing become 30% lower. Discount rates hardly influence the ICER of HAV NAT, as most of the health loss occurs in the acute phase of infection. If the QoL after transfusion is discarded (which allows comparison of the results with other studies), all ICERs become around 20% lower.

Discussion

Interpretation of the results

There are governmental guidelines proposing a cost-effectiveness threshold for clinical interventions in the Netherlands of €80,000 per QALY.[29] The discussion remains on the appropriateness of applying this threshold to ICERs of blood safety interventions. Nevertheless, it is clear that the screening tests analyzed in this article incur high costs per QALY gained.

Strengths and limitations of the models

The CEAs presented in this article differ from other studies in two ways. First, we implemented detailed data on the recipient age and survival after transfusion into the disease progression models. Especially when the disease progression of an infectious disease depends on recipient age, this significantly affects the estimated ICER. Second, we accounted for a reduced QoL in the transfusion recipient population.

Although our analysis provides better estimates of CEAs of blood safety interventions, there is still room for further improvements. For example, we assumed that a donation during the WP of an infection with HBV, HCV or HIV always results in an infected recipient. Actually, it should be taken into account that infectivity is minimal just after infection of the donor and increases over time, as the virus multiplies in the infected donor.[37] However, more research is needed to enable such enhanced modeling. As in other studies, we ignored secondary infections, e.g. in partners of transfusion recipients. Including the effect of avoiding such infections would yield lower ICERs. This effect might be considerable as the (healthy) partners of transfusion recipients are generally expected to have substantially higher life expectations. However, as this is not considered in any other studies on blood safety measures, it would reduce comparability of our study results with others.

The ICERs depend strongly on the reference case considered. The ICERs of the HAV and HTLV-I/II tests were compared to "no testing" as the reference case. The effectiveness of Triplex NAT for HBV, HCV and HIV would be much higher if it would completely replace serological testing instead of being implemented alongside. On the other hand, when a relatively expensive screening test is already implemented, an additional test may appear to be quite cost-effective, while the combination of tests is not cost-effective at all. For example, the CEA for HBV NAT presented in our earlier article motivated Sanquin Blood Supply Foundation to replace Triplex NAT in minipools of 24 donation samples with Triplex MP-6-NAT. However, this article shows that NAT is not cost-effective at all when added to serological testing.

Cost-effectiveness for pediatric recipients only

Averting infectious diseases in pediatric transfusion recipients will in general yield a higher QALY gain. Thus, it might appear that performing a blood test for young recipients only is far more cost-effective than testing all donations. This raises the question whether "safer blood" should be preferably assigned to patients with a relatively high life expectancy after transfusion. Especially when the disease progression of the transfusion transmitted infection amplifies the dependency on age at infection, as in the case of hepatitis B, it might be defendable to perform screening tests with a high ICER for pediatric patients only. Also, it might be reasonable to perform extra safety measures for blood products transfused to immunocomprised patients, as these patients in general do not have longer survival after transfusion, but higher disease burden of the infection. On the other hand, all older people have a lower life expectancy and if there is no difference in the disease progression of the disease, it can be considered unethical and age discrimination to perform a test solely for young people because of the better cost-effectiveness.[38]

Comparison with other studies

A number of cost-effectiveness studies on the screening of blood products have been performed in the past. Comparison of ICERs is quite hard, due to the wide ranges of possible tests and healthcare settings. Therefore, we limit the following discussion to the implementation of transfusion recipient profiles in other CEA's, as this is the new feature in our study. Various sources are used to model age distribution of transfusion recipients and survival after transfusion. Vamvakas and Taswell[39] are referred to in a number of articles.[19,40-44] They calculated survival in a cohort of 802 patients that were transfused in 1981 in a USA county, with 10 years of follow-up. Tynell et al. analyzed the cost-effectiveness of screening donors on HTLV-I/II.[45] They use data on 255 patients transfused in 1992 from a pilot study in a single region. These data included the age of the patient, survival after transfusion, and type of blood components transfused. Stigum et al. modeled the cost-effectiveness of testing

all new blood donors on HTLV-I/II, using survival two years after transfusion in four age groups from Norwegian blood banks.[24] In 2004, Marshall et al. showed a CEA of Triplex NAT in which costs and health consequences were estimated for three age cohorts. They used data from a managed-care administrative claims database to estimate the age distribution of transfusion recipients and survival up to five years after transfusion. The authors of this article performed cost-effectiveness analyses using recipient age data from a Dutch pilot study from 1997, including 817 patients.[4,18] We conclude that the PROTON study fills a gap of information that is needed for cost-effectiveness analyses of blood screening interventions. With these data, cost-effectiveness analyses of blood safety measures can be improved and refined, which results in more reliable estimates of ICERs.

Future research

Despite high ICERs, blood banks and regulators continue to implement new blood screening tests. There are several other considerations in favor of implementation: fear of image loss, potential claims of patients who become infected and infect their partner, and product liability for the safety of blood transfusion. Ideally, the insurance costs, liability claims and possible loss of donors should be incorporated in CEAs of blood safety interventions. It is difficult to quantify these factors, but decision makers might consider CEAs of blood safety more useful when these concerns are taken into account.

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Chapter 6

Demographic changes and predicting future blood supply and demand in the Netherlands

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Mart Janssen
Cees van der Poel

Abstract

Background Concerns have been raised that aging of the general population will increase the demand for blood products. Modeling can be applied to assess trends in blood demand and supply and predict how these will develop over time.

Study design and methods We developed mathematical models to describe and predict the national demand of red blood cell (RBC) products. The first demand model assumes that the mean numbers of transfusions per inhabitant per age and sex are constant. A second demand model incorporates observed changes in clinical blood use over time. Further, a donation model is developed to predict future RBC supply. To estimate the supply of whole blood donations, we used annual donor retention rates, donor recruitment rates, and mean numbers of donations per donor year.

Results The model based on demography only predicts an increase of 23% in RBC demand over 2008 to 2015. The second model, incorporating both demographic changes and trends in clinical RBC use, predicts a decrease of RBC demand by 8% over the same period. The predicted RBC supply closely follows the demand as predicted by the second model.

Conclusions Despite an aging population, RBC demand may not increase as much as predicted in other studies. This depends on the extent to which other effects, like that of optimal blood use, will neutralize the effects of aging of the transfusion recipient population. Still, the observed downward trend in donor recruitment in the Netherlands must be stopped to maintain a sufficient RBC supply.

Introduction

Concerns have been raised that aging of the general population may result in an increased demand of blood products, as a large proportion of blood products is transfused to elderly patients.[1-3] In an ongoing study on characteristics of transfusion recipients, it was observed that in 2006 59% of the red blood cell (RBC) products in the Netherlands was transfused to patients aged 65 years or older.[1] Statistics Netherlands (the national governmental bureau of statistics) predicts that the fraction of Dutch inhabitants of 65 years or older will increase from 14.7% in 2009 to 17.8% in 2015.[4] On the other hand, programs for optimal or restricted blood use have been advocated and implemented in the Netherlands and elsewhere.[5-8] The effectiveness of such programs may vary, but a decrease in RBC demand per inhabitant is observed in the Netherlands, United Kingdom, Switzerland, and Finland in the Council of Europe surveys on blood demand in the years 2001 to 2005.[9] Blood establishments need to prepare and predict how aging and optimal blood use will influence the demand of blood products, to plan for supply and donor management. The aim of this article is to use mathematical modeling to assess trends in RBC demand and supply and to predict how these will develop over the next 5 years.

Materials and methods

Age and sex of RBC recipients

The Netherlands is and has been self-sufficient for blood components for many years. Hospitals are provided, according to their demand, by one national holder (Sanquin Blood Supply Foundation) of the license to collect homologous blood and plasma donations. The number of RBC units distributed by Sanquin to the hospitals of the Netherlands therefore equals the total national demand, because there is no substantial export of blood components. We do not consider fresh-frozen plasma or platelets here, because the demand for RBCs determines the number of whole blood donations donors needed. The total number of RBCs distributed by Sanquin to hospitals is known for the years 1980 to 2007. Age and sex of Dutch RBC recipients for the years 1997 to 2006 are obtained from the PROTON data set, which contains information on 2.4 million blood product transfusions given in 20 Dutch hospitals.[1] Statistics Netherlands yielded historical and future information on age and sex of the general Dutch population.[4]

We calculated the national RBC transfusion incidence as the mean number of RBCs distributed per inhabitant of the Netherlands per age and sex stratum. To predict future RBC demand of hospitals, it is assumed that the probability of non-use of an RBC unit (due to outdating, leakage, lost units, etc.) is independent of the blood recipient profiles and therefore evenly distributed. We developed two models that

describe RBC demand in the Netherlands. These two models are used to predict future RBC demand. Model estimates of RBC demand in past years are used to assess the validity of both models.

Demand Model 1: RBC transfusion incidence per age and sex is constant

For Demand Model 1, it is assumed that the RBC transfusion incidence per age and sex stratum is constant over time. [2,3] Data for 2006 are used to fit two smooth curves for the RBC transfusion incidence as a function of age, one for men and one for women. The assumption behind the smoothness of the model is that the RBC transfusion incidence for a particular age does not differ much from incidence of an adjacent age stratum. The only exception is the age stratum of 0 years, which is treated as a single observation, as the group of neonates forms a distinct cluster of patients with a peak RBC transfusion incidence. The RBC demand, both in future and in past calendar years, is estimated by multiplying the numbers of inhabitants in that year, per age and sex stratum, with the corresponding RBC transfusion incidences of 2006 and summing them. The same procedure is performed with RBC transfusion incidence data from 1997, to validate how well the model fits to data from the past.

Demand Model 2: RBC transfusion incidence per age and sex changes over time

Data from 1997 to 2006 are used to create a generalized additive model, which estimates the RBC transfusion incidence as a function of age, sex, and calendar year.[10] This Demand Model 2 presumes that the shape of the RBC transfusion incidence curve as a function of age and sex does not change over time, but it is multiplied by a smooth time function. Age curves are fitted again, both for men and for women. Again, age 0 is modeled separately. The RBC demand in future and past calendar years is estimated by multiplying the numbers of inhabitants of the Netherlands in that year, per age and sex, with the corresponding RBC transfusion incidences from Demand Model 2 and summing them.

Available donation data

A data set containing information on all successful whole blood donations from 2000 to 2008 is extracted by Sanquin Blood Bank from the national donor database (eProgesa). For three of four blood bank regions of the Netherlands, all data from 2000 to 2008 were included. For one blood bank region, only donation data from 2006 to 2008 were available, because they joined the eProgesa database as of 2006. To retrospectively study trends in donor population characteristics over time, data from the three blood bank regions with data on 2000 to 2008 were used. Over the years 2006 to 2008, on average 3% of the whole blood donations did not result in the distribution of an RBC unit to a hospital. We therefore presumed that the number of RBCs distributed to hospitals is 0.97 times the total number of whole blood donations.

Input and assumptions for the donation model

A decline in the annual total number of whole blood donations over time is observed, as well as a decline in the mean number of donations per inhabitant aged 30 to 50 years. In contrast to being a good predictor of transfusion demand, demography is found to be a bad predictor for the (decreasing) number of donations. This can be explained by the number of donors and donations being dependent on donor recruitment efforts and donor management by the blood bank. Therefore, demographic changes of the general population were not included in the donation model.

We defined the 1-year retention rate of a donor as the probability that a donor with a successful donation in calendar year *x* donated again in year *x+1*. The 2-year retention rate is defined as the probability that a donor with a successful donation in calendar year *y* did not donate in year *y+1*, but had a successful donation again in year *y+2*. All retention rates were calculated according to age and sex, for the years 2000 to 2008. It appeared that both 1- and 2-year retention rates barely changed over time. Hence, it is reasonable to assume, for modeling purposes, that both 1- and 2-year retention rates are constant over time. For the donation model, retention rates per age and sex stratum were calculated using donor data from the years 2006 to 2008 for all four blood bank regions.

We defined a new donor in year *x* as a donor who had at least one successful donation in the observation year *x*, but neither had a successful donation in year *x–1* nor in year *x–2*. From the donation data of three blood bank regions with data on 2000 to 2008 it appeared that a small percentage of about 3.3% of the "new donors" in 2008 actually did donate earlier than 2006. In the donation model we neglect this. The annual number of new donors declined with 24% between 2002 and 2008 in three of four blood bank regions. Only for the ages 18 to 22 an increased influx was observed: there were 29% more new donors in this age group in 2008 compared to 2002. The number of new donors depends on the recruitment effort by the blood bank. Therefore, any assumption on future influx of new donors is disputable. One could continue the downward trend, but the blood bank informed us that they did not actively recruit during many years, due to a declining demand. At present, the Dutch blood bank is aware of the urgency for additional donor recruitment to maintain sufficient blood supply. We chose to study what would happen in case the new donor influx would remain constant. Hence, the influx of new donors is assumed to remain constant from 2008 onward.

The mean number of donations per donor per calendar year (donation frequency) was calculated for the years 2002 to 2008, per age, sex, and donor category: new donor or repeat donor. The mean annual donation frequency showed an increase

from 2.4 to 2.7 donations per year for male repeat donors and 1.7 to 1.8 donations per year for female repeat donors during the years 2000 to 2008. However, donation frequencies did not increase from 2006 onward and were similar in the years 2006 to 2008. Hence, for the model it is assumed that the mean annual donation frequencies will not increase any further and 2008 donations frequencies are used to predict the future number of donations.

Donation model

The donation model is based on data from 2006 to 2008 (as specified above), because data from all four blood bank regions are available for these years. In 2008, there were 394,587 blood donors in the Netherlands, including 336,203 whole blood donors. This means that 3.5% of the Dutch inhabitants in the ages between 18 and 69 years is registered as a blood donor. To estimate the number of donations for 2009, the numbers of donors in 2008 per age and sex stratum were multiplied with the corresponding 1-year retention rates and the corresponding mean number of donations per donor per year. Next, the numbers of donors in 2007 per age and sex stratum were multiplied with the corresponding 2-year retention rates and the mean number of donations per donor year. Summing these numbers yielded the predicted total number of donations in 2009, donated by repeat donors. Adding the number of donations from new donors in 2008 resulted in the total number of donations in 2009. Using the 2009 results, this procedure was repeated to estimate the number of donations in 2010. The procedure was repeated until all predictions of the number of donors and donations for the years 2010 to 2015 were calculated.

Software

Donation and transfusion data were analyzed using computer software (Stata/SE, Version 9.2 for Windows, StataCorp LP, College Station, TX). The demand models were created using the *mgcv* library in R (Version 2.8.1, 2008, The R Foundation for Statistical Computing, Vienna, Austria). Graphs were created using spreadsheet software (Excel, Version 2003, Microsoft Corp., Redmond, WA).

Results

Prediction of blood demand

The observed RBC transfusion incidence per age and sex in the general population in 1997, 2001, and 2006 is shown in Figure 1. Predictions of RBC demand using RBC transfusion incidences from 1997 and 2006, respectively (Demand Model 1) are shown in Figure 2. Based on demography alone, Demand Model 1 predicts that the demand for RBCs will increase over time. Both versions (using 1997 or 2006 incidences) of Demand Model 1 do not yield a good retrospective estimate of the total RBC demand for the years 1999 to 2006. In contrast, it is remarkable how well

Demand Model 1 fits the RBC demand in the years 1984 through 1998, when using 1997 data as reference. This indicates that the trend change toward "optimal blood use" started around 1997. Demand Model 2 results in smoothed incidence curves as a function of age, per calendar year and sex, which are plotted in Figure 1 for 4 different years. As Figure 2 shows, Demand Model 2 predicts RBC demand to decrease with 8% between 2008 and 2015. Further, Demand Model 2 provides a much better retrospective estimate of RBC demand in the years 1999 to 2006 than does Demand Model 1.

Figure 1 Demand model 2: Observed and estimated RBC transfusion incidence per recipient age and sex in the Netherlands in 1997, 2001 and 2006.
Note: Eight outliers are not shown in these graphs.

Figure 1a Male inhabitants

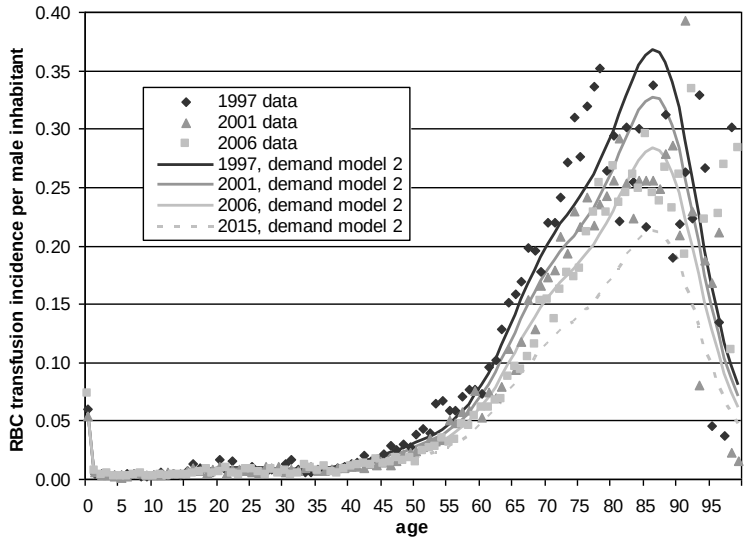
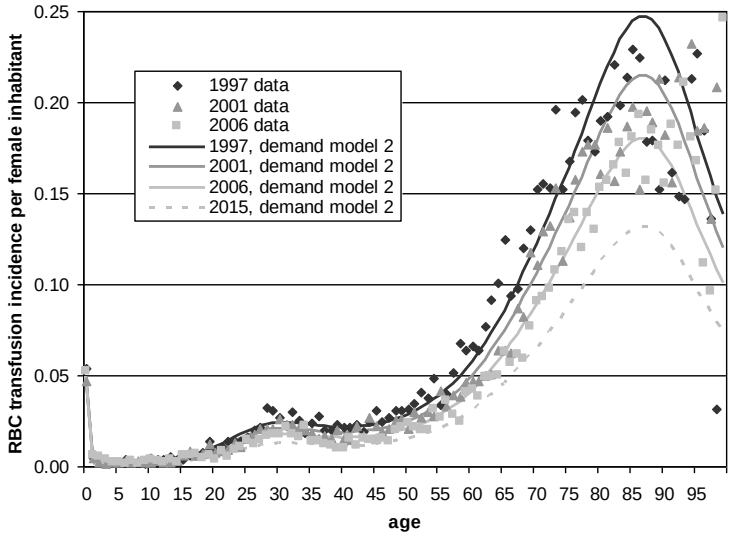


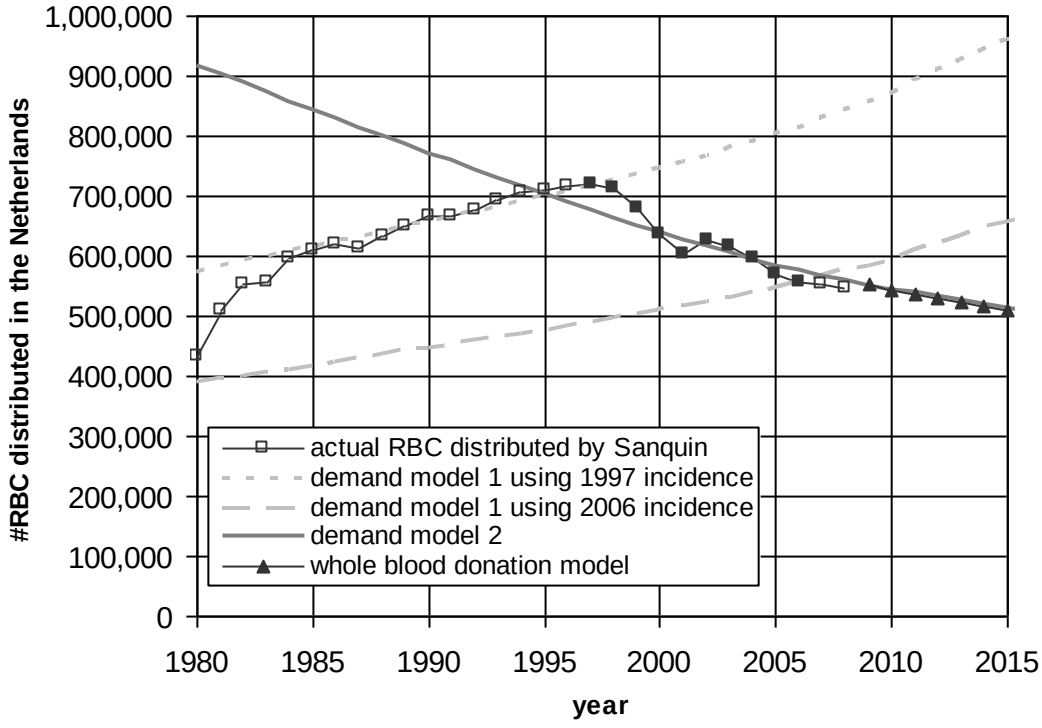
Figure 1b Female inhabitants



Prediction of blood supply

The donor model predicts that in 2015 the number of donations will be 9% less than in 2008. This is very close to the decrease in RBC demand that was predicted by Demand Model 2. The predicted RBC supply is shown in Figure 2 as well. A shortage of approximately 4000 RBC units per year (0.7% of total RBC demand) is expected as of 2011, provided that the number of new donors and their age composition remains unchanged. However, in case the decrease in RBCs in blood demand per inhabitant will discontinue and demography will direct, a shortage of up to 150,000 units (23% of total RBC demand) in 2015 is expected. In that case more effort has to be put into the recruitment of new donors to guarantee sufficient blood supply in future. To do so, at least, the decreasing trend in the influx of new donors in the Netherlands must be halted.

Figure 2 Predictions of total RBC demand and supply The boxed line shows the annual number of RBC units distributed in the Netherlands. Filled boxes represent years from which data are used to construct Demand Model 2.



Discussion

Comparison to other studies

Two other studies on prediction of RBC supply and demand were published elsewhere. In 2004, Currie and colleagues[2] used transfusion data from two large hospitals in the United Kingdom. In 2007, Greinacher and colleagues[3] used data from a region with 415,000 inhabitants in Germany. Both assumed that the RBC transfusion

incidence per age and sex stratum would remain constant. We showed that modeling RBC recipients using demography data alone (Demand Model 1) is sufficient to retrospectively fit the RBC use in the Netherlands up until 1997. However, beyond that year the RBC demand is hugely overestimated by this model. Our more elaborate Demand Model 2 provides a more accurate model for the prediction of blood use. It facilitates global changes in blood use over time. These changes might result from developments in clinical practice (like blood-saving methods). Demand Model 2 uses the total number of RBCs distributed in 1997 to 2006 and information on age and sex of RBC recipients in those years.[1] This model allows a prediction of RBC demand in the near future, assuming that RBC demand per inhabitant of particular age and sex will continue to decrease.

Currie and coworkers[2] and Greinacher and coworkers[3] predicted future blood supply too, using demographic data. However, by studying the donor population in the years 2000 to 2008, we observed that the number of donations is more affected by donor retention rates and the influx of new donors from recruitment activities than by the demography of the general population. Therefore, our donation model does not contain any demographic trends of the general Dutch population. We also note that the proportion of inhabitants aged between 18 and 69 years (eligible donor age limits in the Netherlands) changes very slowly: from 68.1% in 2008 to 67.8% in 2015, according to predictions by Statistics Netherlands.

Strengths and limitations

Our Demand Model 2 incorporates the influence of clinical practice, by modeling RBC demand as a function of time and demography. Hence the model assumes that the reduction of the RBC demand per inhabitant of particular age and sex will continue. However, it is unknown which medical insights and procedures will affect the blood use in the future. Surgical techniques and intervention radiology could further reduce RBC use. It is also unknown which newly introduced therapies might increase the demand of blood.

In our calculations, it was assumed that the annual total number of new donors and their age-sex composition remain the same from 2008 onward. This is an optimistic assumption, because the number of new donors has decreased significantly over the past years, especially in the age group of 30 to 50 years. On the other hand, it is impossible to predict how many new donors will be recruited in the future, as this primarily depends on recruitment efforts managed by the blood bank.

Interpretation of the predictions

Demand Model 2 predicts that continuation of the trend in clinical practice may counterbalance the effects of changing demography on blood demand. The actual

RBC use in the coming years is most likely to lie between the two predictions of Demand Models 1 and 2, because the optimization of blood use is likely to stabilize over time. Nevertheless, we expect the second demand model to be closer to reality. Because the two predictions divert between an 8% decrease and 23% increase of RBC demand over the next 5 years, it remains critical for blood establishments to closely and continuously observe trends and changes in clinical blood use. We recommend future research on developments and trends in RBC use in various patient groups. Trend analyses of data from studies such as the PROTON study, containing detailed information on discharge diagnoses of transfusion recipients, may provide more refined predictions of blood use. Expert opinion elicitation on medical developments in relation to blood transfusions for the major RBC-using patient groups can be used to refine the model and improve the robustness of the predictions.

One may think that our predictions of RBC demand and supply are in line because the blood bank anticipates donor management according to demand. However, the input variables of the demand and supply models are in fact very different (demography vs. donor behavior). Furthermore, we assumed that the decreasing trend in the annual number of new donors would stop while on the other hand we assumed that the decreasing trend in blood demand due to optimal blood use would continue. Hence, it is quite surprising that the predictions of demand and supply are so close together.

The following data are required to predict future blood use for any other country: 1) transfusion data including recipient sex and age, 2) age distributions of the general population over time, and 3) detailed information on donors and donations. In our publication on the PROTON study we described how recipient data can be obtained if no national registry is available.

In conclusion, other studies indicate that demographic changes of recipient populations would endanger the blood supply. However, our study shows that more variables need to be taken into account, such as the (changes in) clinical use of blood and donor attrition. Apart from demography, data on transfusions in hospitals and data on donor behavior are essential, as well as information related to policy changes. Our models showed that the effect of the aging population on the demand of blood products may be largely counterbalanced by other factors, like optimal blood use strategies. Blood use may therefore not increase as fast as predicted in other studies. Still, the observed downward trend in donor recruitment in the Netherlands must be stopped to maintain a sufficient RBC supply.

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General discussion

The PROTON study: profiles of transfusion recipients

Why collecting transfusion recipient data?

Information on age, gender, diagnosis and survival of blood product transfusion recipients is useful to support answering many research questions.[1] First, recipient information is needed to analyze cost-effectiveness of blood safety interventions, as the effects are obtained in the recipients. In the first chapter of this thesis it was shown that the age distribution of transfusion recipients is a very sensitive parameter for the cost-effectiveness of HBV-NAT in minipools of 6 donations or for individual donations compared to testing minipools of 24 donations. Second, transfusion recipient data can be used to predict future demand and supply of blood products. With an aging population, it is important to predict future need of blood products to enable anticipatory strategies in donor recruitment, as most blood is given to elderly patients. Third, monitoring blood use gives insight in the existing transfusion practices and the results of new medical developments. Interventions can be evaluated that aim at reducing the number of blood products needed. Benchmarking between hospitals and countries supports critical evaluation of existing clinical practice and possible areas of improvement.

For the Netherlands, transfusion data are stored in hospital computer systems and not in a national registry. In Denmark and Sweden, a national database (SCANDAT) is available with information since 1966 and complete data are stored in that database as of 1996 for Sweden and 2002 for Denmark.[2] However, this SCANDAT dataset cannot be used for Dutch cost-effectiveness analyses, as blood use differs between countries: in the Netherlands 37 units of red blood cells were used per 1,000 inhabitants in 2004, against 73 per 1,000 Danish inhabitants in 2000-2002 and 51 per 1,000 Swedish inhabitants in 2004.[3,4] So, the motivation to create a Dutch transfusion dataset is clear.

The PROTON dataset

It was decided to work with a sample of hospitals, because it would take much effort to collect the data: first, the hospitals needed to be convinced that it was possible and useful to participate in this study and second, all data must be encrypted within the hospitals and personally brought to Statistics Netherlands (in Dutch: Centraal Bureau voor de Statistiek, CBS). Then the data needed to be cleaned, appended and matched to other data. A transfusion dataset that covers 30% of the total Dutch blood use was aimed at. The final PROTON dataset covers 28% of the total blood use in the Netherlands in 1996 to 2006. The hospital samples are representative per hospital category, because the age and diagnosis distribution of all inpatients in the participating academic and general hospitals appeared to be similar to those distributions in all Dutch academic and general hospitals, respectively. A method to

estimate national distributions of transfusion recipient characteristics was developed, as presented in Chapter 2. The results are thorough estimates of how blood products are distributed over various recipient groups, where in the past only educated guessed could be made.

Benchmarking blood use

'Optimal blood use' means to avoid overuse, underuse, and inappropriate use.[5] The decreasing annual number of red blood cell units used in the Netherlands already indicates that optimizing blood use has been widely introduced with great effect. PROTON data can be used to study this phenomenon in more detail and monitor the effect of new developments. Hospitals can compare their blood use with national estimates. The first step towards this so-called benchmarking was to return a report to each hospital that participated in the PROTON study, with the analysis results of the provided data. These reports contained the distributions as shown in Chapter 2 for the Netherlands as a whole: distributions of age and gender per component, distributions of the number of transfusions per recipient and, if the hospital provided diagnosis data itself, the distribution of blood products over diagnosis groups.

The SCANDAT researchers did not yet publish distributions of blood components over recipients. Other studies on recipient distributions and/or survival after transfusion resulted in smaller and more regional datasets than ours. Comparison of those studies with the PROTON results showed that there are considerable differences in the profiles of blood product recipients between countries, probably reflecting differences in clinical practice. Comparing data from different countries in a benchmark could highlight potential areas where further optimizing of blood use might be possible.

Analyzing survival after transfusion

Survival rates after transfusion are needed for cost-effectiveness analyses. Much effort was put in finding the right method to analyze survival of transfusion recipients, as described in Chapter 3. It appeared that the conventional Kaplan-Meier estimator could be used to construct survival curves, but the confidence intervals around those curves can only be obtained by bootstrapping recipients and not by the standard intervals around Kaplan-Meier curves. In Chapter 4, the results of applying these methods to the whole PROTON dataset are shown. It appeared that Dutch recipients survive better after transfusion than the recipients in older studies from abroad. Differences in the profiles of blood product recipients cause the survival rates after transfusion to vary across countries as well.

Cost-effectiveness of blood screening tests

In Chapter 5, the PROTON data were plugged into models to analyze the cost-

effectiveness of screening blood donations on infectious diseases. The resulting incremental cost-effectiveness ratios are very high: millions of euro's must be invested to gain one quality-adjusted life year. Still such blood screening tests are implemented in many countries. This raises some questions that are discussed in the next section.

Predicting future blood use

Sanquin Blood Supply Foundation asked us to use PROTON data for prediction of future blood use. As described in Chapter 6, we developed models for supply and demand of red blood cell units. PROTON data were combined with demographic data to predict the demand and data on donors and donations were used to analyze trends in blood supply. The result was surprising: the model outcomes were very close to each other. Nevertheless, it was concluded that the decrease in the number of new donors has to be stopped to maintain a sufficient supply of blood products.

Economic evaluations of blood safety interventions

Why study cost-effectiveness?

In the Netherlands, inhabitants are obliged to be insured for healthcare expenses. Since this does not result in an infinite budget for public healthcare, it has to be decided which medical interventions are paid by the public resources (that means: by us). One of the decision criteria for this is the cost-effectiveness. In the Netherlands, there is no hard consensus on a threshold, but medical interventions with an ICER lower than €20,000 are considered "cost-effective", while interventions with an ICER higher than €80,000 are considered not cost-effective.[6] The ICERs of (additional) blood screening tests on infectious diseases are often much higher, as shown in Chapter 1 and 5. This has not always been the case: the first tests on antibodies for HIV were cost-saving at the time of implementation.[7] However, introduction of stricter donor selection criteria reduced the prevalence and incidence of infectious diseases among donors. Also, the stacking of tests causes the effects to be lower: the additional effect Triplex NAT for HBV, HCV and HIV would be much higher if it would replace the antibody tests instead of being implemented alongside. It is remarkable that CEAs are used to decide on implementation of tests, but they have not yet been used to withdraw a test. If a relative expensive test is already introduced, an additional test may appear to be quite cost-effective, while the combination of tests is not cost-effective at all. This can be illustrated by the two CEAs shown in this thesis: the CEA for HBV NAT presented in Chapter 1 motivated Sanquin Blood Supply Foundation to replace Triplex NAT in minipools of 24 with Triplex NAT in minipools of 6 donations. However, in Chapter 6 it is shown that this test is not cost-effective at all when compared to serological testing only.

Missing factors in cost-effectiveness analyses of blood safety interventions

In practice, it seems like the high ICERs do not withhold the blood bank from implementing blood screening tests. Maybe a special threshold should be defined for ICERs of blood safety interventions. However, I do not think this will solve the dilemma. There are serious reasons for implementing particular blood safety interventions although they are not cost-effective. First, blood banks are legally accountable for blood safety.[8] Recipients that have an adverse event as a result of blood transfusion might claim the blood bank for compensation. Sanquin Blood Supply Foundation is insured for this, which is quite expensive. However, not all risks can be covered by insurance. In 1992, two French blood bankers were sentenced to prison for supplying HIV-infected clotting factors to hemophiliac patients.[9] The former director general of the Health Ministry was convicted too. They were involved in the decision not to use heat treated clotting factor concentrates from 1983, because they believed the French blood supply to be safe. At the same time, drug users and practicing homosexuals were not excluded from donating blood yet. Also, French politicians were prosecuted for introducing the ELISA test for blood product screening on HIV only eight months after it was available. In France, in total around 4,000 people (mainly hemophiliacs) were infected with HIV through blood products. Although not all these cases were avoidable, it illustrates the size of the issue. Also in Germany, Switzerland and Japan blood bankers as well as politicians were prosecuted in the '90s for HIV transmission through blood products between 1983 and 1993, while safety interventions were already available. In more than 20 countries, compensation was offered to patients infected with HIV through blood products. The 'infected blood scandal' has certainly changed the way blood bankers perceive risks.

The second reason for implementing expensive blood tests that are not cost-effective lies with the general population. People find it hard to accept that available safety interventions are not performed because of money. The probability of an adverse event may be very low, but people intuitively overestimate the risk of rare events.[10] Moreover, recipients do not choose voluntarily to receive a transfusion, they just need it. This also causes the risk to be perceived as higher than it actually is and people find it less acceptable. If the press reports adverse events due to blood transfusion, this damages the reputation of the blood bank. A good image is essential to maintain the number of donations, which depends on voluntary blood donors.

The result is that decisions are based on availability of safety technologies and cost-effectiveness is hardly taken into account. Ideally, the costs and effects of the insurance, possible compensation claims and possible loss of donors should be incorporated in CEAs of blood safety interventions. It is hard to quantify these factors, but decision makers might consider CEAs of blood safety more as a useful tool when their concerns are taken into account.

Future research

Improving estimates of cost-effectiveness of blood safety interventions

In Chapter 5, a first step was made to incorporate quality of life after transfusion into cost-effectiveness models for blood safety interventions. It was assumed that quality of life is associated with the mortality rate. Another approach is to use the diagnosis codes to estimate quality of life according to recipient diagnosis. Furthermore, we did not include the effect of preventing secondary infections. Other studies also did not include this, probably because many uncertain parameters should be estimated. Nevertheless, this is an important area for further research, because the secondary infections will usually happen in people that do survive better than transfusion recipients. The number of QALYs gained per prevented infection will be much higher if secondary infections are taken into account.

Sanquin Blood Supply Foundation has an expert group to decide on measures against new infectious diseases. A pre-defined decision support model which would encompass both an assessment the risk of infectious diseases and the cost-effectiveness of safety interventions would facilitate and enhance this decision making process.[11]

Improving data collection

From June 1st, 2009, all hospitals in the Netherlands record the Citizen Service Number (Burgerservicenummer, BSN) of each patient. This is a huge improvement for administrative purposes. First, a patient can be followed in various hospitals, where different patient numbers were used before. Second, the matching procedure to CBS data (LMR and GBA) will be improved: there is a higher matching percentage and a lower chance of false matches. For the PROTON study, matching was performed by birth, gender and address. This can lead to errors e.g. for twins and rest-homes.

Other blood safety measures

The high ICERs for additional viral testing suggest that we should better spend our health care budgets on adverse transfusion events that do occur more often. For example, administrative adaptations might reduce the chance of transfusion of the wrong blood product. The question is: how much would patient be willing to pay for hospital personnel to check things even better? Research on risk groups among donors may given insight in the effects of excluding particular donor groups to reduce the number of acute transfusion reactions, like fever, allergic reactions, and transfusion related acute lung injury (TRALI) in particular patient groups.[12] PROTON data can be used as a control group to investigate whether TRALI occurs more often after transfusions from particular donors or in particular recipient groups. It is

suggested that the shelf-life of blood products (time from donation to transfusion) may be associated with lower survival after transfusion and a higher probability of TRALI.[13] PROTON data can be used to investigate whether this is true. Another alternative to screening all blood donations for an infectious disease is to restrict the screening to particular recipient groups. PROTON data are essential to support cost-effectiveness analyses for all these blood safety interventions.

Conclusion

I showed that it is possible to collect transfusion data from hospital computer systems. I also showed that the inpatients in the sample of hospitals we used are representative for the Netherlands, when categorized into academic and general hospitals. The results presented in this thesis are only a fraction of possible analyses of the PROTON dataset. Many other useful analyses can be thought of. Studying blood use over time per diagnosis group allows better models to predict the future need of blood products. Monitoring and analyzing blood use over time will give insight in the impact of new medical developments on the actual use and distribution of blood products. The effects of efforts to optimize blood use in particular patient groups can be directly visualized by studying selected PROTON data. The number of applications of transfusion recipient data and the success of the PROTON study will hopefully result in regular updates of the dataset.

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Abbreviations

ABST	additional blood screening test
ATL	adult T-cell leukemia
AVR	active viral replication
BPI	blood product issued
BPT	blood product transfusion
CBS	Statistics Netherlands, Centraal Bureau voor de Statistiek
CEA	cost-effectiveness analysis
FFP	fresh frozen plasma
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HTLV	human T-cell lymphotropic virus
ICD	international classification of diseases
ICER	incremental cost-effectiveness ratio
ID	individual donation
MP-6	minipools of 6 donations
MP-24	minipools of 24 donations
NAT	nucleic acid amplification testing
PLT	platelets
PROTON	profiles of transfusion recipients
QALY	quality-adjusted life-year
QoL	quality of life
RBC	red blood cell(s)
SAT	survival after transfusion
SCANDAT	Scandinavian Donations and Transfusions database
SFT	survival after first transfusion
SRC	standardized regression coefficient(s)
TSP	tropical spastic paraparesis
WB	whole blood
WP(s)	window period(s)

Summary

Quantitative information on the fate of blood products issued to hospitals is needed to analyze the cost-effectiveness of blood safety interventions such as nucleic acid amplification testing (NAT), leukocyte depletion or pathogen reduction. To know 'where the blood goes' is necessary for estimating the beneficial effects of safety interventions in terms of health gain in the recipients. Information on blood donors, donations and BPI is carefully registered by blood establishments in many countries, as in the Netherlands. Additionally, hospitals must register personal and clinical information on recipients of the blood products, in line with EU regulations. However, no national registry of transfusion recipients exists. In this thesis, the PROfiles of TransfusiON recipients (PROTON) study is presented. The aim of this study was to describe the distribution of blood product over patient groups in the Netherlands. This study resulted in the first national dataset including characteristics of blood product recipients in the Netherlands.

In Chapter 1, a cost-effectiveness analysis of a nucleic acid test for hepatitis B virus is presented. The aim of this study was to estimate the incremental cost-effectiveness ratio (ICER) in the Netherlands of employing a triplex NAT assay aimed at HBV nucleic acid detection in individual donations (ID-NAT) or in minipools of six donations (MP-6-NAT), compared to a triplex NAT assay in minipools of 24 donations (MP-24-NAT). A mathematical model was made of the whole transfusion chain from donors to recipients of blood in the Netherlands. The annual number of avoided HBV transmissions was estimated with the window-period incidence model. The disease progression after HBV infection in recipients is described by a Markov model. The ICER of adding HBV MP-6-NAT or HBV ID-NAT in the Netherlands was estimated to be €303,218 and €518,995 per quality-adjusted life year, respectively.

When this analysis was performed, the PROTON study had just been initiated. The age distribution from a study of 1000 donations in 1997 was used in this analysis. Preliminary results from the University Medical Center of Utrecht were used for modeling the survival of transfusion recipients. It was shown that the ICER strongly correlates with the age of transfusion recipients and with the corresponding survival after transfusion. This implies that accurate transfusion recipient data are needed for correct estimation of cost-effectiveness, for the effect of blood safety interventions is obtained in the blood product recipients.

In Chapter 2, the main part of the PROTON study is described. A sample of 20 of 93 Dutch hospitals was selected. Datasets containing all blood product transfusions between 1996 and 2006 (as far as possible) were extracted from hospital blood bank computer systems, containing transfusion date, blood product type and recipient characteristics such as gender, address, date of birth. The datasets were appended and matched to national hospitalization datasets including primary discharge

diagnoses (ICD-9). Using these data, distributions of blood recipient characteristics in the Netherlands were estimated. The resulting PROTON dataset contains information on 290,043 patients who received 2,405,012 blood components (1,720,075 red blood cell products, 443,697 fresh-frozen plasma products, 241,240 platelet products) from 1996 to 2006. This is 28% of total blood use in the Netherlands during this period. Diagnosis and age distributions of hospitalized patients in the participating hospitals were comparable to those distributions in all hospitals in the Netherlands. This indicated the PROTON hospital sample to be representative for the Netherlands, distinguishing per hospital category (academic, general and cancer hospitals). Of all red blood cells (RBC), fresh-frozen plasma (FFP) and platelets (PLT), respectively 1.7%, 2.5% and 4.5% were transfused to neonates. Recipients of 65 years or older received 58% of RBC, 41% of FFP and 29% of PLT. Most of the blood products were transfused to patients with diseases of the circulatory system (25%) or neoplasms (22%).

In Chapter 3, methods for analyzing survival after blood transfusion are studied. Analysis of survival after transfusion differs from normal survival analysis as patients often obtain multiple transfusions and therefore the patient's survival is counted multiple times: once for each transfusion. Two methods for analyzing survival after any transfusion were evaluated. Direct estimation of survival after transfusion and the commonly used Kaplan-Meier estimator were applied to data from the University Medical Center of Utrecht between 1995 and 2003. In general the Kaplan-Meier method provides a correct estimate for survival after transfusion, but the confidence intervals obtained with standard procedures are incorrect. The alternative is to bootstrap patients instead of transfusions.

Cost-effectiveness analyses of blood safety interventions require estimates of the life expectancy after blood product transfusion. In Chapter 4, survival after transfusion as obtained from the PROTON dataset is presented. PROTON data were individually matched to mortality data of the Netherlands. Survival after transfusion was calculated and life expectancy after transfusion was estimated, per blood component type and age group. Of all 2,405,012 blood product transfusions in the PROTON dataset, 92% was matched to the national Dutch Municipal Population Register, which registers all deaths. After one year, survival after any transfusion was 65%, 70% and 54% for RBC, FFP and PLT respectively. After five years, this was 47%, 59% and 39% for RBC, FFP and PLT respectively. Ten years after transfusion, mortality rates of recipients are still elevated compared to the general population. The mortality rates after transfusion found for the Netherlands are lower than those found in comparable studies for other countries.

In Chapter 5, cost-effectiveness was analyzed for the following blood screening interventions: 1. Hepatitis B virus, hepatitis C virus and HIV Triplex NAT in addition to

serological testing, in minipools of six or for individual donation samples, 2. human T-cell lymphotropic virus (HTLV) antibody test for all donations, for first-time donors only and for pediatric patients only, and 3. hepatitis A virus and Parvovirus B19 NAT for all donations. The disease progression of the studied viral infections was described in five Markov models. The ICER of Triplex NAT is €5,199,220 per quality-adjusted life-year (QALY) for testing minipools of six donation samples and €4,647,062 per QALY for individual donation testing. The ICER of testing all donations on HTLV is €45,182,666 per QALY, whereas the ICER of testing new donors only €2,234,041 per QALY. The ICER of HTLV testing of blood products for pediatric patients only is €26,984,140 per QALY. The ICER of hepatitis A virus NAT is €18,562,483 per QALY.

In Chapter 6 a side project is described, in which PROTON data are used. Sanquin Blood Bank wondered whether the results of the PROTON study could be used to assess trends in blood demand and supply and predict how these will develop over time. The motivation behind this was the concern that aging of the general population might increase the demand for blood products. So, mathematical models were developed to describe and predict the national demand and supply of RBC. Two models for the demand were created. The first demand model assumes that the mean numbers of transfusions per inhabitant per age and gender are constant. A second demand model incorporates observed changes in clinical blood use over time. Based on demography only, RBC demand is expected to increase. The second model predicts that RBC demand decreases by 8% from 2008 to 2015. RBC demand depends on the extent to which further trends in optimal blood use will neutralize the effects of the ageing of the transfusion recipient population. A donation model was developed to predict future RBC supply. A shortage of about 4,000 RBC units per year (0.7% of total RBC demand) is expected as of 2011, provided that the number of new donors and their age composition remains unchanged. We can conclude that the observed decrease of new donor influx has to be stopped to prevent shortages of RBC.

Samenvatting

Bloedtransfusie is vaak levensreddend. Dit motiveert mensen om vrijwillig bloed te doneren. Aan de andere kant is bloedtransfusie ook verbonden met verschillende (kleine) risico's, bijvoorbeeld transfusie van een bloedproduct van de verkeerde bloedgroep, allergische reacties of besmetting met een virus. Hierdoor komen er veel emoties kijken bij bloedtransfusie: donoren voelen zich goed omdat ze andere mensen kunnen helpen, ontvangers zijn dankbaar omdat ze bloed krijgen van vrijwilligers, maar ontvangers kunnen ook erg boos worden als ze een infectieziekte krijgen door bloedtransfusie.

Bij Sanquin, de Nederlandse bloedbank, worden veel maatregelen genomen om bloedproducten zo veilig mogelijk te maken. Zo worden alle donaties getest op de aanwezigheid van bekende virussen die overgedragen kunnen worden door bloed. Voorbeelden van zulke virussen zijn hepatitis B, hepatitis C en HIV, het virus dat AIDS kan veroorzaken. Virustesten kosten vaak veel geld. Daarom wil de bloedbank graag weten of ze ook waar krijgt voor haar geld: wat leveren de testen op en wat is de verhouding met wat het kost? Deze vragen kunnen worden beantwoord door een kosten-effectiviteitsanalyse. Om zo'n analyse goed te kunnen uitvoeren is informatie over ontvangers van bloedproducten nodig. Het effect van een nieuwe virustest wordt behaald in de ontvangers van bloedproducten, die dan minder kans hebben om het virus te krijgen. Om de grootte van dit effect te schatten is informatie nodig over de verdeling van bloedproducten over verschillende soorten ontvangers. Als de transfusie van een besmet bloedproduct aan een jong kind wordt voorkomen, valt er immers vaak meer te winnen dan wanneer een besmet bloedproduct in een oudere meneer met een hartziekte terechtkomt.

In Nederland wordt informatie over bloeddonoren, donaties en uitgegeven bloedproducten geregistreerd door de bloedbank Sanquin. Ziekenhuizen registreren informatie over de ontvangers van deze producten. Er is echter geen nationale registratie van ontvangers. In dit proefschrift worden de resultaten van de PROTON-studie beschreven. PROTON staat voor PROfielen van Transfusie-ONtvangers. Het doel van deze studie was het beschrijven van de verdeling van bloedproducten over verschillende patiëntengroepen in Nederland. Om dit te doen is de eerste nationale dataset (gegevensverzameling) samengesteld waarin eigenschappen van transfusie-ontvangers zijn verzameld.

In het eerste hoofdstuk wordt een kosten-effectiviteitsanalyse van de NAT-test (waarmee DNA of RNA wordt gedetecteerd) voor het hepatitis B virus beschreven. Deze test werd uitgevoerd door bloedmonsters van 24 donaties samen te testen. Het alternatief is om de test uit te voeren met monsters van zes donaties of voor elke donatie apart. We hebben de bijkomende kosten en effecten van deze alternatieve testen geschat. Hiertoe hebben we een wiskundig model gebouwd van de hele

transfusie-keten van donoren tot ontvangers van bloed in Nederland. Daarna werd geschat hoeveel extra gevallen van overdracht van hepatitis B voorkomen kunnen worden door de alternatieve testen in te voeren. Het ziekteverloop van een infectie met hepatitis B bij een transfusie-ontvanger is beschreven in een Markovmodel. Dat is een model waarin personen in verschillende gezondheidstoestanden terecht kunnen komen, met jaarlijkse kansen om van de ene naar de andere toestand te gaan. De kosten-effectiviteitsratio (ICER) van de NAT per 6 donaties werd geschat op €303.218 per QALY. Een QALY is een gewonnen levensjaar, gecorrigeerd voor de kwaliteit van leven. De incrementele kosten-effectiviteitsratio (ICER) van de NAT voor individuele donaties werd geschat op €518,995 per QALY.

Toen deze analyse uitgevoerd werd, was de PROTON-studie nog maar net gestart. Daarom werd de leeftijdsverdeling uit een oude studie naar 1000 bloeddonaties in 1997 gebruikt. Overleving na transfusie was al wel bestudeerd in data van het Universitair Medisch Centrum Utrecht en deze resultaten werden ook gebruikt. Door deze data te gebruiken, werd al duidelijk dat de ICER sterk wordt beïnvloed door de leeftijd van de transfusie-ontvangers en de bijbehorende overleving na transfusie. Dit betekent dat nauwkeurige informatie over transfusie-ontvangers nodig is om een goede schatting te maken van de kosten-effectiviteit. Het effect van bloedveiligheidsmaatregelen wordt immers behaald door een hogere levensverwachting en betere kwaliteit van leven van de transfusie-ontvangers.

In hoofdstuk 2 wordt het belangrijkste deel van de PROTON-studie beschreven. Van de 93 Nederlandse ziekenhuizen werden er 20 geselecteerd om mee te doen aan de PROTON-studie. Uit de computersystemen van de laboratoria van de ziekenhuizen werden data over alle bloedtransfusies tussen 1996 en 2006 verkregen, voor zover dat mogelijk was. De data bevatten transfusie-datum, type bloedproduct en eigenschappen van de ontvanger, zoals geslacht, adres en geboortedatum. De data werden bij elkaar gevoegd en gekoppeld aan de Landelijke Medische Registratie, waarin informatie over alle bijna ziekenhuisopnames in Nederland wordt bijgehouden, inclusief de hoofdontslagdiagnoses (ICD-9-codes). Met deze data werd de verdeling van eigenschappen van transfusie-ontvangers in Nederland geschat. De hele PROTON-dataset bevat informatie over 290.043 patiënten die 2.405.012 bloedproducten ontvingen (1.720.075 eenheden rode bloedcellen, 443.697 eenheden vers bevroren plasma, 241.240 eenheden bloedplaatjes) in 1996 tot en met 2006. Dit is 28% van het totale bloedgebruik in Nederland in deze periode. De verdelingen van diagnoses en leeftijd van opgenomen patiënten in de deelnemende ziekenhuizen waren vergelijkbaar met de verdelingen in alle Nederlandse ziekenhuizen. Dit geeft aan dat de ziekenhuizen die meededen aan de PROTON-studie representatief zijn voor Nederland, wanneer onderscheid gemaakt wordt tussen ziekenhuiscategorieën (academische, algemene en kankerziekenhuizen). Van alle eenheden rode bloedcellen

(RBC), vers bevroren plasma (FFP) en bloedplaatjes (PLT), werd respectievelijk 1.7%, 2.5% en 4.5% getransfundeerd aan neonaten. Ontvangers van 65 jaar of ouder kregen 58% van de RBC, 41% van de FFP en 29% van de PLT. De meeste bloedproducten werden getransfundeerd aan patiënten met hart- en vaatziekten (25%) of kanker (22%).

In hoofdstuk 3 worden methodes beschreven voor het analyseren van overleving na bloedtransfusie. Dit verschilt van normale overlevingsanalyses, omdat patiënten vaak meer dan één bloedproduct ontvangen. Zo'n patiënt telt dan zwaarder mee in het berekenen van de overleving na een transfusie. We hebben twee methodes geëvalueerd: directe schatting en de veelgebruikte Kaplan-Meierschatter werden toegepast op gegevens van het Universitair Medisch Centrum Utrecht van 1995 tot en met 2003. In het algemeen geeft de Kaplan-Meierschatter een correcte schatting van de overleving na transfusie, maar de betrouwbaarheidsintervallen berekend met de standaardmethodes zijn niet correct. Het alternatief is om patiënten te bootstrappen[1] in plaats van transfusies.

Voor kosten-effectiviteitsanalyses van bloedveiligheidsmaatregelen is een schatting van de levensverwachting na bloedtransfusie nodig. In hoofdstuk 4 worden overlevingskansen na transfusie beschreven, zoals verkregen uit de PROTON-dataset. De PROTON-data werden hiervoor bij het CBS (Centraal Bureau voor de Statistiek) gekoppeld aan Nederlandse sterftedata. De overleving na transfusie werd berekend en de levensverwachting na transfusie werd geschat, per type bloedproduct en per leeftijdsgroep. Van alle 2.405.012 bloedtransfusies in de PROTON-dataset kon 92% bij het CBS gekoppeld worden aan de Gemeentelijke Basisadministratie, waarin alle sterftegevallen worden geregistreerd. Uit de analyse bleek dat respectievelijk 65%, 74% en 54% van de RBC, FFP en PLT getransfundeerd wordt naar ontvangers die na één jaar nog in leven zijn. Verder wordt respectievelijk 47%, 59% en 39% getransfundeerd naar ontvangers die na 5 jaar nog in leven zijn. Na tien jaar zijn de sterftekansen van transfusie-ontvangers nog steeds hoger dan die in de algemene bevolking. De sterftekansen na transfusie in Nederland zijn lager dan in studies in andere landen gevonden is.

In hoofdstuk 5 is de kosten-effectiviteit geanalyseerd van de volgende bloedtesten: 1. Triplex NAT: een gecombineerde test voor hepatitis B-virus, hepatitis C-virus en HIV, toegevoegd aan de testen op antilichaampjes, per zes bloedmonsters of voor individuele monsters, 2. antilichaampjes-test van HTLV voor alle donaties, alleen voor nieuwe donoren en alleen voor kinderen tot 16 jaar en 3. hepatitis A virus en Parvovirus B19 NAT voor alle donaties. Het natuurlijke verloop van de bestudeerde virusinfecties is beschreven in vijf Markovmodellen. De ICER van de Triplex NAT is

[1] Bootstrappen is een bekende statistische methode om betrouwbaarheidsintervallen te schatten.

€5,2 miljoen per QALY voor het testen per zes bloedmonsters en €4,6 miljoen per QALY voor het testen van individuele bloedmonsters. De ICER van hepatitis A virus NAT is €19 miljoen per QALY. De ICER van het testen van alle donaties op HTLV is €45 miljoen per QALY, terwijl de ICER van het testen van alleen nieuwe donoren €2,2 miljoen per QALY is. De ICER van het testen van bloedproducten die bestemd zijn voor kinderen op HTLV is €27 miljoen per QALY.

In hoofdstuk 6 wordt een zijproject beschreven waarvoor PROTON-data zijn gebruikt. Vanuit Sanquin Bloedbank werd gevraagd of de resultaten van de PROTON-studie gebruikt zouden kunnen worden om trends in vraag en aanbod van bloedproducten te bestuderen en om te voorspellen hoe dit zich in de nabije toekomst zal ontwikkelen. De motivatie hierachter was de bezorgdheid over de vergrijzing van de bevolking, waardoor de vraag naar bloedproducten zou kunnen toenemen. Daarom hebben we wiskundige modellen ontwikkeld om de vraag en aanbod van RBC te beschrijven en voorspellen. We hebben twee verschillende modellen voor de vraag gebouwd. In het eerste model wordt aangenomen dat het gemiddeld aantal transfusies per inwoner per leeftijd en geslacht constant is. Het tweede model houdt rekening met geobserveerde veranderingen in bloedgebruik over de jaren heen. Wanneer alleen naar demografie wordt gekeken, dan is de verwachting dat de vraag naar RBC zal stijgen. Het tweede aanbod-model voorspelt echter dat de vraag naar RBC met 8% zal dalen tussen 2008 en 2015. De vraag naar RBC hangt af van de mate waarin de ontwikkelingen in optimaal bloedgebruik de effecten van de vergrijzing zullen opheffen. We hebben een donatiemodel gebouwd om het toekomstige aanbod van RBC te voorspellen. Volgens dit model zal er in 2011 een tekort van slechts ongeveer 4.000 eenheden RBC (0,7% van het totale bloedgebruik) zijn, mits het aantal nieuwe donoren en hun leeftijdssamenstelling niet verandert. We kunnen concluderen dat de geobserveerde daling van de instroom van nieuwe donoren gestopt moet worden om de bloedvoorziening in Nederland op peil te houden.

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Curriculum vitae

Barbara Anna Raven was born on November 20th 1981 in Leiden, the Netherlands. In the year 2000 she graduated from the Johan van Oldenbarneveltgymnasium in Amersfoort. Barbara studied mathematics with life sciences at the Vrije Universiteit in Amsterdam, during which she followed mathematics as well as biology courses and focused at applications of mathematical models in (medical) biology. She obtained her Master's degree in 2006, after a six month internship at the National Institute of Public Health and the Environment (RIVM). On September 8th 2006 Barbara married Michiel Borkent in Amersfoort. Ten days later she started to work as a junior researcher at the Julius Center for Health Sciences and Primary Care. The result of this work is presented in this thesis. As of May 2010, Barbara works as a quantitative policy officer at the Stichting DBC-Onderhoud.