

Survival after transfusion in the Netherlands

B. A. Borkent-Raven,¹ M. P. Janssen,¹ C. L. van der Poel,^{1,2} W. P. Schaasberg,³ G. J. Bonsel⁴ & B. A. van Hout^{1,5}

¹Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

²Sanquin Blood Supply Foundation, Amsterdam, the Netherlands

³Statistics Netherlands, The Hague, the Netherlands

⁴Department of Obstetrics & Gynaecology, Erasmus University Rotterdam, the Netherlands

⁵University of Sheffield, Sheffield, UK

Vox Sanguinis

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 In the PROTON (PROfiles of TransfusiON recipients) study transfusion recipient data was collected 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 identification details. 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 with 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.

Key words: blood product transfusion, cost-effectiveness analysis, survival after transfusion, transfusion recipients.

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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 renew 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

Correspondence: Mart Janssen, Julius Center, UMC Utrecht, Str 6-131, P.O. Box 85500, 3508 GA Utrecht, the Netherlands
E-mail: m.p.janssen@GRO-C

documented, little information is available on the average survival after blood transfusions without 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 loss 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. paediatric recipients) are considered, survival for these specific groups is 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 analyse 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 analyse 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 1996–2006 [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 date of death of people who deceased in the Netherlands since 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 because of 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. To our knowledge all studies estimated SFT, except two [8, 9]. To reduce the bias introduced by recipients that possibly were transfused before the start of the observation period of a hospital, recipients transfused in the first year of observation of each hospital were excluded from the patient's SFT estimation.

Next, SAT was estimated for age strata of 5 years. We made two exceptions to this stratification: (i) 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]; (ii) 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 that of the general population.

Life expectancy after transfusion

To estimate the life expectancy after transfusion, according to recipient age, we needed 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 those 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 was found or the recipient was 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

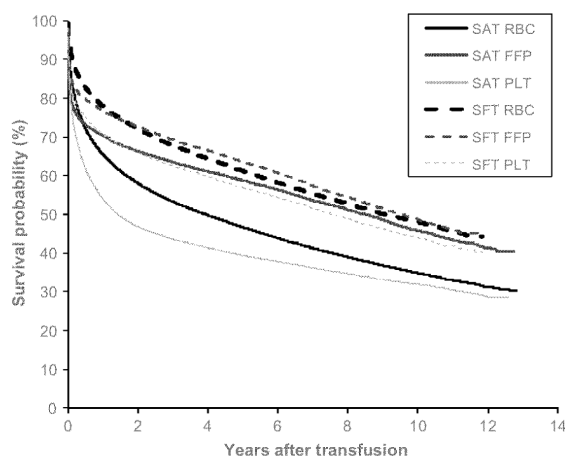


Fig. 1 Survival after transfusion (SAT) and survival after first transfusion (SFT) of RBC, FFP or PLT.

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.

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. Young adults survive better after FFP transfusions and children survive better after PLT transfusions.

Comparison with survival in the general population

SMRs after any transfusion for four age groups and for each blood component type are shown in Fig. 3. There is a dip after 8 years in the SMRs for the group aged 0–16, because of one recipient who received a very large number of

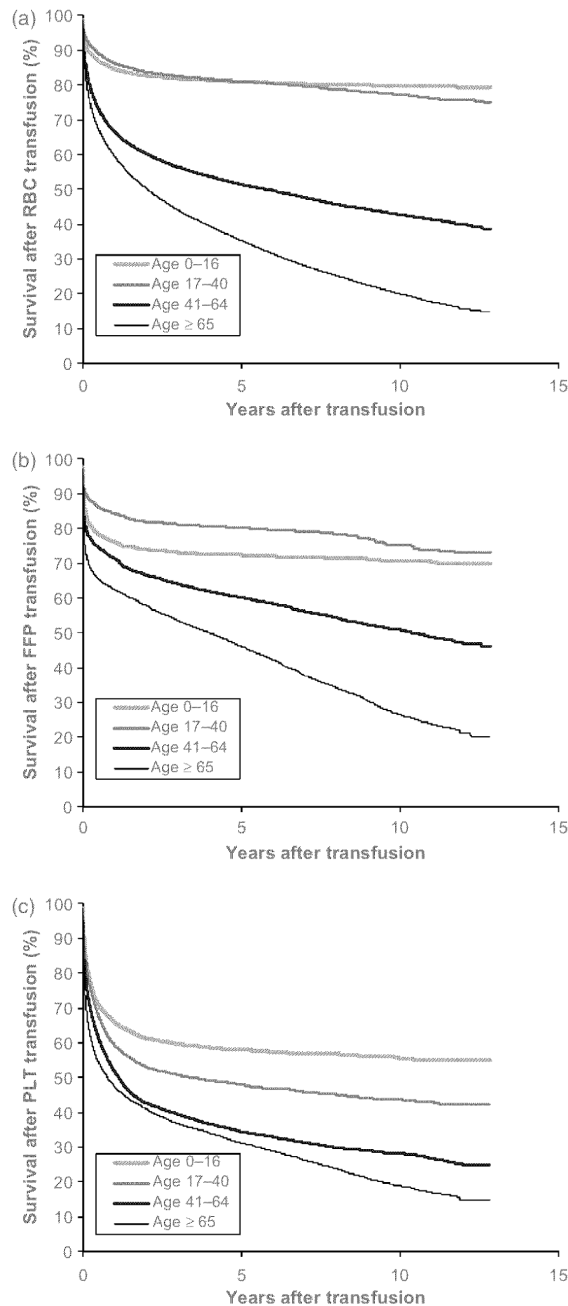


Fig. 2 (a) Survival after any RBC transfusion according to age, 1 580 018 transfusions in total: 105 618 for ages 0–16, 208 965 for ages 17–40, 513 038 for ages 41–64 and 752 397 for ages 65 and older. (b) Survival after any FFP transfusion according to age, 408 258 transfusions in total: 45 135 for ages 0–16, 83 703 for ages 17–40, 138 294 for ages 41–64 and 141 126 for ages 65 and older. (c) 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.

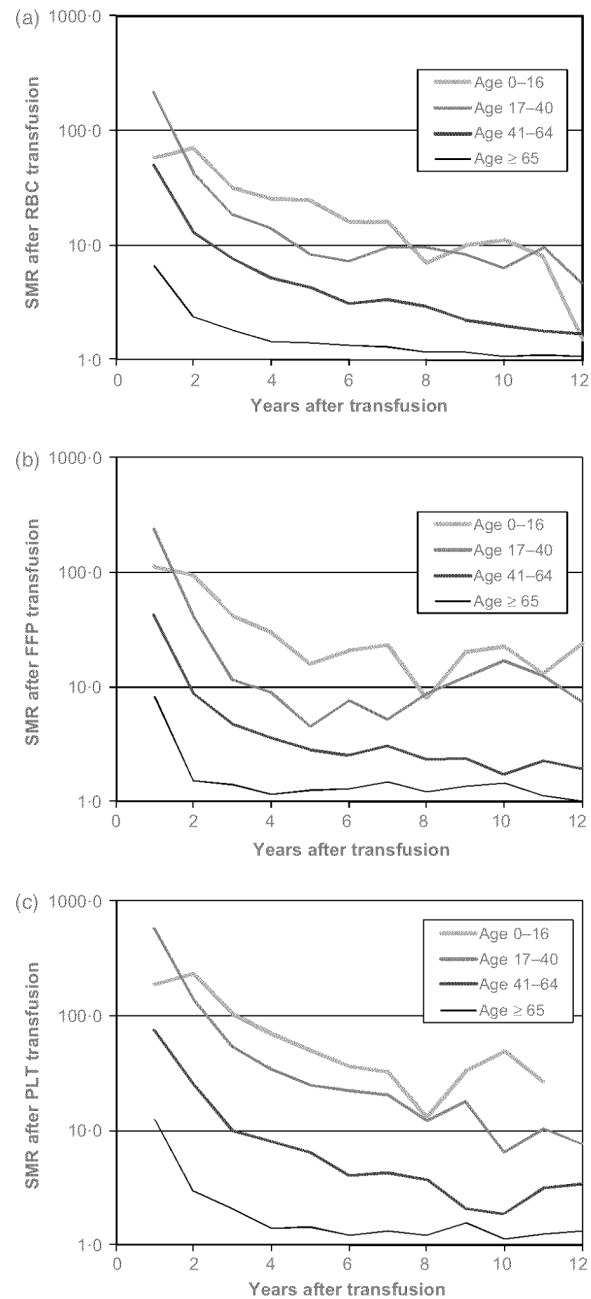


Fig. 3 Standardized mortality ratios (SMRs) of transfusion recipients as a function of time since any transfusion. SMR is the ratio of the mortality rates of recipients after transfusion and mortality rates of the general population, adjusted for age and gender. (a) Standardized mortality ratios of RBC transfusion recipients. (b) Standardized mortality ratios of FFP transfusion recipients. (c) Standardized mortality ratios of PLT transfusion recipients.

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 17–40 years in the first year after transfusion.

For recipients older than 80 years, the mortality rates become equal to those of the general population: for RBC recipients the difference disappears after 5–8 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 71–75 years, in Fig. 4. 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 Fig. 5. The overall life expectancy after any transfusion is 12.9 years, while the overall life expectancy after first transfusion is 16.1 years. Adjustment for gender has no significant effect on the estimates of life expectancy, so this effect is 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 when 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

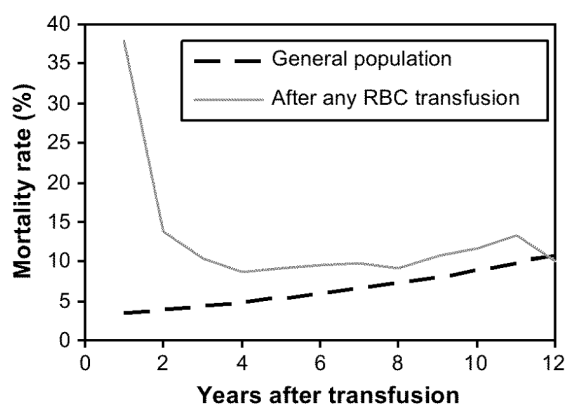


Fig. 4 Example of stabilizing difference between the mortality ratio of RBC recipients and the general population (recipient age 71–75 years).

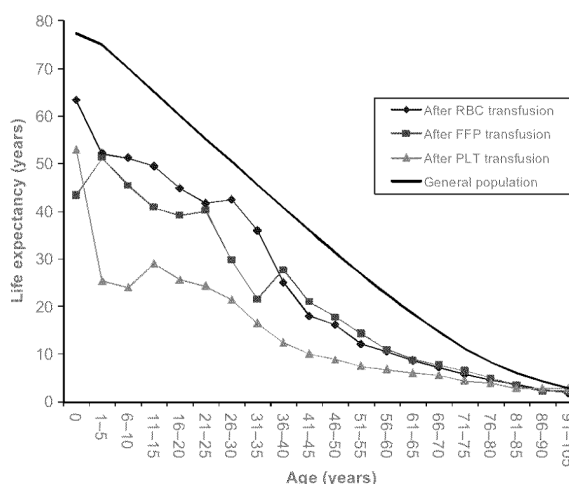


Fig. 5 Life expectancy after any transfusion per type of blood component. It is assumed that the mortality rates beyond 10 years after blood transfusion remain elevated by a constant rate (estimated per age group and blood component type).

diminishes over time, as mortality rates of an individual in the general population increases with age. The average differences relative to survival of the general population are therefore only 2%, 7% and 8% respectively.

Discussion

The difference between SFT and SAT

SAT is considerably lower than SFT, for all component types (Fig. 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 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 an 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 (Fig. 2b) is a direct result of the diseases for which these recipients are transfused. Of all FFP transfusions in children aged 0–16, 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 because of 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.* [11] reported a lower SFT than we found in our recipient population in 2001. This might be caused by differences in the mean age at the time of first transfusion. In their study this was 66 years, compared to 60.6 years in our study. The SFT reported by Wallis *et al.* [8] is also lower, for each component type considered. In 2004, Kleinman *et al.* [12] showed SFT for three age groups. 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 caused by the difference in age distribution of transfusion recipients in Scandinavia and in the Netherlands.

Only Wallis *et al.* [8, 9] presented SAT per blood component type, while SCANDAT showed SAT regardless of the type of blood component transfused. 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 years 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 estimates 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, 4410 FFP and 1985 PLT). Furthermore, blood use has changed over time and so has the survival of transfusion recipients. This renders it impossible to provide an up-to-date 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 analyses in regions where detailed information on post-transfusion survival is lacking [6].

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Appendix

Table A1 Transfusion recipient age distribution and probability of survival after transfusion according to type of blood component and recipient age

RBC transfusions										FFP transfusions										PLT transfusions									
Age distribution		Survival probability (%)					Age distribution		Survival probability (%)					Age distribution		Survival probability (%)													
Recipient age	% Transfusions	Years since transfusion					Recipient age	% Transfusions	Years since transfusion					Recipient age	% Transfusions	Years since transfusion													
		1	2	3	5	10			1	2	3	5	10			1	2	3	5	10									
0	1.7	85	84	83	83	83	0	2.4	73	71	71	70	69	0	4.5	71	70	69	68	68									
1-5	0.5	84	80	79	78	76	1-5	1.4	79	77	76	76	74	1-5	4.1	67	61	59	58	53									
6-10	0.4	86	83	82	80	78	6-10	1.0	80	75	74	71	69	6-10	2.2	64	58	55	51	45									
11-15	0.7	85	81	80	79	77	11-15	1.3	77	76	75	75	71	11-15	3.3	61	54	52	51	49									
16-20	1.3	87	85	83	82	76	16-20	2.4	83	81	80	79	76	16-20	2.8	58	55	54	52	50									
21-25	1.6	86	84	83	81	78	21-25	3.3	88	87	87	87	83	21-25	3.0	57	51	48	46	44									
26-30	2.6	89	87	87	86	84	26-30	3.8	83	81	80	80	76	26-30	3.4	62	54	51	48	46									
31-35	3.1	88	86	85	84	81	31-35	4.5	82	79	78	76	69	31-35	4.4	61	53	51	50	45									
36-40	2.9	81	77	76	73	67	36-40	5.1	85	81	80	79	75	36-40	4.7	58	52	49	44	37									
41-45	3.2	73	68	65	61	54	41-45	4.3	74	71	69	67	60	41-45	5.9	55	44	41	35	30									
46-50	4.3	70	65	62	58	52	46-50	5.6	74	71	69	66	61	46-50	6.5	52	42	40	35	30									
51-55	5.8	65	59	55	51	43	51-55	6.9	74	69	66	63	56	51-55	8.8	51	42	38	34	29									
56-60	7.2	65	58	54	48	39	56-60	8.8	68	61	58	54	43	56-60	9.8	52	44	40	35	26									
61-65	9.1	64	57	53	47	35	61-65	9.7	69	64	60	55	39	61-65	9.7	50	42	38	34	25									
66-70	12.1	63	56	51	44	31	66-70	12.8	66	62	59	52	35	66-70	9.4	49	42	39	34	24									
71-75	14.6	62	54	48	40	23	71-75	13.1	65	61	56	48	28	71-75	9.2	48	42	37	32	18									
76-80	13.3	59	50	43	34	16	76-80	9.0	60	54	50	42	19	76-80	5.6	46	40	36	30	15									
81-85	9.0	56	46	38	26	10	81-85	3.6	48	43	39	29	11	81-85	2.8	41	35	30	21	8									
86-90	4.6	51	37	28	17	3	86-105	1.0	43	35	28	16	0																
91-105	1.7	45	31	21	9	1																							
All	100	65	58	53	47	35	All	100	70	66	63	59	46	All	100	54	47	44	39	32									