

ORIGINAL PAPER

Direct costs of transfusion reactions – an expert judgement approach

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Background and Objectives Despite increasingly meticulous haemovigilance reporting throughout the world, a systematic assessment of the cost of transfusion reactions is still lacking. This is partly caused by the fact that such an assessment requires a subjective expert assessment of the additional costs linked to the adverse reaction. Data on the cost of transfusion reactions could support decision-making regarding blood transfusion safety measures.

Materials and Methods Thirteen experts from nine hospitals were asked to estimate the additional care required following various types of transfusion reactions. Additional care was quantified as the proportion of reactions requiring care, and the amount of care required (e.g. hospitalization days, additional physician's time). Experts were also asked to provide, per type of transfusion reaction, an estimate of the proportion of transfusion reactions preventable. Structured quantitative expert elicitation methods were applied to obtain and combine expert estimates.

Results The estimated annual in-hospital cost of transfusion reactions in the Netherlands is €933 356 per year (€1.52 per transfusion). Two-thirds (64%) of these are incurred by non-serious transfusion reactions. Circulatory overload, TRALI and anaphylaxis clearly dominate the costs of serious adverse transfusion reactions (66% in total); non-haemolytic transfusion reactions incur 46% of the cost of non-serious transfusion reactions. Additional safety measures targeting circulatory overload and new antibody formation potentially offer the highest cost reduction.

Conclusion In-hospital costs of transfusion reactions are substantial but contribute to less than 1% of the total cost of transfusion in the Netherlands. A considerable part of these costs (24%) might be preventable.

Key words: transfusion reactions, direct costs, expert judgement.

Received: 24 March 2017,
revised 24 October 2017,
accepted 24 October 2017

Introduction

Patient safety in the Netherlands, as in most countries, is one of the top priorities of healthcare policy [1, 2]. Reporting and root cause analysis of unintended adverse

reactions and incidents during treatment of patients contributes to patient safety. Since 2003, the TRIP Foundation (Transfusion and Transplantation Reactions In Patients), the Dutch national haemovigilance and biovigilance office have collated and publicly reported on adverse reactions and incidents associated with the transfusion of labile blood products [3]. The objective of this activity is to map risks associated with blood transfusion and make recommendations to reduce adverse reactions.

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The considerable efforts associated with the implementation of measures to further increase blood transfusion safety (e.g. Rhesus phenotype compatible blood component selection for multitransfused patients or introduction of bedside electronic checking of patient and blood component) require a careful assessment of costs and benefits, as there is a limit to what expenditures can be considered acceptable for increasing patient safety [4, 5]. For the justification of interventions to reduce transfusion reactions, it is therefore essential to quantify the associated costs and health outcomes. Costs consist of additional costs for diagnosis, patient treatment and follow-up. Such data are scarce in general and are unavailable for the Netherlands in particular. Determining the impact of transfusion reactions in terms of costs and patient health is complicated, as these have to be separated from the costs and health effects imposed by the condition for which the patient is being treated. In this study, we describe an expert elicitation approach to estimate costs attributable to transfusion reactions. In addition, we asked experts to estimate the proportion of transfusion reactions that might be preventable, which allows estimation of potential savings from the implementation of further safety interventions. Our study highlights areas where transfusion safety may be improved and can be seen as a first step towards a complete assessment of the consequences of transfusion reactions.

Materials and methods

Methodological considerations

Determining the impact of transfusion reactions is complex in part because they are unintentional and occur unpredictably, which means that they can only be evaluated post hoc. More importantly, however, their impact has to be separated from the impact that the primary treatment has on the patient. For example, if a transfusion reaction occurs in a patient undergoing heart surgery, the additional costs of the transfusion reaction have to be determined and separated from the cost of the heart surgery itself. For this study, it was decided to use expert estimates of the additional requirements for patients after transfusion reactions. Advantages of this approach are: (1) it is relatively easy to perform, (2) one obtains input from a broad range of experts, (3) it is transparent about what has been included in the assessment and what has not, and (4) one can report reproducible findings in a detailed manner. Formal expert elicitation is a structured method to systematically consult experts on subjects where there is insufficient knowledge (or where such knowledge is difficult to extract), which is applied in an expanding range of applications [6–8].

Haemovigilance reporting

Haemovigilance reporting to TRIP, which functions under the auspices of the professional societies, is mandated as the professional standard in the Netherlands although the reporting is formally voluntary. The objective is to collect information and report on the safety of the clinical use of blood components on a national level. This allows assessment of trends in transfusion reactions and effective targeting of areas of highest concern. Since 2006, more than 95% of the Dutch hospitals have reported transfusion reactions to TRIP each year [3]. Reporting is anonymous and encompasses both serious and non-serious transfusion reactions and incidents. Between 1800 and 2400, transfusion reactions are reported annually, with an average of 2146 reactions [3]. In the Netherlands, there is only one single blood operator which in the reporting period on average delivered around 484 000 leucoreduced RBC units, 58 000 buffy coat platelet units (each pooled from five donations) and 72 000 units of fresh frozen plasma. Cases of post-transfusion bacteremia/sepsis and cases of post-transfusion viral infection are among the captured reactions and require investigation; however, only a minority of cases are found to be actually caused by pathogens in the transfused blood component (i.e. can be confirmed as transfusion-transmitted infections). The number of reported hospital-based incidents – these include incorrect blood component transfused, near misses and other incidents – is substantially smaller, namely approximately 230 per year [3]. The reports to TRIP also provide information about reactions which resulted from or were associated with errors or incidents. Annually, these account for some 15 reactions (2–3 of grade 2, 3 or 4) which are included in the results of this study.

To score the severity of reported transfusion reactions a five-step grading system is in place, of which the definitions are given in Table 1. Severity grades 2–4 combined are classed as 'Serious', in conformity with the definitions of the International Society for Blood Transfusion as well as European legislation [9]. In addition, an assessment is given of the imputability, the likelihood that the observed reaction can be attributed to the transfusion. All definitions are available on the TRIP website (<https://www.tripnet.nl/en/hemovigilance/definitions>). Reporting of the serious reactions to the competent authority and to the national blood service (Sanquin) is mandatory in case of a product safety issue. In these cases, hospitals can use the web-based reporting system to simultaneously report to authorities, blood service and TRIP.

Table 1 Grading of transfusion reactions

Severity grade	Definition
0	No morbidity (only laboratory abnormalities)
1	Minor morbidity, not life-threatening
2	Moderate-to-serious morbidity, may or may not be life-threatening; or leading to hospitalization or prolongation of illness; or associated with chronic disability or incapacity
3	Serious morbidity, directly life-threatening
4	Mortality following a transfusion reaction

Expert elicitation

A group of thirteen volunteer experts who are specialists in the fields of haemovigilance, haematology and clinical chemistry was recruited in the haemovigilance network that supports the reporting system in the Netherlands. The experts, coming from four general hospitals, three teaching hospitals and two university hospitals, filled out our questionnaire on transfusion reactions, one per hospital. The experts had to estimate the likelihood that a patient with a specific transfusion reaction would require various additional diagnostic tests, medication, hospital stay and/or involvement of hospital staff (nurses, doctors, specialists). A preliminary list was compiled specifying additional investigations and components of care according to recommendations in the national transfusion guideline [10] and drawing on practical experience in one teaching hospital and experience of the national haemovigilance office. The items were listed per type of transfusion reaction. As the level of investigation will be dependent on the severity of reaction or adverse event, the experts were asked to estimate the proportion of cases where various sub-activities (e.g. haptoglobin/antibodies/antiglobulin testing/IgA testing) were performed for both serious and non-serious transfusion reactions. Also, respondents could add any additional items they felt were missing in the list of sub-activities provided.

In addition to the questions on activities associated with transfusion reactions, the experts were asked how likely they considered various types of transfusion reactions avoidable. This information allows estimation of potential savings by further safety interventions and can be used to identify the most viable and most cost-saving risk reduction strategies. The full set of questions on transfusion reactions, investigations and preventability of transfusion reactions is available in the additional online materials for this study [Data S1].

Costs of transfusion reactions

We used the standard hospital tariffs and 2012 laboratory tariffs to derive costs associated with all items listed in

the questionnaire [11, 12]. Costs for nursing, medical and laboratory staff plus costs of laboratory testing and additional hospitalization were used to determine the total cost of transfusion reactions. All costs were adjusted to reflect 2016 Euros using the appropriate national inflation correction indices [13].

The total costs per item were determined by multiplying the calculated costs per item by the average likelihood that this item was needed as specified by the experts. The total costs of transfusion reactions in the Netherlands were calculated by multiplying the costs per type of transfusion reaction by the total number of cases reported to TRIP [3]. The total costs per transfusion unit were calculated in order to enable international comparisons to be made. The numbers of blood components distributed in the Netherlands were obtained from the Council of Europe reports on blood use [14]. The costs included in the calculations were limited to hospital and blood service costs incurred for investigation and treatment of the reaction. Costs for the patient (e.g. travel, sick leave from work) as well as potentially increased costs for future transfusions were not included.

Avoidable costs of transfusion reactions

All experts were asked to estimate the proportion of transfusion reactions which might be prevented by currently available means. The experts provided values for their minimum, maximum and most likely estimates. This provides a means to evaluate consistency among experts but also shows widely dispersed and even contradicting estimates of potential reductions. The estimates obtained may assist in the selection of risk-reducing strategies with potential to achieve the greatest cost reduction. Avoidable costs were obtained by multiplying total costs per type of transfusion reaction by the proportion of cases perceived to be preventable.

Calculations and sensitivity assessment

As in most health economic assessments, sensitivity analyses were performed to provide insight into the variability of the obtained cost estimates. Sensitivity of the cost estimates was attained by bootstrapping individual expert responses [15]. A procedure with 10 000 bootstraps was performed to obtain robust 95% confidence intervals (CI) for the estimates, meaning that the error due to sampling for the confidence intervals was less than 1%. All cost calculations were performed using Microsoft Excel 2010, using the Simtools add-in for Excel (Version 3.31a). A 'maximum cost estimate' for the cost of transfusion reactions was also calculated using the maximum value provided by any of the experts for each item.

Results

In Table 2, the costs of various items of extra investigation or treatment associated with transfusion reactions are shown. The costs for each type of transfusion reaction were calculated using the estimates on the requirement for each of the items as obtained from the experts. Details on the expert estimates are available in the online materials for this study.

In Table 3, the number of transfusion reactions reported to TRIP over a five-year period (from 2010 to 2014), and the estimated costs per case of both serious (Table 3A) and non-serious (Table 3B) transfusion reactions are shown [3]. Costs per case were calculated by multiplying the individual cost of items by the mean proportion of applicability or mean duration of additional stay indicated by the experts per severity level of the reaction.

From the assessment, it is clear that the costs of serious adverse reactions (€337 222) are dominated by circulatory overload, TRALI and anaphylaxis, which account for 66% of the total costs of serious transfusion reactions. The total costs of non-serious transfusion reactions (€596 134) are dominated by the costs associated with non-haemolytic transfusion reactions (46%), which together with costs of new antibody formation (25%) comprise 71% of the total costs. Of note, the non-serious transfusion reactions incur almost twice the costs of serious transfusion reactions as there are 18 times as many

non-serious reactions whereas the costs of serious reactions are on average only 10 times higher. This means that non-serious transfusion reactions contribute up to 64% of the cost of transfusion reactions (€933 356).

Out of the total number of serious reactions, 2.6% are associated with reports of incorrect blood component transfused (acute or delayed haemolytic transfusion reactions) or other incidents (chiefly transfusion-associated circulatory overload or other reaction following an unnecessary transfusion, data not presented here). Among non-serious reactions, only 0.5% is associated with errors. These reactions were included in the total numbers per reaction used in this study. The costs from transfusion errors, incidents or failures in the transfusion chain will be topic of a separate study, but this does not affect the current cost estimates per transfusion reaction.

The proportions of preventable cases, as presented in Table 4, indicate that acute haemolytic transfusion reactions are consistently perceived to be the transfusion reaction that may be further reduced. The narrow interquartile range (IQR, which represents the spread between the 25% and 75% percentiles of the expected cumulative probability distribution) indicates the strong agreement between the experts on this issue. This kind of reaction occurs with administration of incompatible transfusions. However, in our data, only 15% of all cases of AHTR were reported as such. This category contributes only 5% of the total cost of serious and only 1% of non-serious transfusion reactions, implying that the financial impact of a potential reduction in this reaction is limited (at most 10% of the total cost reduction potential). The reduction in transfusion-associated circulatory overload and the formation of new antibodies could have a more substantial impact: the anticipated median reduction of 64% for circulatory overload would result in a reduction of €56 871 per annum on serious transfusion reactions, and the formation of new antibodies in a reduction of €74 198 per annum on non-serious transfusion reactions. The potential savings through the reduction in these transfusion reactions would be €136 315 per annum (62% of the total cost reduction perceived feasible). However, there is clearly disagreement among the experts on the extent of the reduction achievable, which is reflected in the relatively large interquartile ranges, reflecting both the experts' individual uncertainty and the variability among experts. The disagreement among experts is even bigger when considering the potential reduction in TRALI cases: here the IQR is 0–97% indicating that experts are either convinced that this reaction can be completely prevented or that no further reduction is possible.

The maximum cost estimate for the transfusion reactions was determined by calculating the costs covering the highest value per item provided by any expert,

Table 2 Estimated costs of elements of additional investigations and care

Description	Cost in Euros (€)
Additional blood product	220-13
Additional hospitalization (per day)	480-41
Additional haemovigilance employee time (per hour) ^a	28-19
Additional physician time (per hour)	160-63
Additional nurse time (per hour)	28-19
Bacteriology	84-91
Blood group serology	110-47
Broad spectrum antibiotic medication	103-97
Chest X-ray	52-63
ECG	38-11
Hb determination	16-20
Determining biochemical haemolysis parameters	31-02
HLA typing	105-43
ICU admission (per day)	2033-65
IgA diagnostics	69-55
Medication following an anaphylactic reaction	40-31
Ruling out administrative errors	25-64
Virological screening	90-85

^aThe haemovigilance employee is the Dutch term for a transfusion safety officer (transfusion practitioner).

Table 3 (A) Frequency and costs per serious adverse transfusion reaction (Grades 2, 3 and 4). (B) Frequency and costs per non-serious adverse transfusion reaction (Grade 0–1)**(A)**

Transfusion Reactions Grade 2, 3, 4	Total number of reactions in 2010–2014	Estimated costs per case (€)	Estimated total costs per year (€) (95% CI)	% of total costs
Non-haemolytic transfusion reaction (fever $\geq 2^{\circ}\text{C}$ and/or rigours) and mild febrile reactions (fever >1 and <2)	83	723	14 281	4%
Acute haemolytic transfusion reaction ^a	32	1539	16 676	5%
Delayed haemolytic transfusion reaction	14	1027	2877	1%
Transfusion-related acute lung injury ^a	47	6652	71 635	21%
Transfusion-associated circulatory overload ^a	113	3227	88 860	26%
Anaphylaxis	95	3188	60 569	18%
Other allergic reaction	9	342	615	0%
New antibody formation	3	184	110	0%
Post-transfusion bacteremia/sepsis ^a	45	1610	21 315	6%
Post-transfusion viral infection ^a	13	277	2997	1%
Other reaction	134	1543	57 286	17%
Total	588	574	337 222 (273 604–410 627)	100%

(B)

Transfusion Reactions Grade 0–1	Total number of reactions in 2010–2014	Estimated costs per case (€)	Estimated total costs per year (€) (95% CI)	% of total costs
Non-haemolytic transfusion reaction (fever $\geq 2^{\circ}\text{C}$ and/or rigours)	4011	341	273,839	46%
Acute haemolytic transfusion reaction	46	665	6,122	1%
Delayed haemolytic transfusion reaction	25	404	2,021	0%
Transfusion-related acute lung injury	5	2086	2,086	0%
Transfusion-associated circulatory overload	178	228	8,112	1%
Anaphylaxis	225	409	18,418	3%
Other allergic reaction	891	87	15,517	3%
New antibody formation	4124	180	148,396	25%
Post-transfusion bacteremia/sepsis	212	716	30,371	5%
Post-transfusion viral infection	2	257	103	0%
Other reaction	907	502	91,150	15%
Total	10 635	56	596,134 (476,463–673,917)	100%

^aDeaths: TRALI 4x, TACO 7x, AHTR 3x, post-transfusion bacteremia/sepsis 3x, post-transfusion viral infection 1x, Other reaction 7x, NHTR 1x. For each of these cases, additional costs (€2276 per case) have been added to the total costs [16].

leading to the highest cost estimate per transfusion reaction. This results in an estimate of €609 724 for the cost of serious transfusion reactions and €1 218 921 for the non-serious transfusion reactions. The maximum cost estimates are 1.8 times higher for serious reactions and 2.0 times higher for the non-serious reactions, which overall results in a twofold increase in the total cost of transfusion reactions.

Discussion

Despite the fact that transfusion reactions are common (in the Netherlands these are reported around 4 per 1000

transfusions), little is known on associated costs and health effects [3]. Some references to costs of transfusion reactions are available [17–20], but even in studies where the cost-effectiveness of measures to prevent transfusion reactions have been evaluated, explicit information on costs and effects of such reactions is missing [21–23]. For insight into the complete impact of transfusion reactions on hospitals and patients, however, an integral assessment is required. In this study, an estimate was made of the direct costs associated with investigation and treatment of transfusion reactions. Total annual costs for hospitals and blood service caused by transfusion reactions in the Netherlands are estimated to be €933 356 per year

Table 4 Estimation of preventability and avoidable costs per year

Transfusion Reactions	Estimated proportion preventable (interquartile range)	Estimated preventable costs associated with serious transfusion reactions (% of total)	Estimated preventable costs associated with non-serious transfusion reactions (% of total)	Estimated preventable total costs associated with transfusion reactions (% of total)
Non-haemolytic transfusion reaction (fever $\geq 2^{\circ}\text{C}$ and/or rigours)	2.5% (0–6%)	357 (0%)	6846 (6%)	7203 (3%)
Acute haemolytic transfusion reaction	95% (85–99%)	15 842 (14%)	5816 (5%)	21 658 (10%)
Delayed haemolytic transfusion reaction	8.0% (4–73%)	231 (0%)	163 (0%)	394 (0%)
Transfusion-related acute lung injury	30% (0–97%)	21 490 (19%)	626 (1%)	22 116 (10%)
Transfusion-associated circulatory overload	64% (26–91%)	56 871 (50%)	5192 (5%)	62 062 (28%)
Anaphylaxis	18% (9–30%)	10 600 (9%)	3223 (3%)	13 823 (6%)
Other allergic reaction	30% (3–80%)	185 (0%)	4655 (4%)	4840 (2%)
New antibody formation	50% (10–75%)	55 (0%)	74 198 (69%)	74 253 (34%)
Post-transfusion bacteremia/sepsis	15% (3–90%)	3197 (3%)	4556 (4%)	7753 (4%)
Post-transfusion viral infection	70% (3–98%)	2098 (2%)	72 (0%)	2170 (1%)
Other reaction	3.1% (0–24%)	1790 (2%)	2848 (3%)	4639 (2%)
Total		112 716	108 194	220 910

and €1 828 645 for a maximum cost estimate. Almost two-thirds (64%) of these costs are caused by non-serious transfusion reactions. With 614 373 transfusions per year on average in the observation period, the direct costs of transfusion reactions alone amount to a €1.52 per transfusion in the Netherlands. On basis of the experts' judgement, it is expected that 24% of these costs might still be avoidable.

Expert elicitation is increasingly used in health services research and health technology assessment as a means to obtain fair estimates of parameters that are difficult or even impossible to measure, often due to a structural lack of data [24, 25]. The assessment of the costs of transfusion reactions is an exemplary illustration for such an application. There are simply too few occurrences of serious transfusion reactions, and for non-serious transfusion reactions, the average increase in costs as a result of transfusion reactions is too small to be measured accurately. A traditional approach would involve reviewing the dossiers of patients with transfusion reactions and identifying those interventions that resulted from the transfusion reaction. However, this would not only require a substantial research effort, but also detailed clinical (expert) knowledge in order to separate activities related to the transfusion reaction from those associated with regular treatment. The approach adopted here – where experts estimate the additional treatment required by patients suffering from various transfusion reactions – overcomes these hurdles to a certain extent and assumptions and outcomes can be easily communicated and verified. This enables a discussion on the validity of various assumptions and expert estimates, which allows for an improvement of the estimates obtained. Another clear

advantage of the expert elicitation approach is that specific expert knowledge can be drawn upon, for example their estimate of the proportion of transfusion reactions that might potentially be avoided.

Finally, the fact that additional care required for various types of transfusion reactions is made explicit, enables calculation of costs of transfusion reactions in completely different settings, for example for a country with a completely different cost structure. Also, extending the expert base internationally might provide information on differences in transfusion reactions in different countries which could again lead to the identification of areas where treatment of patients, or measures taken for the prevention of transfusion reactions, may be improved.

Note that in our assessment, only the direct costs of transfusion complications were considered (costs of additional hospitalization, hospital diagnostics and additional care). Long-term costs, such as the costs of treatment of viral infections, as well as indirect costs (e.g. costs of productivity loss), were not considered. These may however constitute a substantial part of the adverse effects of in particular serious transfusion reactions. Another cause for underestimating the total costs is that transfusion reactions and incidents are likely to be underreported. For instance, not all hospitals report red cell antibody formation as transfusion reaction. Also, experts were asked to provide estimates of the proportion of patients that would require additional clinical treatment and estimates on additional length of stay. Such estimates might be biased as a result of framing of the questions [26, 27]. An example of framing is asking for additional length of hospitalization in days. This will generally result in estimates in the order of days rather than weeks or hours. In practice, rare

transfusion reactions with severe consequences will strongly affect the average costs and length hospitalization, even if these only occur seldom. However, as such cases are hardly ever observed experts are likely not to include these in their assessment which may lead to experts underestimating the average length of stay and patients' additional medical needs. On the other hand, experience with such extreme cases might also bias estimates towards the high end as such experiences are likely to be remembered, possibly also as more severe than actually was the case [25, 28]. Also, the selection of experts with specific fields of expertise is a potential source of bias. For instance, our expert group consisted largely of transfusion specialists of which only a minority are practicing clinicians. A further limitation of our study is that future costs, such as premedication after a serious allergic reaction or additional costs for component selection after new antibody formation, are not included. This will also result in an underestimation of the total cost. Finally, in this study, we only considered the direct costs of investigation and treatment of transfusion reactions. A study on the impact of transfusion reactions would be more complete if it included an estimate of health effects, most commonly expressed in Quality Adjusted Life Years (QALYs) [29, 30]. These health effects might also be estimated using expert opinion. Such an assessment is a topic for future research.

Our study shows that circulatory overload, TRALI and anaphylaxis clearly dominate the costs of serious adverse transfusion reactions. These contribute almost equally to 66% of the total costs of serious adverse transfusion reactions whilst representing 43% of all serious transfusion reactions. The total costs of non-serious transfusion reactions are dominated by the cost associated with non-haemolytic transfusion reactions, covering 38% of all non-serious transfusion reactions but contributing 46% of the total cost.

Our results allow selecting transfusion reactions that would be good targets for increasing blood transfusion safety: these would be those transfusion reactions that would be considered preventable and have a substantial financial impact. The two most eligible types of transfusion complications would therefore be circulatory overload, which contribute substantially (26%) to the cost of serious transfusion reactions, and new antibody formation, contributing substantially (25%) to the cost of non-serious transfusion reactions. These two transfusion reactions combined account for 62% (28% + 34% respectively) of the total cost savings potential anticipated by the experts. Whether interventions that would increase transfusion safety would be cost-effective, however, would require further study.

The estimated total costs of transfusion reactions in this study are modest, in the order of 1% of the direct cost of blood components for transfusion. Avoiding transfusion reactions, however, not only reduces hospital

expenditure, but also improves the recovery and well-being of patients. A haemovigilance system contributes to the body of knowledge on transfusion reactions, which not only enables the reporting of reactions by physicians, but also provides insights into the risks of transfusion reactions and possibilities for preventing them. This overview of the costs per type of transfusion reaction and the likelihood of preventability will support clinicians, hospitals and blood services in prioritizing their efforts to reduce transfusion complications. Furthermore, it enables organizations in the transfusion chain to take informed decisions to refrain from adopting certain technologies or justify the costs of additional safety measures.

Acknowledgements

We would like to gratefully thank all of the consulted experts for their commitment to a demanding expert elicitation process and its invaluable contribution to our study. The experts, including their field of expertise, who are all based in the Netherlands, were (in alphabetical order) as follows: Astrid van Empel, transfusion/coagulation specialist in the laboratory for clinical chemistry at the St. Anna hospital, Geldrop; Gerda van Grootveld, haemovigilance officer at the St. Jansdal hospital, Harderwijk; Wim Koolwijk, haemovigilance and biovigilance coordinator, Hagaziekenhuis, the Hague; Lizzy van Pampus MD PhD, transfusion specialist at the University Medical Center St. Radboud, Nijmegen; Martin Schipperus MD PhD, haematologist at the Haga hospital and president of the TRIP Foundation, the Hague; Henk Schonewille, researcher at Sanquin Blood Supply Foundation, Amsterdam; Vera Siera-Wiedijk BSc, haemovigilance officer and haematology specialist at the Rijnland hospital, Leiderdorp; Hans Soons PhD, clinical chemistry, haematology, coagulation and blood transfusion specialist at the St. Anna hospital, Geldrop; Cisca van der Toorn, haemovigilance and biovigilance officer at the Haaglanden Medical Center, the Hague; Karen de Vooght PhD, clinical chemistry and blood transfusion specialist at the University Medical Center Utrecht, Utrecht; Paul Wetzer BSc, haemovigilance and biovigilance officer at the Jeroen Bosch hospital, 's-Hertogenbosch; Jaap-Jan Zwaginga MD PhD, haematologist and blood transfusion specialist at Leiden University Medical Center and Sanquin Research, Leiden. There was one additional expert (a transfusion specialist from the University Medical Center St. Radboud) that participated, but who did not confirm to be acknowledged by name. In addition, we would like to acknowledge Ron Treffers MD (former member of the advisory board to the TRIP Foundation, the national office for haemovigilance and biovigilance) for initiating this research. The study was designed by JW and MJ, data

analyses were performed by MJ, and interpretation of the results was performed by all authors, who also contributed actively to the writing of the manuscript.

Conflict of interest

None to declare.

Disclaimers

None.

Funding

No external funding was obtained for this study.

References

- 1 NFU: Project safety agenda 2013–2015 [Project Veiligheidsagenda 2013–2015, in Dutch]. Utrecht, the Netherlands, NFU, 2014: p. 10
- 2 Waring J, Allen D, Braithwaite J, *et al.*: Healthcare quality and safety: a review of policy, practice and research. *Sociol Health Illn* 2016; 38:198–215
- 3 TRIP: TRIP Report 2015 Hemovigilance [TRIP Rapport 2015 Hemovigilantie]. The Hague, TRIP, 2016
- 4 Nuttall GA, Abenstein JP, Stubbs JR, *et al.*: Computerized bar code-based blood identification systems and near-miss transfusion episodes and transfusion errors. *Mayo Clin Proc* 2013; 88:354–359
- 5 Menitove JE, Leach Bennett J, Tomasulo P, *et al.*: How safe is safe enough, who decides and how? From a zero-risk paradigm to risk-based decision making. *Transfusion* 2014; 54:753–757
- 6 Knol AB, Slottje P, van der Sluijs JP, *et al.*: The use of expert elicitation in environmental health impact assessment: a seven step procedure. *Environ Health* 2010; 9:1
- 7 Goossens LH, Cooke R, Hale AR, *et al.*: Fifteen years of expert judgement at TUDelft. *Saf Sci* 2008; 46:234–244
- 8 Hunger T, Schnell-Inderst P, Sahakyan N, *et al.*: Using Expert Opinion in Health Technology Assessment: A Guideline Review. *Int J Technol Assess Health Care* 2016; 32:131–139
- 9 Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003: setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. 2003
- 10 CBO: Dutch Blood Transfusion Guideline. 2011. Available from: <https://www.sanquin.nl/repository/documenten/en/prod-en-dienst/287294/blood-transfusion-guideline.pdf>
- 11 ZIN: Cost manual: Methodology of cost research and reference prices for economic evaluations within health care [Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijszinnen voor economische evaluaties in de gezondheidszorg, in Dutch]. 2015
- 12 Dutch Health Authority (NZA); Care rates [Nederlandse ZorgAutoriteit (NZA);Zorgtarieven]. <http://www.nza.nl/regelgeving/tarieven/> [Last accessed 29/11/2013]
- 13 CBS: Consumer prices; price index [Consumentenprijzen; prijsindex]. <http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=83131ned&D1=a&D2=0&D3=64,77,90,103,116,129,142,155,168,181,1-94,207,220,233,246,259,&HDR=T&STB=G1,G2&VW=T> [Last accessed 30/01/2017]
- 14 Council_of_Europe: Reports on the Collection, Testing and Use of Blood and Blood Components in Europe. <https://www.edqm.eu/en/blood-transfusion-reports-70.html> [Last accessed 24/10/2017]
- 15 Chernick MR: Bootstrap Methods: A Guide for Practitioners and Researchers. Hoboken, NJ, John Wiley & Sons, 2011
- 16 De Bruijne MC, Zegers M, Hoonhout LHF, *et al.*: Unintended damage in Dutch hospitals. Dossier research on hospital admissions in 2004 [Onbedoelde schade in Nederlandse ziekenhuizen. Dossieronderzoek van ziekenhuisopnames in 2004, in Dutch]. 2004
- 17 Kacker S, Ness PM, Savage WJ, *et al.*: The cost-effectiveness of platelet additive solution to prevent allergic transfusion reactions. *Transfusion* 2013; 53:2609–2618
- 18 Magee G, Zbrozek A: Fluid overload is associated with increases in length of stay and hospital costs: pooled analysis of data from more than 600 US hospitals. *Clinicoecon Outcomes Res* 2013; 5:289–296
- 19 Janssen MP, van der Poel CL, Buskens E, *et al.*: Costs and benefits of bacterial culturing and pathogen reduction in the Netherlands. *Transfusion* 2006; 46:956–965
- 20 Custer B, Agapova M, Martinez RH: The cost-effectiveness of pathogen reduction technology as assessed using a multiple risk reduction model. *Transfusion* 2010; 50:2461–2473
- 21 Powers A, Stowell CP, Dzik WH, *et al.*: Testing only donors with a prior history of pregnancy or transfusion is a logical and cost-effective transfusion-related acute lung injury prevention strategy. *Transfusion* 2008; 48:2549–2558
- 22 Kacker S, Ness PM, Savage WJ, *et al.*: Economic evaluation of a hypothetical screening assay for alloimmunization risk among transfused patients with sickle cell disease. *Transfusion* 2014; 54:2034–2044
- 23 Ezidiegwu CN, Lauenstein KJ, Rosales LG, *et al.*: Febrile nonhemolytic transfusion reactions. Management by premedication and cost implications in adult patients. *Arch Pathol Lab Med* 2004; 128:991–995
- 24 Hadorn D, Kvizhinadze G, Collinson L, *et al.*: Use of expert knowledge elicitation to estimate parameters in health economic decision models. *Int J Technol Assess Health Care* 2014; 30:461–468
- 25 Morgan MG: Use (and abuse) of expert elicitation in support of decision making for public policy. *Proc Natl Acad Sci U S A* 2014; 111:7176–7184

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- 26 Tversky A, Kahneman D: The framing of decisions and the psychology of choice. *Science* 1981; 211:453–458
- 27 De Martino B, Kumaran D, Seymour B, *et al.*: Frames, biases, and rational decision-making in the human brain. *Science* 2006; 313:684–687
- 28 Kahneman D, Slovic P, Tversky A: *Judgment Under Uncertainty: Heuristics and Biases*. 1st edn (April 30, 1982): Cambridge, Cambridge University Press, 1982.
- 29 Whitehead SJ, Ali S: Health outcomes in economic evaluation: the QALY and utilities. *Br Med Bull* 2010; 96:5–21
- 30 Dolan P, Shaw R, Tsuchiya A, *et al.*: QALY maximisation and people's preferences: a methodological review of the literature. *Health Econ* 2005; 14:197–208

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Data S1 Expert questionnaire and response summary.

EXPERT QUESTIONNAIRE AND RESPONSE SUMMARY

The mean expert response is provided per item, as well as the range of answers given (in brackets).

Respondent information	
Respondent name	
Institution	
Function	
E-mail address	
Phone number	

Section A: Transfusion reactions			
Non-hemolytic transfusion reaction (Fever $\geq 2^{\circ}\text{C}$ and/or rigors)	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Exclusion of administrative errors (%)	88 (1-100)	89 (1-100)	
Hemolysis Investigation (%)	75 (0-100)	62 (0-100)	
Blood group serology investigation (%)	88 (1-100)	87 (1-100)	
Bacteriology (%)	85 (1-100)	82 (1-100)	
Longer hospital stay (in days)	0.8 (0-1.5)	0 (0-0)	
Additional Hb check(s) (average)	0.6 (0-1)	0.3 (0-1)	
Extra nurse time (minutes)	38 (10-60)	33 (10-120)	
Haemovigilance co-worker time (minutes)	46 (0-120)	44 (0-120)	
Extra physician time (minutes)	17 (4-30)	14 (5-30)	
Other	60 (60-60)	75 (60-90)	Additional analyst time (minutes)

Acute transfusion Hemolytic Transfusion Reaction	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Exclusion of administrative errors (%)	88 (1-100)	89 (1-100)	
Hemolysis Investigation (%)	88 (1-100)	89 (1-100)	
Blood group serology investigation (%)	88 (1-100)	89 (1-100)	
Bacteriology (%)	71 (1-100)	42 (0-100)	
Additional check(s) blood biochemistry (average)	2.8 (1-5)	1.9 (0-5)	
Additional check(s) antibody screening / blood group serology (average)	1.4 (0-2)	0.9 (0-2)	
Longer hospital stay (in days)	1 (0-2)	0.3 (0-1)	
Additional Hb check(s) (average)	2.6 (1-4)	1.4 (0-2)	
Extra nurse time (minutes)	181 (15-1050)	52 (10-180)	
Haemovigilance co-worker time (minutes)	46 (0-120)	44 (0-120)	
Extra physician time (minutes)	37 (15-120)	20 (5-60)	

Additional blood transfusion(s) (average)	1.8 (1-4)	0.4 (0-2)	
Other	60 (60-60)	75 (60-90)	Additional analyst time (minutes)

Delayed Hemolytic Transfusion Reaction	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Exclusion of administrative errors (%)	75 (0-100)	69 (0-100)	
Hemolysis Investigation (%)	88 (1-100)	88 (1-100)	
Blood group serology investigation (%)	88 (1-100)	88 (1-100)	
Bacteriology (%)	75 (0-5)	13 (0-1)	
Additional check(s) blood biochemistry (average)	1.5 (1-3)	0.8 (0-2)	
Additional check(s) antibody screening / blood group serology (average)	1.4 (0-2)	1 (0-2)	
Longer hospital stay (in days)	0.8 (0-2)	0 (0-0)	
Additional Hb check(s) (average)	2.1 (1-4)	1.1 (0-2)	
Extra nurse time (minutes)	19 (0-60)	10 (0-30)	
Haemovigilance co-worker time (minutes)	43 (0-120)	38 (0-120)	
Extra physician time (minutes)	34 (5-120)	14 (0-30)	
Additional blood transfusion(s) (average)	0.7 (0-2)	0.3 (0-2)	
Other	60 (60-60)	60 (60-60)	Additional analyst time (minutes)

Transfusion-Related Acute Lung Injury	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Exclusion of administrative errors (%)	100 (100-100)	100 (100-100)	
Hemolysis Investigation (%)	65 (0-100)	65 (0-100)	
Blood group serology investigation (%)	78 (0-100)	78 (0-100)	
Bacteriology (%)	46 (0-100)	36 (0-100)	
Chest X-ray (%)	96 (75-100)	83 (25-100)	
HLA investigation (%)	82 (0-100)	59 (0-100)	
Longer hospital stay (in days)	3 (2-5)	1 (0-3)	
Admission to ICU (in days)	2.3 (1-3)	0.6 (0-2)	
Extra nurse time (minutes)	74 (20-120)	34 (15-60)	
Haemovigilance co-worker time (minutes)	84 (0-300)	81 (0-300)	
Extra physician time (minutes)	61 (30-120)	36 (5-120)	
Other			

Transfusion-associated Circulatory overload	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Exclusion of administrative errors (%)	83 (1-100)	75 (0-100)	
Hemolysis Investigation (%)	27 (0-100)	28 (0-100)	
Blood group serology investigation (%)	27 (0-100)	28 (0-100)	
Bacteriology (%)	15 (0-100)	15 (0-100)	

Chest X-ray (%)	78 (20-100)	48 (0-100)	
HLA investigation (%)	5.6 (0-50)	6.3 (0-50)	
Longer hospital stay (in days)	1 (0-2)	0 (0-0)	
Admission to ICU (in days)	1.2 (0-3)	0 (0-0)	
Extra nurse time (minutes)	62 (10-120)	28 (5-60)	
Haemovigilance co-worker time (minutes)	57 (0-120)	41 (0-120)	
Extra physician time (minutes)	41 (15-120)	17 (5-30)	
Administration of diuretics	100 (100-100)	100 (100-100)	
Other			

Anaphylactic reaction	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Exclusion of administrative errors (%)	100 (100-100)	94 (50-100)	
Hemolysis Investigation (%)	40 (0-100)	40 (0-100)	
Blood group serology investigation (%)	55 (0-100)	40 (0-100)	
Bacteriology (%)	49 (0-100)	32 (0-100)	
Chest X-ray (%)	30 (0-100)	7 (0-50)	
HLA investigation (%)	15 (0-100)	14 (0-100)	
IgA investigation (%)	58 (0-100)	44 (0-100)	
Additional medication (antihistamine, adrenalin, possibly corticosteroids)	100 (100-100)	100 (100-100)	
Longer hospital stay (in days)	1.9 (1-3)	0.2 (0-1)	
Admission to ICU (in days)	0.9 (.5-1)	0 (0-0)	
Extra nurse time (minutes)	40 (15-60)	28 (10-60)	
Haemovigilance co-worker time (minutes)	53 (0-120)	38 (0-120)	
Extra physician time (minutes)	42 (15-120)	16 (5-30)	
Other	15 (15-15)	15 (15-15)	Additional analyst time (minutes)

Other allergic reaction	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Exclusion of administrative errors (%)	63 (0-100)	63 (0-100)	
Hemolysis Investigation (%)	15 (0-100)	15 (0-100)	
Blood group serology investigation (%)	15 (0-100)	15 (0-100)	
Bacteriology (%)	3.1 (0-25)	0.6 (0-5)	
Additional medication (antihistamine)	100 (100-100)	86 (0-100)	
Longer hospital stay (in days)	0.5 (0-2)	0 (0-0)	
Extra nurse time (minutes)	26 (5-60)	16 (5-30)	
Haemovigilance employee time (minutes)	41 (0-120)	38 (0-120)	
Other			

New allo-antibody formation	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Blood group serology investigation (%)	88 (0-100)	88 (0-100)	
Hemolysis Investigation (%)	36 (0-100)	29 (0-100)	
Extra nurse time (minutes)	0 (0-0)	0 (0-0)	
Haemovigilance co-worker time (minutes)	28 (0-60)	23 (0-60)	
Inform patient, card, record in national registry	100 (100-100)	100 (100-100)	
Other	60 (60-60)	60 (60-60)	Additional analyst time (minutes)

Post transfusion bacteremia/sepsis	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Exclusion of administrative errors (%)	81 (0-100)	75 (0-100)	
Hemolysis Investigation (%)	53 (0-100)	46 (0-100)	
Blood group serology investigation (%)	65 (0-100)	65 (0-100)	
Bacteriology (%)	100 (100-100)	100 (100-100)	
Longer hospital stay (in days)	2.3 (0-5)	0.7 (0-2)	
Extra nurse time (minutes)	56 (15-120)	26 (5-60)	
Haemovigilance co-worker time (minutes)	43 (0-120)	38 (0-120)	
Extra physician time (minutes)	55 (15-120)	29 (10-60)	
Broad-spectrum antibiotics	100 (100-100)	100 (100-100)	
Other	60 (60-60)	60 (60-60)	Additional analyst time (minutes)

Post transfusion viral infection	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Hemolysis Investigation (%)	0 (0-0)	0 (0-0)	
Extra nurse time (minutes)	14 (0-50)	3.6 (0-15)	
Haemovigilance co-worker time (minutes)	31 (0-60)	26 (0-60)	
Extra physician time (minutes)	58 (15-180)	53 (10-180)	
Virological investigation	100 (100-100)	100 (100-100)	
Treatment and check-ups	100 (100-100)	100 (100-100)	
Other	30 (30-30)	30 (30-30)	Additional time out patient clinic nurse (minutes)

Other reactions	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Exclusion of administrative errors (%)	100 (100-100)	100 (100-100)	
Hemolysis Investigation (%)	86 (50-100)	76 (25-100)	
Blood group serology investigation (%)	83 (50-100)	69 (25-100)	
Bacteriology (%)	68 (25-100)	54 (5-100)	
Longer hospital stay (in days)	1.6 (0-3)	0.3 (0-2)	

Admission to ICU (in days)	0.2 (0-1)	0 (0-0)	
Extra nurse time (minutes)	28 (5-60)	34 (5-120)	
Haemovigilance co-worker time (minutes)	41 (0-120)	39 (0-120)	
Extra physician time (minutes)	38 (5-120)	20 (5-60)	
Chest X-ray (%)	36 (1-50)	13 (0-50)	
ECG (%)	36 (0-75)	4 (0-10)	
Other	60 (60-60)	75 (60-90)	Additional analyst time (minutes)

Section B: Complementary investigation

Ruling out administrative errors	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Identification check of the patient (in bed) (%)	89 (0-100)	89 (0-100)	
Identification of correct transfusion bag (%)	100 (100-100)	100 (100-100)	
Identification check patient (when sampling blood) and identification of sample tubes (%)	94 (50-100)	79 (0-100)	
Check correct selection of blood component (+ lab technician) (%)	94 (50-100)	89 (0-100)	
30 minutes of work for the nurse in total per transfusion reaction (%)	70 (10-100)	53 (0-100)	
Other	30 (30-30)	30 (30-30)	Additional analyst time (minutes)

Hemolysis diagnostics	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Assess plasma + urine color (%)	86 (0-100)	81 (30-100)	
LDH after 24-48 hours (%)	89 (0-100)	76 (5-100)	
Bilirubin (unconjugated) (%)	89 (0-100)	71 (0-100)	
Haptoglobin (%)	87 (0-100)	76 (5-100)	
Other	0 (0-0)	0 (0-0)	LDH determination 2 hrs post transfusion

Blood group serology diagnostics	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Repeat ABO and Rhesus D blood group	81 (0-100)	92 (25-100)	
Antibody screening in indirect anti-globulin test (%)	79 (0-100)	90 (10-100)	
Direct anti-globulin test (check for mixed field) (%)	79 (0-100)	84 (10-100)	
Full crossmatch with patient samples from before and after transfusion (%)	79 (0-100)	84 (10-100)	
Determination of ABO and Rhesus D blood group of all donor RBC units	75 (0-100)	75 (0-100)	
(if applicable) antibody identification (%)	70 (0-100)	80 (10-100)	
In any case excluding other antibodies according to guideline before and after transfusion (%)	79 (0-100)	90 (10-100)	
If (biochemical) hemolysis present,	58 (0-100)	41 (0-100)	

investigation of eluate in a sensitive technique (even if DAT is negative) (%)			
If eluate is positive, testing of patient for the cognate antigen (check for to mixed field) (%)	79 (0-100)	79 (0-100)	
Testing donor unit for the cognate antigen (%)	67 (0-100)	78 (0-100)	
If (biochemical) hemolysis found but negative findings in above investigations, consulting the reference laboratory (%)	40 (0-100)	40 (0-100)	
Other			

Bacteriological diagnostics	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
Blood cultures (aerobic/anaerobic) from patient (%)	82 (0-100)	86 (30-100)	
Cultures (aerobic/anaerobic) on remaining blood and all units administered before or during the transfusion reaction (%)	70 (0-100)	68 (0-100)	
Other	86 (0-100)	93 (50-100)	

Chest X-ray	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
When clinical and X-ray TRALI: HLA and granulocyte antibodies in donor(s) and patient in consultation with Sanquin (%)	100 (100-100)	88 (0-100)	
Other			

IgA diagnostics	Severity grade 2, 3 or 4	Severity grade 0-1	Further comments
IgA level, anti IgA, possibly IgA subclass investigation (%)	64 (0-100)	58 (0-100)	
Other			

Section C: preventability of transfusion reactions			
Transfusion reaction	Point estimation	Range	
		min	max
NHTR (%)	2 (0-5)	0 (0-0)	5 (0-10)
AHTR (%)	52 (0-100)	71 (0-98)	78 (10-100)
DHTR (%)	19 (0-80)	19 (0-70)	51 (10-95)
TRALI (%)	25 (0-99)	35 (0-98)	44 (5-100)
Transfusion-associated circulatory overload (%)	57 (0-95)	49 (10-90)	68 (20-100)
Anaphylactic reaction (%)	18 (0-50)	14 (0-40)	30 (20-60)
Other allergic reaction (%)	23 (0-90)	31 (0-85)	44 (0-95)
New allo-antibody+B246 (%)	38 (0-80)	38 (0-70)	53 (0-90)
Post transfusion bacteremia / sepsis	34 (0-90)	41 (0-85)	51 (0-100)
Post transfusion viral infection (%)	36 (0-99)	45 (0-98)	53 (0-100)
Other reactions (%)	5 (0-30)	7 (0-20)	13 (0-40)