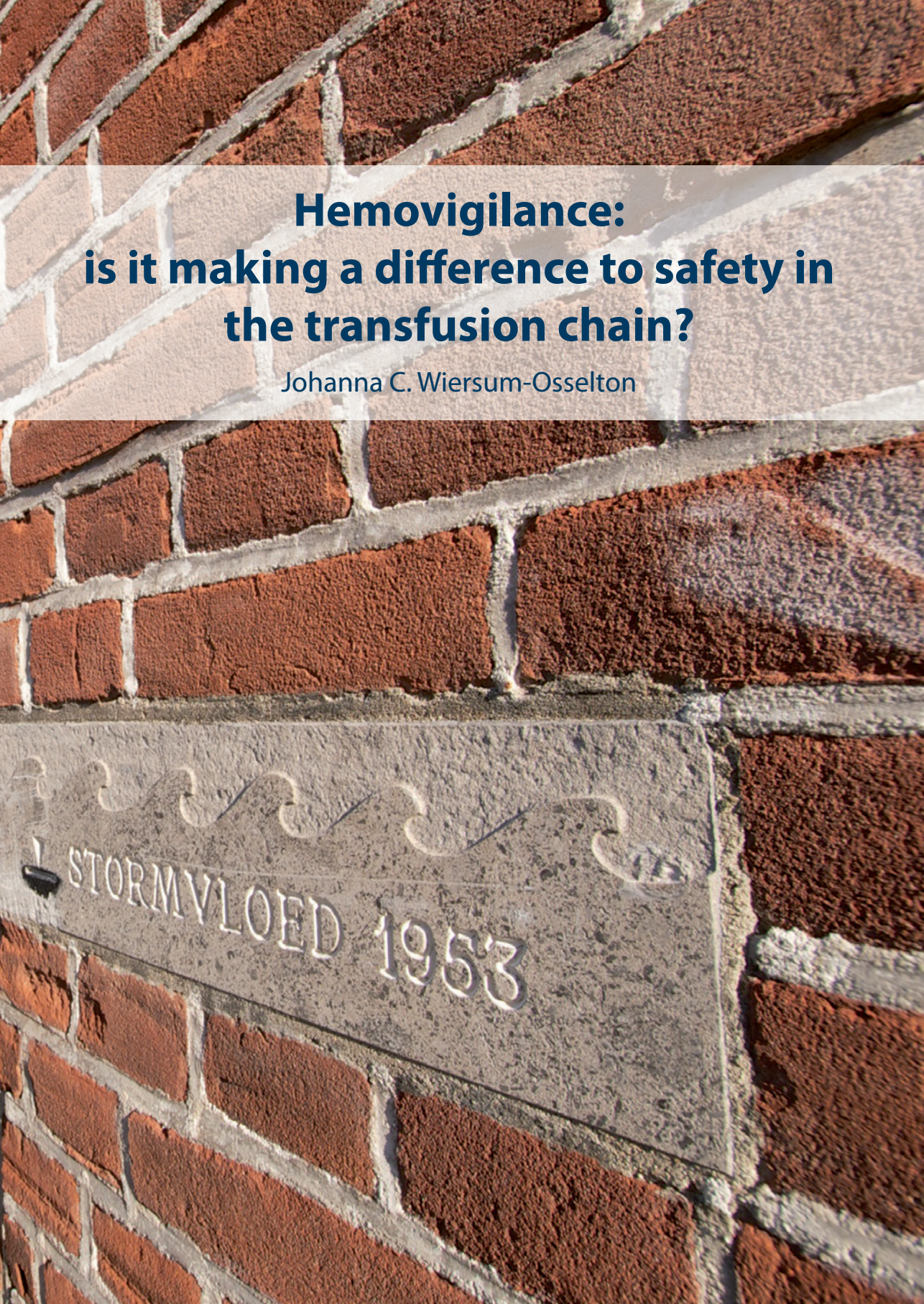


# Hemovigilance: is it making a difference to safety in the transfusion chain?

Johanna C. Wiersum-Osselton

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**TRIP Promotiereeks**

Stichting TRIP (Transfusie- en transplantatiereacties in patiënten) heeft ten doel het bevorderen van hemovigilantie en biovigilantie in Nederland. TRIP biedt promovendi die relevant onderzoek hebben verricht de mogelijkheid hun dissertatie te publiceren in de TRIP promotiereeks.

**Hemovigilance: is it making a difference to safety in the transfusion chain?**

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Dreischor village. Stone marking the water level in the 1953 flood, after which dykes were strengthened and dams constructed. Hemovigilance is about learning from what went wrong in the past and taking measures to increase safety.

# Hemovigilance: is it making a difference to safety in the transfusion chain?

(met een samenvatting in het Nederlands)

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te verdedigen op dinsdag 19 maart 2013
klokke 15.00 uur

door

Johanna Caroline Wiersum-Osselton
geboren te Southampton (Verenigd Koninkrijk)
in 1956

**PROMOTIECOMMISSIE:**

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# Introduction

**Chapter 1**
Introduction

# CHAPTER 1

# Introduction

Adapted from:
Quality validation of data in national hemovigilance systems in Europe:
report of a survey of current state of practice

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*Short paper, Vox Sanguinis 2012, DOI: 10.1111/j.1423-0410.2012.01659.x*

## INTRODUCTION

Reporting systems for adverse reactions or adverse events associated with blood transfusion arose in Europe in the aftermath of public outcry following the contaminated blood scandals and legal cases of the 1980s and 1990s. Hemovigilance can be defined as 'a set of surveillance procedures covering the whole transfusion chain from the collection of blood and its components to the follow-up of its recipients, intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence and recurrence'.[1] The first hemovigilance systems, those in France and in the United Kingdom, are quite different from each other.[2,3] SHOT (Serious Hazards of Transfusion) in the UK requests the reporting of "all serious hazards" whereas in France it is mandatory to report all adverse transfusion reactions and transfusion errors, regardless of severity of patient morbidity and the relationship (imputability) to transfusion. (Brief descriptions of the French hemovigilance system and SHOT are given in Annexes 1 and 2 to this chapter.) Countries outside Europe have followed suit – the Quebec province in Canada was among the early uptakers and developed a comprehensive system similar to the French but based within the public health structures and on a voluntary basis.[4] In The Netherlands a recommendation on hemovigilance was issued by the Blood Transfusion Advisory Council (College voor Bloedtransfusie of the – then – 22 Red Cross Blood Banks) in 1997 but it was not till 2002 that the TRIP (Transfusion Reactions In Patients) Dutch National Hemovigilance Office became functional. The Dutch Hemovigilance Office is run by an independent foundation which is governed by representatives of professional bodies. In this aspect it is modelled on SHOT, however it collects reports of all severity levels of transfusion reactions as well as errors and incidents including near miss (see www.tripnet.nl and Annex 3).

Since 2005 European Union (EU) legislation has mandated that member states must have a system for receiving and registering reports of serious adverse reactions and serious adverse events relating to quality and/or safety of blood or components for transfusion.[5] A serious adverse reaction is defined as 'an unintended response in donor or in patient associated with the collection or transfusion of blood or blood components that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalisation or morbidity'. A serious adverse event is defined in the directive as 'any untoward occurrence associated with the collection, testing, processing, storage and distribution, of blood and blood components that might lead to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalisation or morbidity'. The latter definition is at variance with usage of 'adverse event' in the setting in clinical studies since it denotes an error or untoward occurrence (incident) irrespective of whether there was actual patient harm. When the legislation came into force the existing hemovigilance systems made modifications where necessary in order to ensure compliance. Other countries had to create systems de novo. The

European legislation also requires the submission of an annual overview of serious adverse reactions and serious adverse events to the European Commission according to specified definitions. The serious adverse reactions are to be listed according to their imputability, i.e. the likelihood that they can be ascribed to the blood or blood component. Also the definite and probable cases are to be listed separately according to whether there was a link with the quality and/or safety of the blood component (e.g. when an infection is transmitted). To date the collected information has been publicly presented by Commission representatives at a number of symposia in anonymous fashion as to the countries which submitted the data and with the explicit statement that the reporting so far must be seen as a learning exercise. Variations have been seen between country data but it has not been possible to examine possible explanations.

## Survey

For hemovigilance to be an instrument for improving safety of blood transfusion, it must be based on quality-assured data. The value of data for comparisons, benchmarking and trending depends firstly on the coverage: have all relevant organisations contributed information and if not, is it known which proportion of national blood use is covered? Secondly, have the reactions and events been assessed according to the same criteria and can this assessment be verified? For instance, did all the reports of TRALI (Transfusion-related acute lung injury) in a country meet certain criteria? These two quality aspects have an obvious impact on the number of events which will be reported in a particular category. We performed a simple descriptive survey of whether the data collected by the European national hemovigilance systems are validated as to completeness of coverage and capture information by which the type of reaction may be verified.

## Methods

The mandatory European reporting is laid down in the European Directives 2002/98/EC and 2005/61/EC. Briefly, blood establishments are required to report serious adverse reactions and events which may be attributable to the quality and safety of blood and blood components to the national competent authority for blood. Hospitals must report to the blood establishment if a serious reaction or event may have a relation to component quality or safety; they may also report directly to the competent authority. A non-binding guidance document has been provided to assist countries in their data classification,[5] which includes the International Society of Blood Transfusion (then still in draft form) definitions for the non-infectious transfusion reactions and the SHOT definition for transfusion-transmitted infection.[6,7]

We sent hemovigilance contact persons from the national competent authorities a short email questionnaire. The questionnaire requested information on the hemovigilance system,

documentation of coverage, validation of report types and outputs. If the reply was supplied by a different person, this was accepted providing that the intended responder was in agreement, as documented by email "copying-in".

## RESULTS

### Response and organisation of hemovigilance systems

Responses were received from 23 out of the 27 (85%) European Union member states. Nine responding countries created their national hemovigilance system subsequent to the Directive. Three countries made major changes to previous activity in order to become compliant. In seven the reporting of serious adverse reactions and events became mandatory while in four there was already mandatory reporting as required under the Directive. The system is directly run by the competent authority in 17 countries and by a separate organisation and/or the blood establishment(s) in six. In four responding countries a separately run non-mandatory system exists which feeds information to the mandatory system to a varying extent. Table 1 summarises basic characteristics of the reporting systems.

### Documentation of coverage

In five responding countries there is a single national blood establishment. Out of the 18 countries with multiple blood establishments, seven confirmed that all submitted reports. Eight received reports from median 80% (range 25 – 90%) of blood establishments and confirmation of "nil to report" or activity levels from the others. In three responding countries it was not known what percentage of blood establishments participated.

Four of the 23 countries state that 100% of hospitals contributed reports or confirmed nil to report. Ten specify that median 76% (range 47 – 96%) of hospitals provided information while nine systems do not know what percentage of hospitals participated.

### Assessment of reported data and outputs

In 12 responding countries (52%), supporting data were supplied with all (eight countries) or only serious reports (four countries). This data, it was confirmed, could lead to modification of event type. In eleven countries most or all reports are accepted without verification. In eighteen (78%) countries the hemovigilance system makes a public report of aggregate findings. Ten systems provide specific feedback to reporting hospitals and/or blood establishments about their reported events.

## Discussion of the survey findings

This mini-survey showed that the legislation has resulted in all the responding countries having an established national hemovigilance system. The majority but not all of the systems (87%) document the participation level of blood establishments and only 14 countries (61%) document the coverage of hospitals. Usefulness of the data for comparisons can be improved if all systems document the participation of reporting organisations and the coverage of the total distributed blood components so that this can be taken into account.

**Table 1** Characteristics of national hemovigilance systems broken down by organisation of blood supply

| Characteristic of hemovigilance system | Responding countries | | |
|---|---|---|---|
| | Countries with single nationwide BE[a] (n=5) | Countries with multiple BE (n=18) | Total (n=23) |
| **Organisation of blood supply** | | | |
| Hospital-based | | 7 | 7 |
| Independent | 5 | 2 | 7 |
| Both | | 9 | 9 |
| **Hemovigilance system run by** | | | |
| Competent authority | 3 | 14 | 17 |
| Other and/or BE[a] | 2 | 4 | 6 |
| **Changed by legislation** | | | |
| No | 1 | 3 | 4 |
| New system | 1 | 8 | 9 |
| Serious reports became mandatory | 3 | 4 | 7 |
| Other change | - | 3 | 3 |
| **Reports captured** | | | |
| Transfusion reactions and adverse events | | | |
| Serious only | 1 | 9 | 10 |
| All | 4 | 9 | 13 |
| Donor adverse reactions | | | |
| Serious only | 3 | 9 | 12 |
| All | 2 | 8 | 10 |

[a] A blood establishment (BE) is an organisation which performs collection, testing and/or processing of blood or blood components, i.e. hospital blood transfusion laboratories which themselves perform secondary processing such as irradiation of blood components must be licensed as blood establishments even if they do not perform collection and donor testing.

In twelve countries the hemovigilance system receives supporting information with at least the serious reactions so these can be verified. In practice the assessment of reports is not easy; not infrequently the category is modified from the original reporting category. In our opinion, external expert review of serious reports should be formally included by all systems prior to preparation of annual reports. Communicating the review panel's advice to reporting professionals is a way of improving uniformity of assessment and data quality as well as

showing that the reports are taken seriously by the receiving body. This practice is in place in at least six systems.

Eighteen out of the 23 responding countries annually publish the findings. Additionally, five respondents commented that data are presented in national or regional meetings. Public reporting is desirable because it provides transparency and knowledge of documented risks. Moreover public reporting will encourage participation and ensure that any recommendations for improvement are heard by those who are involved in the transfusion "chain".

Commendably, the European Commission representatives have consistently asserted that the reporting is a learning exercise and that the hemovigilance reporting systems should first and foremost be useful for the countries themselves. For future data collection exercises, the Commission could improve annual reporting by modifying the reporting form to include the percentage of reporting establishments which supplied information and the percentage of national blood use that is covered.[1]

A strength of this study is the high response rate of 23 out of 27 countries, which is remarkable for a non-mandatory survey. However the brevity of the questionnaire constitutes a limitation, for instance it did not capture details about how the system communicates with those who submit reports, nor of methods of assessing adverse event (error and incident) reports. Another limitation is that it was impossible to assess the level of compliance of physicians and other professionals within reporting establishments.

In summary, our survey of European Union member states' hemovigilance systems found that nine out of 23 responding systems started as a consequence of the legislation which rendered reporting mandatory. Currently the coverage is not always documented and almost half of the systems do not routinely verify the serious reports. These aspects should be included in the ongoing efforts to improve reporting.

### Final conclusion of the survey and introduction to the thesis question

In our mini-survey we considered quality aspects of the collected data within different European hemovigilance systems and found that there is room for improvement as regards documenting coverage and validating the types of reported event. The Dutch hemovigilance system meets these basic quality criteria: the coverage is documented and has run at approximately 96% of hospitals since 2006. Its procedures include expert review of all serious reports; findings have been published.[6]

1 These features were included in the form for the 2012 reporting exercise, circulated in July 2012

Hemovigilance reporting is regarded as the norm in Europe as well as in many non-European countries. The stated objective of collecting hemovigilance data is to analyse the reported adverse reactions and events and make recommendations for improving transfusion safety. This has prompted the study question of this thesis: after ten years of national hemovigilance activity in The Netherlands, can we say that it has made a difference to transfusion safety?

In the first part of the thesis we focus on donor vigilance and the safety of those who donate blood or hematopoietic stem cells. Chapter 2 introduces this section with a description of recent developments in studying blood donor complications and their prevention. Chapter 3 studies risk factors for various donor complications and collection problems at first whole blood donation in comparison to repeat donors, and examines the impact of these problems on donor return. In chapter 4 we present a study of short-term safety in a cohort of related healthy donors who underwent G-CSF mobilisation and collection of peripheral blood stem cells by hemapheresis and also consider whether there is any indication of long-term increased risk of malignancy or cardiovascular events.

The second part of this thesis considers topics from recipient hemovigilance. Chapter 5 uses the reports to TRIP as the basis for a case-control study of risk factors for the most common type of report, that of new allo-antibodies. In chapter 6 we study the effect of the intervention of introducing male-only plasma for transfusion in order to reduce the risk of TRALI. Chapter 7 collates information from several years of national hemovigilance reporting to examine the question: do hospitals with a relatively high incidence of reported transfusion reaction have fewer reports of incorrect blood component transfused, i.e. do they appear to be safer?

The final chapter gives an overview of the reported studies and considers whether they have demonstrated a beneficial effect of hemovigilance on transfusion. The discussion will also reveal directions in which future development of hemovigilance activity can open up further prospects for improving safety for donors or recipients of blood or blood components.

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## ANNEX 1 THE FRENCH HEMOVIGILANCE SYSTEM

(reference 1 and http://ansm.sante.fr/Produits-de-sante/Produits-sanguins-labiles)

Hemovigilance was introduced as a mandatory activity in 1994. From the beginning, all severity levels of transfusion reaction were included, as well as all degrees of imputability to the transfusion.

In each of the approximately 1500 hospitals or clinics which perform blood transfusions a physician is responsible for hemovigilance reporting (hemovigilance correspondent) and ensuring compliance with regulations concerning blood transfusion. In France, pre-transfusion blood testing and crossmatching are generally performed by the Établissement de Transfusion Sanguine (ETS) of the blood service (Établissement Français du Sang, EFS). The hemovigilance correspondent of the ETS coordinates the necessary additional investigations following a transfusion reaction. The third actor at the local/regional level is the regional hemovigilance coordinator at the regional health agency (coordonnateur régional d'hémovigilance, CRH), who oversees compliance with regulations in the region and follows up on actions taken by hospital transfusion committees following a reported transfusion error. The hospital hemovigilance correspondent, the ETS hemovigilance correspondent and the regional hemovigilance coordinator all verify the details of a hemovigilance report and sign it off in the digital reporting system (e-fit, taken into use in 2004).

At the national level, the role of the competent authority was assumed by the hemovigilance department at the Agence française de sécurité sanitaire de produits de santé, Afssaps, until May 2012. This has now been replaced by the Agence nationale de sécurité du médicament et des produits de santé, ANSM. The staff of the competent authority can add queries to the reports in the e-fit database, as can staff from the central hemovigilance department of the EFS. The Afssaps/ANSM publishes an annual hemovigilance report (available on the website) based on all reports of which the investigations have been concluded. The EFS also compiles a report; because e-fit is a real-time database the figures may differ depending on the date of downloading. The overall level of reported transfusion reactions was 3.0 per 1000 units issued in 2000 and has gradually declined to 2.5 in 2010. Variation in reporting level is noted between the regions and between individual hospitals. A decline in ABO-incompatible red blood cell transfusions has been observed since approximately 2000 (discussion in Chapter 7).

Important themes have been addressed by national working parties of professionals who work with Afssaps/ANSM staff to develop new forms and guidance documents. These themes include allergic transfusion reactions, TRALI and transfusion-associated circulatory overload and root cause analysis of incidents. Recommended (mandatory) changes of practice are

generally introduced through ministerial circulars. At the time of writing the full effect of the restructuring of the national competent authority and the new arrangements regarding the working groups are not yet clear.

## ANNEX 2 SHOT (SERIOUS HAZARDS OF TRANSFUSION), UNITED KINGDOM

(Reference 2 and www.shotuk.org)

The SHOT scheme was launched in 1996. It is run by a steering group comprised of representatives of professional bodies involved with blood transfusion. The scheme captures reports on serious reactions or errors/incidents associated with transfusion of blood components or with the use of anti-D. The SHOT reporting scheme is voluntary in principle but professionally mandated. Practitioners in hospitals submit an initial report, about which additional details are requested using a further questionnaire which is specific to on the type of reaction or event which has been reported.

With the advent of the obligation under EU legislation to report serious adverse reactions and serious adverse events, these serious reports have been collected by the competent authority, the Medicines and Healthcare Products Regulatory Agency (MHRA). An online reporting system, SABRE (Serious adverse blood reactions and events), was introduced to facilitate reporting to SHOT and/or MHRA as appropriate. Dendrite, an improved reporting module for SHOT and/or MHRA reports, became operational in 2010.

SHOT received reports from 95% of NHS organisations in 2010. Each year a hemovigilance report is published under the responsibility of the SHOT steering group. The reports incorporate multiple learning points and recommendations for practice. Through the years, SHOT has particularly highlighted the hazards of incorrect transfusions and, more recently, incidents leading to inappropriate and unnecessary transfusion. Near miss reports were analysed for the first time in the 2010 annual report. As the scope of reporting has widened, the annual total number of reports has gradually increased from 0.13 per 1000 units distributed in 2001-2 to approximately 1.0 per 1000 in 2011. A decline in ABO-incompatible red blood cell transfusions has been observed since approximately 2004 (discussed in chapter 7).

In the years during which SHOT has been operational, a series of Department of Health (governmental) Better Blood Transfusion circulars (1998, 2002, 2007) have issued recommendations on blood transfusion laboratory and clinical transfusion practice. In hospitals, transfusion practitioners have an important role in overseeing transfusion practice and staff training. The hospital transfusion team (generally a subgroup of a larger hospital transfusion committee) assesses hemovigilance reports and leads actions to monitor and improve transfusion safety. The report "An organisation with a memory" (2000) by a Department of Health expert group was key in claiming awareness for patient safety issues in healthcare in general.

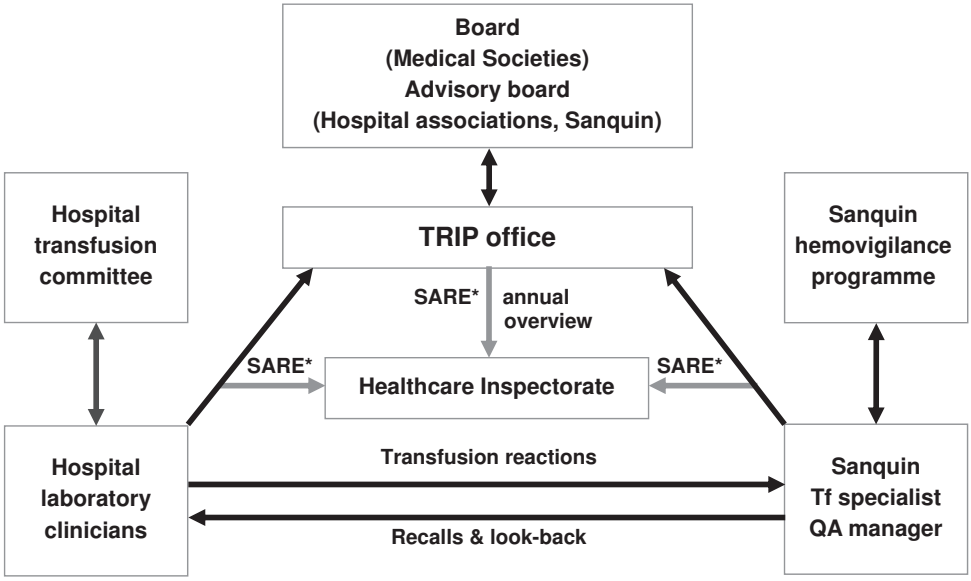
## ANNEX 3 TRIP DUTCH NATIONAL HEMOVIGILANCE OFFICE (WWW.TRIPNET.NL)

TRIP (Transfusion Reactions In Patients) Foundation was founded in 2001 by representatives of the various professional organisations involved in the field of blood transfusion. Since December 2002, the TRIP National Hemovigilance Office has managed the national reporting system for transfusion reactions in collaboration with contact persons in the hospitals and the blood service, Sanquin Blood Supply (Sanquin Bloedvoorziening). Reporting to TRIP is anonymous and voluntary in principle. Participation is considered the norm by the Healthcare Inspectorate (IGZ) and the national "CBO" blood transfusion guideline.

TRIP receives and analyses reports of all levels of severity. The digital reporting form captures data on relevant clinical findings and results of investigations and allows for questions and provision of additional comment. The TRIP staff assess all reports and communicate with the reporters if necessary to verify the stated category, severity grade and imputability of (potentially) serious reports. An Expert Committee appointed from the TRIP Governing Board assesses all serious reports and a sample of non-serious reports.

Figure 1 shows the communication lines for hemovigilance reporting in The Netherlands. In the hospitals TRIP communicates with a regular contact person, the hemovigilance officer who is often the chief biomedical scientist in the transfusion laboratory. Most hospitals have also appointed transfusion safety officers who prepare the transfusion reaction or incident reports, provide training, perform audit etc.

Under the European directive 2002/98/EC there is an obligation to report serious adverse reactions and adverse events that may be associated with the quality and/or safety of blood components to the competent authority, IGZ. TRIP provides the analysis and reporting of these serious (grade 2 or higher) reports on behalf of the IGZ. Hospitals can use the TRIP online reporting system to make reports available to the IGZ; this is not automatic but remains the hospital's responsibility. Figure 2 shows the participation from 2003 to 2011.




*SARE = Serious adverse reactions and events
Abbreviations: Tf = transfusion; QA = quality assurance

**Figure 1.** Communication lines for hemovigilance reporting

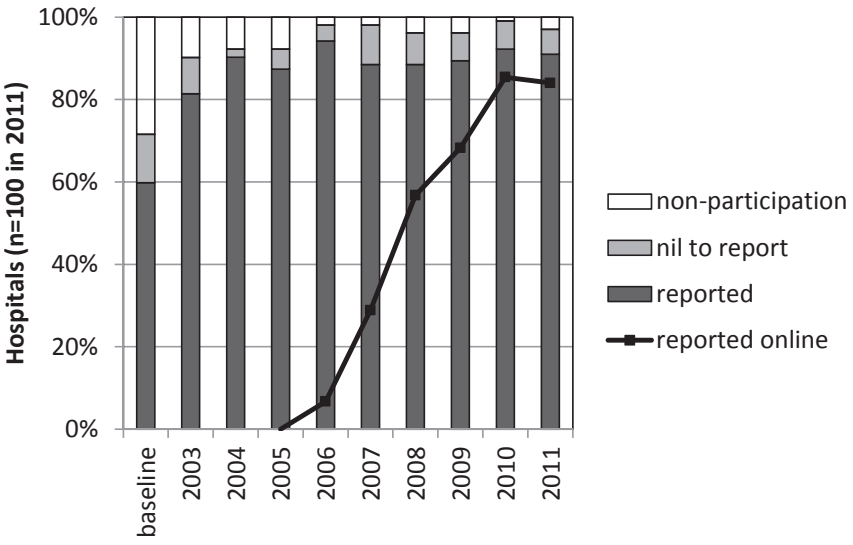



**Figure 2.** Participation in reporting to TRIP

# PART 1

## Donor (hemo)vigilance

# CHAPTER 2

# Donor vigilance – what are we doing about it?

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## ABSTRACT

Donor vigilance is the systematic monitoring of adverse reactions and incidents in blood donor care with a view to improving quality and safety for blood donors. Standard international definitions are available for surveillance purposes. In recent years advances have been made in determining risk factors for vasovagal and other adverse reactions to blood donation as well as in evaluating preventive measures. Blood establishments should record all adverse reactions in blood donors. Besides its use for individual donor care, this information can be reviewed within and between organisations to guide policy decisions and research for improving donor care.

## 1. INTRODUCTION: WHAT IS DONOR HEMOVIGILANCE?

The impressive advances which have been made in transfusion therapy and in treatments which are not possible without transfusion support, are only possible because of voluntary, most often unremunerated donation of whole blood or blood components by donors worldwide. In recent years awareness has grown of the importance of monitoring safety and quality of care for blood donors, both as a professional obligation and in the interests of maintaining public willingness to donate.

Hemovigilance is "a set of surveillance procedures covering the whole transfusion chain from the collection of blood and its components to the follow-up of its recipients, intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence and recurrence".[1] Donor (hemo) vigilance is part of this process, and can be defined as the systematic monitoring of adverse reactions and incidents in the whole chain of blood donor care, with a view to improving quality and safety for blood donors.[2] The full term, donor hemovigilance, draws the distinction between vigilance concerning blood donors and other donors, for instance stem cell or organ donors. For the remainder of this paper, for the sake of brevity we shall refer to donor vigilance.

Donor vigilance firstly concerns the surveillance of adverse reactions (complications) from blood donation and an organized approach to attempting to reduce them as far as possible. Donor vigilance should also encompass the systematic recording and analysis of errors (incidents) in blood donor care. Additionally, procedures should be in place for handling post-donation information as well as for donor counseling following unexpected findings, such as positive or false-positive test results. In the remainder of this paper the focus will be on complications of blood donation.

## 2. INTERNATIONAL ADVANCES IN DONOR VIGILANCE

A standard reference list of surveillance definitions for complications of blood donation has been developed by the Haemovigilance working party of the International Society for Blood Transfusion (ISBT) in collaboration with the International Haemovigilance Network (IHN; then: European Haemovigilance Network). This list is available on the websites of the ISBT and IHN.[3] As well as the definitions for different types of complication, criteria are given for severe (serious) complications, which are broadly: hospitalization, life-threatening nature, long-term morbidity or fatal outcome. The standard also draws attention to the consideration of imputability, the likelihood that an adverse outcome can be attributed to the blood donation; critical assessment of the imputability is particularly relevant for events which did not immediately follow the donation (e.g. a heart attack several days after donating). For the

sake of international collaboration, it is desirable for countries to ensure that their definitions are the same as, or can be mapped to, the international definitions.

There is increased interest in reporting, treating and attempting to reduce complications of blood donation. Table 1 presents selected findings from a number of recent studies reporting rates of vasovagal reaction and risk factors. Of note, it is seen in large datasets that the risk of a vasovagal reaction is increased in female donors, younger and first-time donors as well as donors with lower blood volume as estimated from height and body weight.[4,5] Delayed vasovagal reactions are a particular cause for concern because they occur off site and are more likely to lead to accidents; these have been found to be associated with female sex and lower estimated blood volume.[6] A water drink before donation, use of applied muscle tension and social support during donation have been found effective in reducing minor vasovagal reactions and/or increasing likelihood of donors returning for subsequent donations.[7-9] In these intervention studies use is commonly made of an inventory questionnaire so that occurrence of milder reactions can be studied, using smaller groups because of the higher rate of occurrence.[10]

## 3. INTERNATIONAL SURVEILLANCE DATABASE FOR TRANSFUSION-ASSOCIATED REACTIONS AND EVENTS (ISTARE)

At the initiative of the IHN and in collaboration with the ISBT Haemovigilance working party, an international surveillance database is under development for transfusion-associated adverse reactions and events. The database also captures information on blood donation complications. Pilot rounds of data collection have collected data from 2006 up to and including 2009; over 15 national hemovigilance systems have participated in one or more of these rounds. It is hoped that online data collection will take place in the autumn of 2011 for the first time.[1]

Not all participating countries have been able to provide data on complications of blood donation: this rose from 6 out of 11 (54%) for 2006 to 11 out of 17 (65%) for 2009.[11] Because the rates of complications differ appreciably between whole blood donation and apheresis, data are submitted separately if this is possible; however not all countries are able to differentiate between donation types and levels of severity of complications. In the data considerable variation is seen between national rates of recorded donation complications. For instance, the median rate of vasovagal reactions (faints and pre-faints taken together) to whole blood donation in 2009 was 4.1 per 1000 (6 countries) and ranged from 0.05 to 10.6; serious vasovagal complications were reported with a median rate of 0.06 per 1000 collections (range

1 Note (November 2012) This took place; results presented by C. Politis at International Haemovigilance Seminar, Montreal, April 2012

0-0.3, whole blood and apheresis taken together) by 9 countries. Local complications, predominantly hematomas, were reported at a median rate of 1.1 per 1000 for whole blood donation and apheresis combined (range 0.04 to 5.9; 11 countries).

**Table 1.** Rates of vasovagal reactions and risk factors described in recent publications

| First author, year of publication | No. of collections | VVR (all donation types)* | VVR (whole blood donation)* | Remarks Risk factors |
|---|---|---|---|---|
| Newman 2003[19] | 1000 | | 53 | Telephone interview 3 weeks after donation |
| ISTARE pilot data 2008[11] | 10,363,270 | 4.1 (0.05-21)# | 6.1 (6 countries) | 9 countries supplied data |
| Sorensen 2008[20] | 41274 | | 4.0 (3.43-4.63) | Aarhus region in Denmark |
| Eder et al 2008[4] | 1,776,445 | | 30 (29.8-30.3) (0.13 excl. presyncope[$]) | 14% of donors aged 16-19 yrs. 16-17 yrs[1]: OR 4.8x (4.75-4.95; presyncope) |
| Wiltbank 2008[5] | 422,231 | | 14.3 (14.0-14.7) | Risk factors (univariate) 17-18yrs[2]: OR 4.19 (3.94-4.45) Female: OR 2.21 (2.09-2.35) 1st donation: OR 2.80 (2.66-2.94) |
| Kamel 2009[15] | 793,293 | 4.2 (4.0-4.3) | 5.2 (5.0-5.4) | "Moderate and severe" |
| NL July – Dec 2010 | 436,571 | 5.5 (5.3-5.7) | 6.0 (5.7-6.3) | [Unpublished data] |

VVR = vasovagal reactions per 1000 collections
# median, range of national rates
[$] reactions with loss of consciousness, prolonged recovery or injury
[1] reference group: 20 years and older
[2] reference group: 25 to 65 years

The progressive improvement in availability of data is encouraging but the large differences in reported rates in the pilot data need to be examined further. They may be partly explained by differences in procedures, for instance the volume drawn, is it adjusted according to donor size, is intravenous volume replacement given. Differences in completeness of reporting are also likely. Future discussion between national reporters on the nature and quality of the information should assist in achieving better comparability of data.

## 4. DONOR VIGILANCE IN THE NETHERLANDS: IMPLEMENTING AN IMPROVED CODING SYSTEM FOR RECORDING COMPLICATIONS OF BLOOD DONATION

In The Netherlands over 500,000 whole blood collections and 340,000 apheresis procedures (plasma and platelets) are performed annually, from a total of nearly 400,000 volunteer donors. The national code list for donor complications was revised in order to record more details and cover new procedures such as Rhesus immunisations.

After staff training in the autumn of 2009, the revised codes were introduced by administrative region during the first half of 2010. Following implementation, staff received feedback on wrongly used codes and were asked to correct them. Data were extracted from the blood service information system (eProgesa version 5.0.2, Mak-System International Group, Paris, France) for analysis. We performed a before-and-after comparison of routinely recorded information.

The overall rate of recorded donor complications increased. For instance, the rate of recorded vasovagal reactions (faints and prefaints) was 0.46 per 100 whole blood collections in 2009 and rose to 0.60 per 100 in the second half of 2010 [unpublished data]. There were no changes in donor demographics or procedures to explain such a rise so we conclude it is most likely the result of improved recording. Using the new codes, rates of specific (sub) types of donor complications can be calculated; causes of failed collections and product loss in the collection centres can be analysed using the same data. The recorded complications and procedural problems have been reviewed with a view to developing specific projects to reduce complications and reduce rates of unsuccessful procedures. The improved recording also opens opportunities for scientific analysis, international comparisons and benchmarking.

Additional improvement measures which have been undertaken by Sanquin include revision of the SOP for venepuncture performance which now cautions explicitly against needle manipulation and repeated stabs if puncture is not immediately successful. Recertification in skin cleansing and venepuncture technique has been introduced. Extra precautions have been implemented to further reduce the risk of mix-up of saline and citrate solutions during apheresis procedures.

## 5. CHALLENGES FOR DONOR VIGILANCE

As described above, international collaboration and comparison of data open possibilities for benchmarking and hypothesis generation for further research. Furthermore, data sharing is the only way to advance knowledge of very low-frequency events, such as needle injury associated with long-term morbidity. For all data comparisons, use of common definitions is essential. Nevertheless, there are still differences between countries and blood establishments in types of collection procedures, volumes collected etc.

There are several challenging areas. One of these is that of iron depletion, particularly but not exclusively in whole blood donors. It is well established that repeated phlebotomy reduces iron stores, demonstrated by lower serum iron or ferritin levels[12,13] even within guidelines for minimum intervals between donations and maximum number per year (e.g. in The Netherlands

a maximum of three whole blood donations per year for women, five for men and always a minimal interval of 56 days). This leads to deferrals because of hemoglobin (or hematocrit or other screening test) and in some cases frank anemia for which iron supplementation treatment is required. Recent studies have started to assess the possible place of serum ferritin determination as a tool to monitor and improve the iron status of at-risk donors.[14] For donors who repeatedly fail the hemoglobin screen, the interval between donation can be extended and some donors may opt for plasmapheresis instead of whole blood donation. A recent Sanquin study has evaluated predictive factors for hemoglobin deferrals, so that donation intervals could in future adjusted pre-emptively.[15] Meanwhile it remains less clear what, if any, are the health consequences of depleted iron stores for asymptomatic healthy donors who maintain their hemoglobin levels. Some blood establishments favour oral iron supplementation (replacement) for some or all donors. Objections raised by others include the risk of masking iron loss caused by pathologies or of toxicity following accidental ingestion of the medication, as well as the consideration that volunteer donors should not be asked to take medication with the attendant risk of side effects. Further work is needed in this area to improve the evidence base for donor management recommendations; national policies will need to take account of local factors such as availability of donors and dietary patterns.

Another challenging area is that of possible long-term complications of repeated apheresis procedures: might development of osteoporosis be accelerated? Frequent plasmapheresis is associated with lower immunoglobulin content of the products.[16] Might repeated removal of plasma lead to depletion of immune capacity? It is important that further research is undertaken and published in these areas so that evidence-based measures can be implemented to safeguard donors' health.

Concern has been expressed about whether it is wise to publish information about complications of blood donation. Might it not put off potential blood donors and threaten the blood supply? This concern can be countered by a firm statement that it is an ethical obligation to be open and transparent about the occurrence of complications. This information should be supplied to donors before their donation, so that truly informed consent is obtained. If blood services take this responsibility seriously, they will ensure that balanced information is available. This information can incorporate recent knowledge about methods of reducing complications. Donors will thus be empowered and enabled to prepare adequately for their donation, thereby reducing the risk of complications and increasing their likelihood of becoming committed regular donors.[17]

In conclusion, the last years have seen advances in monitoring and studying the occurrence and prevention of complications of blood donation. It is recommended that all blood services

adopt a systematic approach to monitoring the rates of donor adverse reactions, in the interests of improving donor care.[18]

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# CHAPTER 3

# Risk factors for donor complications at first and repeat whole blood donation: cohort study with assessment of the impact on donor return

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## ABSTRACT

### Background

First-time donation is among recognized risk factors for vasovagal reactions (VVR) to blood donation and reactions are known to reduce donor return. We assessed associations between potential risk factors and VVR and needle-related complications at first-time whole blood donation in comparison to repeat donation and analysed the impact of complications on donor return.

### Study design and methods

We performed a cohort study on whole blood donations in The Netherlands from 1-1-2010 to 31-12-2010 using data extracted from the blood service information system. Donation data till 31-12-2011 were used to ascertain donor return.

### Results

In 2010 28,786 donors made first whole blood donations and there were 522,958 repeat donations. VVR occurred in 3.9% of first donations by males and 3.5% of female first-time donations compared to 0.2% and 0.6% respectively of repeat donations. Associations of VVR with other factors including age, body weight, systolic and diastolic blood pressure were similar in first-time versus repeat donors. Needle-related complications occurred in 0.2% of male and 0.5% of female first-time donations and in 0.1% and 0.3% respectively of repeat donations. Among first-time donors, 82% returned within one year following uncomplicated first donation and this was 55% and 61% respectively following VVR and needle-related complications; these percentages among repeat donors were 86%, 58% and 82%.

### Conclusion

Among first-time donors, females suffered less from VVR than males. Other risk factors had similar associations among first-time and repeat donors. VVR and needle-related complications at first as well as subsequent donation are followed by reduced donor return.

## INTRODUCTION

In the last two decades the occurrence of adverse reactions to whole blood donation and component apheresis has been increasingly studied[1-3]. Suggested risk factors for vasovagal reactions (VVR) include young age, low body weight or small size (small estimated blood volume), female sex and first-time donor status[4-8].

The occurrence of an adverse reaction reduces the likelihood of a donor returning and becoming a repeat donor[9-12]. It is important for blood centers to minimize donor complications, particularly at the first donation, in the interests both of donor safety and of maximizing the number of returning donors.

Hitherto most studies of risk factors have analysed first-time status as one among various parameters. This does not answer the question of whether the risk factors are the same for first-time donors and repeat donors. Analyses of risk factors among first-time donors for donation complications have been performed only for a limited number of parameters[13]. We examined risk factors among first-time whole blood donors in 2010 for the occurrence of vasovagal reactions, local needle-related complications or procedural problems in comparison to repeat donors, and assessed the impact of the different types of donation problems on donor return.

## MATERIALS AND METHODS

### Study design and population

We performed a cohort study including all first-time and repeat whole blood donations in 2010. Records of whole blood and plasmapheresis attendances to the end of 2011 were examined to evaluate the impact of problems at the index donation on donor return.

### Data extraction

We extracted data from existing databases on all whole blood donations in 2010 including recorded donor complications and procedural problems. Parameters included collection center (fixed site or mobile site), donor age, sex, donation type, month, pre-donation hemoglobin (Hb) and blood pressure, successful (≥ 450ml) or incomplete collection, time of day, donor height and weight; however the height and weight were not obligatory data in 2010 and 2011 so are not known for all donors. Data on daily outdoor maximum temperature in the center of the country were downloaded from the national meteorological institute website. In addition, all donor complication reports into the national quality management database were examined.

For each donor we determined whether they had returned for screening and potential donation within one year (whole blood or plasmapheresis). We also noted whether the donor had been deferred permanently before a subsequent donation and the coded reason for deferral. For all donors who made their subsequent whole blood donation up to the end of 2011, we extracted information on whether this donation had been successful and what donor complication or collection problem, if any, was recorded.

### Setting: blood supply organisation

In the Netherlands there has been a national, non-commercial blood service since 1998. All donations are from volunteer non-remunerated blood donors. At their first attendance they are interviewed and a sample is given for testing; the first donation takes place on a subsequent visit. At this intake interview, body weight and height are recorded, hemoglobin level and blood pressure are measured and venous accessibility is assessed. Blood donation is permitted from age 18 up to and including 69 years (new donors must be < 65 years); body weight must be above 50 kg. All donor, donation, testing, processing and distribution data are recorded in the blood service computer system (e-)Progesa (MAK systems, Paris, France).

Whole blood donors are sent invitation cards according to supply needs. (Walk-in attendances of registered donors provide a small minority of collections.) Women may donate up to three times a year, men up to five times – all donors donate the standard volume of 500 ml plus test samples, in total not exceeding 550 ml. A donor physician is present at all collections. As a general principle a first-time donor donates whole blood at least once before apheresis is considered; apheresis is not further discussed in this article.

### Recording of donor complications and procedural problems

The occurrence of donor complications or procedural problems is recorded in eProgesa using codes. A new coding system was introduced in the first half of 2010 to improve its usefulness for analysis. Donor complications are classified into types that can be mapped to the International Society for Blood Transfusion surveillance classification based on clinical signs and symptoms[14]. Complications which involve outside medical care are also reported separately in the quality management database. The (obligatory) recording of complications and procedural problems is intended to capture all cases occurring on site. Donors are encouraged in written and verbal information at the first interview to inform the blood service about problems occurring off site. Also the standard questionnaire filled in by returning donors includes the question whether the previous collection went well and staff are instructed to retrospectively record any complications which are mentioned.

We classified donor complications into broad categories: needle-related complications (painful arm, arterial puncture and haematoma), vasovagal reactions (pre-faints consisting of pallor, dizziness, sweating, nausea and/or vomiting as well as faints (loss of consciousness) with or without complications, injury or hospital admission); the phase of occurrence of a reaction was noted (during collection, afterwards in center or off site). We also examined the outcomes of procedural problems: failed stab (no blood flow following attempt to insert needle into vein for collection; repeat attempt in other arm is permitted if no blood entered tubing), flow problems (e.g. low flow or collection terminated because of exceeding maximum collection time of 15 minutes) or miscellaneous problems (e.g. machine failure). The term venepuncture-related problem is used for the combined outcome of needle-related complication, failed stab and/or flow problems.

### Statistical analyses

For all calculations the total number of (needle in) collections was used as the denominator. Rates of events per 1000 were calculated for first-time and for repeat donations separately. Multivariable logistic regression analysis to assess the associations of different variables was performed using IBM SPSS Statistics version 18 (IBM corporation, New York, USA). Associations are expressed by means of the odds ratio (OR) and 95% confidence interval (CI). Because of the low rate of the outcomes being studied, the odds ratio can be interpreted as a relative risk.

## RESULTS

### Whole blood collections, recorded donor complications and procedural problems

A total of 551,744 whole blood collections were performed from 1st January 2010 to 31st December 2010; 28,786 (5.2%) came from first-time donors. Table 1 summarizes the key metrics of this cohort in comparison to the collections from repeat donors.

During the study period a total of 4,183 (0.76%) donor complications were recorded: 1,173 (4.1%) in first-time donors and 3,010 (0.58%) in repeat donors. All rates were higher in first-time donors. Table 2 shows data on vasovagal reactions: the rate for first-time donations was approximately nine times higher than for repeat donations, 3.6 and 0.39% respectively. Vasovagal reactions in first-time donors occurred during (as opposed to after) collection in 74% of reacting female donors and 80% among males whereas a lower percentage of reactions presented during the collection of repeat donations (57% and 65% in reacting female and male donors respectively). The rate of vasovagal reactions with loss of consciousness (fainting) was 1.0% in female and 1.2% in male first-time donors, compared to 0.2% for female and 0.1% for male repeat donations; however in the first-time group this gender difference was not statistically significant.

**Table 1**. Donor and donation characteristics of whole blood collections in 2010

| | First time | | Repeat | | Total | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| **Overall** | **28786** | | **522958** | | **551744** | |
| Successful | 27126 | 94% | 514958 | 98% | 541684 | 98% |
| **Sex** | | | | | | |
| Male | 10059 | 35% | 308662 | 59% | 318721 | 58% |
| Female | 18727 | 65% | 214296 | 41% | 233023 | 42% |
| **Age (years)** | | | | | | |
| Mean; median | 32; 29 | | 47; 49 | | 46; 48 | |
| 18-19 | 3827 | 13% | 5587 | 1% | 9414 | 2% |
| 20-24 | 6907 | 24% | 31747 | 6% | 38654 | 7% |
| 25-35 | 6994 | 24% | 62927 | 12% | 69921 | 13% |
| 35-45 | 5116 | 18% | 96607 | 18% | 101723 | 18% |
| 45-55 | 4078 | 14% | 146895 | 28% | 150973 | 27% |
| 55-65 | 1850 | 6% | 144064 | 28% | 145914 | 26% |
| 65-69 | 14 | 0% | 35131 | 7% | 35145 | 6% |
| **Type of facility** | | | | | | |
| Fixed | 23258 | 81% | 407288 | 78% | 430546 | 78% |
| Mobile (setup or bus) | 5528 | 19% | 115670 | 22% | 121198 | 22% |

Among all the reported vasovagal reactions in the period July-December 2010 (the period after full implementation of the new codes which record the time of occurrence of a reaction), 53 of the total number of vasovagal reactions in all donors commenced off site (3.3%), the majority in female donors (4.6% of vasovagal reactions in women) and five of the total in first-time donors. In all, 34 complications required further medical care: 26 vasovagal reactions (six of these were delayed reactions after the donor had left the center and three were with injury; five of the total were in first-time donors), two donors with painful arm or nerve injury who in due course made a full recovery, five cases of local inflammation (phlebitis) and one donor who presented to hospital with a cardiac arrhythmia within 24 hours of donation.

Table 2 (pages 42-3) presents the analyses regarding associations between risk factors and vasovagal reactions. Female donors were less likely than men to experience a vasovagal reaction at their first donation except above the age of 45 years (overall OR 0.86, 95% CI 0.63-0.98). At repeat donations, females were more likely to have a vasovagal reaction (OR 2.2, 95% CI 2.0-2.4). Younger donors had more vasovagal reactions than donors aged 35 years and older. The odds of vasovagal reactions were lower with greater body weight: OR 0.75, 95% CI 0.64-0.88 for >70 kg vs ≤70 kg in first-time donors after adjustment for sex and age group. The odds for a vasovagal reaction showed a rising trend with increasing hemoglobin level in both male

and female first-time donations, with or without adjustment for age group and other variables; this was also seen in repeat donations. Regarding blood pressure, analyzed only for above- and low-normal ranges vs normal values, in the group with the highest blood pressures there were marginally lower odds for vasovagal reactions. The time of day and maximum daily outdoor temperature had no clear association with the occurrence of vasovagal reactions in first-time or repeat donations. The data on type of collection facility showed lower odds for vasovagal reactions for mobile in comparison to fixed sites; however the mobile collections represent small numbers with combined data for setup sites and bus collections so the statistically significant lower odds ratio should not be over-interpreted.

The overall rate of needle-related complications for first-time donations was 0.5% in female and 0.2% in male donors in comparison to 0.3% and 0.1% respectively for female and male repeat donations. Likewise the rates of flow problems and failed stab for first-time donations were approximately double compared to those for repeat donations and higher in female donors. Associations of donor sex, age and body weight with needle-related complications, flow problems and failed stab in the first-time group are presented in Table 3 (page 44). In addition to the increased rates in females, heavier donors were more likely to be affected by failed stab. There were no apparent associations of hemoglobin level or the variables of blood pressure level, type of center, temperature or time of day with needle-related complications (data not shown).

**Donor return**

In the first-time cohort 130 female (0.7%) and 36 male (0.2%) donors were permanently deferred without subsequent donations because of complications or unsuitable veins. A total of 287 female and 65 male donors in the repeat donor cohort were permanently deferred for complications or venous access reasons, for rates of 0.1% and 0.02% per donation or 0.3% and 0.1% per donor among female and male donors respectively. The return rate was 77% among female first-time donors and 81% among males; 85% and 91% among female and male repeat donors respectively. Among all donor attendances, return was associated positively with male sex (females OR 0.59; 0.58-0.60) and negatively with first-time donation (OR 0.67; 0.65-0.69), age groups 20-24, 25-34 and 35-44 (but not 18-19 years) in comparison to over 45 years. Table 4 (page 45) summarizes the findings on return rate among first-time donors. If the first collection was successful despite a complication or problem during the collection or recovery period, a vasovagal reaction led to reduced donor return (return rate 61% in females and 67% in males) but there was no reduction from venepuncture-related problems. If the first donation was not successful, all types of problems were associated with lower donor return but the reduction was strongest for vasovagal reactions. The same effects were seen in repeat donors (repeat donor data not shown).

**Table 2.** Rates of recorded vasovagal reactions (VVR) in first time and repeat whole blood donors

| Variables | First time | | | | | | Repeat | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Females 18753 | | Males 10066 | | Odds Ratio (OR; 95% CI) | | Females 214296 | | Males 308655 | | OR (95% CI) | |
| VVR: N, rate in group (%) | 656 | 3.5% | 395 | 3.9% | Females*: 0.86 (0.76-0.98) | | 1362 | 0.6% | 692 | 0.2% | Females:* 2.2 (2.0-2.4) | |
| VVR, successful collection | 335 | 1.8% | 193 | 1.9% | | | 977 | 0.5% | 443 | 0.1% | | |
| Subgroup during collection† | 253 | 2.7% | 159 | 3.1% | | | 420 | 0.4% | 232 | 0.2% | | |
| Subgroup LOC‡ | 98 | 1.0% | 60 | 1.2% | Females*: 0.87 (0.63-1.2) | | 227 | 0.2% | 90 | 0.1% | Females*: 2.9 (2.2-3.7) | |
| **Age (years)** | | | | | OR in females* | OR in males* | | | | | OR in females* | OR in males* |
| 18-19 | 117 | 4.2% | 53 | 5.0% | 1.5 (1.1-1.9) | 1.8 (1.3-2.4) | 80 | 2.5% | 34 | 1.4% | 6.0 (4.8-7.6) | 10.7 (7.5-15.3) |
| 20-24 | 168 | 3.4% | 82 | 4.1% | 1.2 (1.0-1.5) | 1.4 (1.1-1.9) | 298 | 1.5% | 120 | 1.0% | 3.7 (3.2-4.2) | 7.2 (5.9-8.9) |
| 25-34 | 182 | 4.2% | 135 | 5.1% | 1.5 (1.2-1.9) | 1.8 (1.4-2.4) | 310 | 0.9% | 182 | 0.6% | 2.2 (1.9-2.5) | 4.6 (3.8-5.5) |
| 35-69 | 189 | 2.8% | 125 | 2.9% | 1.0 | 1.0 | 674 | 0.4% | 356 | 0.1% | 1.0 | 1.0 |
| **Weight§** | | | | | OR in females¶ | OR in males¶ | | | | | OR in females¶ | OR in males¶ |
| ≤70 kg | 369 | 4.2% | 70 | 5.6% | 1.0 | 1.0 | 826 | 0.8% | 139 | 0.5% | 1.0 | 1.0 |
| >70 kg | 163 | 3.1% | 247 | 4.0% | 0.75 (0.62-0.91) | 0.73 (0.55-0.97) | 352 | 0.4% | 439 | 0.2% | 0.62 (0.55-0.70) | 0.49 (0.40-0.60) |
| **Hemoglobin (mmol/L)‖** | | | | | | | | | | | | |
| Threshold+0.5 | 217 | 3.1% | 50 | 3.1% | 1.0 | 1.0 | 530 | 0.6% | 129 | 0.2% | 1.0 | 1.0 |
| 0.6-1.5 | 367 | 3.6% | 213 | 3.8% | 1.2 (1.0-1.4) | 1.2 (0.9-1.7) | 703 | 0.6% | 344 | 0.2% | 1.1 (1.0-1.3) | 1.3 (1.1-1.7) |
| >1,5 | 72 | 4.5% | 132 | 4.6% | 1.5 (1.1-2.0) | 1.4 (0.9-2.0) | 129 | 0.7% | 219 | 0.4% | 1.3 (1.0-1.6) | 2.3 (1.8-2.9) |
| **Blood pressure (mm Hg)** | | | | | Odds Ratio¶ (95% CI) | | | | | | Odds Ratio¶ (95% CI) | |
| Diastolic ≤60 and/or systolic ≤100 | 52 | 3.4% | 24 | 4.4% | 1.9 (0.7-1.2) | | 99 | 0.9% | 24 | 0.4% | 1.0 (0.8-1.3) | |
| Mid range | 589 | 3.5% | 355 | 4.0% | 1.0 | | 1226 | 0.6% | 617 | 0.2% | 1.0 | |
| Diastolic >90 and/or systolic >160 | 15 | 2.8% | 16 | 2.7% | 0.8 (0.7-1.0) | | 37 | 0.3% | 51 | 0.2% | 0.8 (0.6-1.0) | |

**Table 2.** Rates of recorded vasovagal reactions (VVR) in first time and repeat whole blood donors *(Continued)*

| Variables | First time | | | | | | Repeat | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Females 18753 | | Males 10066 | | Odds Ratio (OR; 95% CI) | | Females 214296 | | Males 308655 | | OR (95% CI) | |
| **Outside temp. level**** | | | | | | | | | | | | |
| <10 °C | 240 | 3.7% | 137 | 3.8% | 1.0 | | 412 | 0.5% | 257 | 0.2% | 1.0 | |
| 10-20 °C | 236 | 3.2% | 159 | 4.0% | 0.93 (0.77-1.1) | | 605 | 0.7% | 277 | 0.2% | 1.2 (1.1-1.3) | |
| >20 °C | 180 | 3.8% | 99 | 4.0% | 1.1 (0.9-1.3) | | 345 | 0.6% | 158 | 0.2% | 1.1 (0.9-1.2) | |
| **Type of facility** | | | | | | | | | | | | |
| Fixed | 572 | 3.8% | 337 | 4.1% | 1.0 | | 1126 | 0.7% | 564 | 0.2% | 1.0 | |
| Mobile†† | 84 | 2.3% | 58 | 3.0% | 0.7 (0.6-0.9) | | 236 | 0.5% | 128 | 0.2% | 0.8 (0.7-0.9) | |
| **Time of day** | | | | | OR in females¶ | OR in males¶ | | | | | OR in females¶ | OR in males¶ |
| Morning | 153 | 4.2% | 64 | 3.8% | 1.0 | 1.0 | 275 | 0.6% | 146 | 0.2% | 1.0 | 1.0 |
| Afternoon | 291 | 3.8% | 162 | 4.4% | 0.96 (0.77-1.2) | 1.2 (0.86-1.6) | 666 | 0.7% | 258 | 0.2% | 1.1 (1.0-1.3) | 0.9 (0.7-1.1) |
| Evening | 215 | 2.9% | 169 | 3.6% | 0.79 (0.62-1.0) | 1.0 (0.74-1.4) | 418 | 0.6% | 288 | 0.3% | 1.0 (0.8-1.1) | 1.1 (0.9-1.4) |

* Adjusted for age (categorical) and observation period
† data available for July-Dec 2010
‡ Loss of consciousness, data available for July-Dec 2010
§ Known for 466342 (85%) donation records
‖ Donation permitted from 7.8 mMol/L for females (12.6 g/dL) and 8.4 mMol/L for males (13.5 g/dL)
¶ Adjusted for other variables (categorical) in multivariable model
**Maximum daily outdoor temp in center of country
†† mobile site may be setup or bus; some sites switched in 2010

**Table 3.** Rates of venepuncture-related problems at first whole blood donation (total N=28786)

| Variables | Needle-related complication* | | | Flow problems | | | Failed stab† | | |
|---|---|---|---|---|---|---|---|---|---|
| N; rate (%) | 117 | 0.4% | OR (95% CI)‡ | 819 | 2.8% | OR (95% CI)‡ | 314 | 1.1% | OR (95% CI)‡ |
| Incomplete N§ | 93 | 0.3% | | 731 | 2.5% | | 205 | 0.7% | |
| (% of total) | | | | | | | | | |
| **Sex** | | | | | | | | | |
| Female | 93 | 0.5% | 2.1 (1.3-3.2) | 670 | 3.6% | 2.0 (1.5-2.6) | 253 | 1.3% | 2.9 (1.9-4.4) |
| Male | 24 | 0.2% | 1.0 | 149 | 1.5% | 1.0 | 61 | 0.6% | 1.0 |
| **Age group (years)** | | | | | | | | | |
| 18-19 | 20 | 0.5% | 1.2 (0.7-2.1) | 141 | 3.7% | 1.5 (1.2-1.8) | 51 | 1.3% | 1.4 (1.0-1.9) |
| 20-24 | 29 | 0.4% | 1.0 (0.6-1.6) | 234 | 3.4% | 1.3 (1.1-1.6) | 94 | 1.4% | 1.4 (1.1-1.9) |
| 25-34 | 24 | 0.3% | 0.8 (0.5-1.4) | 183 | 2.6% | 1.1 (0.9-1.3) | 68 | 1.0% | 1.1 (0.8-1.4) |
| 35-69 | 44 | 0.4% | 1.0 | 261 | 2.4% | 1.0 | 101 | 0.9% | 1.0 |
| **Weight**" | | | | | | | | | |
| 50-70 kg | 53 | 0.5% | 1.0 | 400 | 4.0% | 1.0 | 118 | 1.2% | 1.0 |
| >70 kg | 43 | 0.4% | 0.93 (0.6-1.4) | 235 | 2.0% | 0.7 (0.6-0.8) | 137 | 1.2% | 1.5 (1.2-2.0) |

***** Hematoma, arterial puncture, painful arm

† Failed stab: failed venepuncture, either leading to failure of collection or to successful collection after repeat venepuncture.

‡ Odds Ratio and 95% confidence interval, adjusted for sex and age group (categorical)

§ Collection <450mL (standard = 500mL excluding samples)

" Weight known for 21633 donations

**Recurrence of complications at subsequent donation**

In all 83% of female and 88% of male donors who experienced a vasovagal reaction at the first donation had an uncomplicated second donation (Table 5). For females the rate of vasovagal reactions at the second donation was 10.5% compared to 2.4% among donors who had smooth first donations, i.e. 4.4 times higher. In male donors the rate of recurrence was 9.7% compared to 1.7% VVR in male donors who had a smooth first donation, i.e. 5.7 times higher. All these rates were higher than in the whole group of repeat donations (0.6 and 0.2% respectively, Table 2). Among the donors who made a second whole blood donation during the study period the occurrence of a vasovagal reaction on that occasion was associated with younger age (e.g. OR 1.7, 95% CI 1.3-2.4 for 18-19 year olds compared to donors older than 34 years) and lower body weight (1.6, 95% CI 1.3-2.1 for weight <70 kg after adjustment for sex and age group). There was no sex difference for vasovagal reactions at second donation after adjustment for the other factors. In repeat donors who made a subsequent whole blood donation after a vasovagal reaction at the index donation the rate of recurrence of VVR was 6% in both male and female donors.

**Table 4.** Donor return within 1 year by first time donors depending on experience at first donation

| Experience at first donation | Females (all) N per variable; return % | | Successful first donation Return %; OR* (95% CI) | | Incomplete first donation Return %; OR* (95% CI) | |
|---|---|---|---|---|---|---|
| No problem | 17038 | 79% | 79% | 1.0 | N=81, added to miscellaneous | |
| Vasovagal | 654 | 55% | 61% | 0.42 (0.34-0.53) | 50% | 0.24 (0.19-0.30) |
| Subgroup LOC† | 98 | 47% | 53% | 0.36 (0.21-0.64) | 41% | 0.20 (0.11-0.36) |
| VP-related‡ | 1014 | 62% | 79% | 1.0 (0.69-1.4) | 58% | 0.36 (0.31-0.42) |
| Miscellaneous | 21 | 67% | 75% | 0.79 (0.21-2.9) | 66% | 0.26 (0.17-0.39) |
| Total | 18727 | 77% | 79% | 1.0 | 55% | Incomplete (all)¶ 0.40 (0.32-0.49) |
| **Experience at first donation** | **Males (all) N per variable; return %** | | **Successful first donation Return %; OR* (95% CI)** | | **Incomplete first donation Return %#; OR* (95% CI)** | |
| No problem | 9425 | 82% | 83% | 1.0 | N=16, added to miscellaneous | |
| Vasovagal | 392 | 56% | 67% | 0.44 (0.32-0.59) | 47% | 0.19 (0.14-0.25) |
| Subgroup LOC† | 60 | 45% | 60% | 0.38 (0.15-0.93) | 43% | 0.18 (0.10-0.34) |
| VP-related‡ | 234 | 76% | 85% | 1.2 (0.54-2.7) | 73% | 0.59 (0.42-0.81) |
| Miscellaneous¶ | 8 | 40% | 33% | 0.11 (0.01-1.3) | 52% | 0.23 (0.10-0.55) |
| Total | 10059 | 81% | 82% | 1.0 | 59% | Incomplete (all)** 0.39 (0.27-0.55) |

* Odds Ratio and 95% confidence interval, adjusted for age (categorical)
† Loss of consciousness: data available for July-Dec 2010
‡ venepuncture-related: needle-related complication, failed stab or flow problems
¶ other complication or procedural problem
** Incomplete v. successful, adjusted for age (categorical) and type of complication

**Table 5.** First-time donors with subsequent whole blood donation during study period: how did it go?

| **Female donors** ***Experience at first donation*** | **N** | **No problem** | **Vasovagal reaction** | **VP-related*** | **Miscellaneous** |
|---|---|---|---|---|---|
| No problem | 13209 | 93.4% | 2.4% | 4.2% | 0.1% |
| Vasovagal | 351 | 82.6% | 10.5% | 6.3% | 0.6% |
| VP-related* | 641 | 83.5% | 4.2% | 12.3% | 0 |
| Miscellaneous | 13 | 92.3% | 0 | 0 | 7.7% |
| Total | 14214 | 92.7% | 2.7% | 4.6% | 0.1% |
| **Male donors** ***Experience at first donation*** | **N** | **No problem** | **Vasovagal reaction** | **VP-related*** | **Miscellaneous** |
| No problem | 7752 | 96.2% | 1.7% | 2.1% | 0.1% |
| Vasovagal | 227 | 88.5% | 9.7% | 1.3% | 0.4% |
| VP-related* | 182 | 83.5% | 3.8% | 12.1% | 0.5% |
| Miscellaneous | 6 | 100% | 0 | 0 | 0 |
| Total | 8167 | 95.7% | 1.9% | 2.3% | 0.1% |

* VP-related = venepuncture-related: needle-related complication, failed stab or flow problems

Among the 4.4% of female and 2.2% of male donors who experienced needle-related complications (hematoma, painful arm or arterial puncture), flow problems or failed stab at first donation, 83% had second donations without problems; the rates of venepuncture-related problems were 12% and 11% respectively in comparison to 2.7% and 1.2% respectively for female and male 2nd-time donations overall. Among the repeat donors the rate of recurrent venepuncture-related problems was 10% in female donors compared to 2.4% among female repeat donors overall; these figures were 5% vs.1.2% in male repeat donors.

## DISCUSSION

### Vasovagal reactions

In our cohort we found that female first-time donors had fewer vasovagal reactions than male donors, in contrast to the reverse in repeat donations. The more severe reactions with loss of consciousness were similar in first time male and female donors but showed a trend in the same direction. The associations with lower values for donor age, body weight and blood pressure in first-time donors were similar to those in repeat donors.

An increased risk of vasovagal reactions in male first-time donors has not previously been focused on, although collection center staff are generally well aware that men can faint at or even before their first donation[8]. Interestingly Eder et al found a rate of approximately 10% in females and 6% in males for vasovagal reactions recorded by the blood center in first-time 18-19-year olds (in their study, which also included donors younger than 18, analyzing the effect of introducing deferral of young candidate donors with a calculated blood volume of less than 3.5 L)[13], i.e. a rate which was higher in female than male donors in contrast to our study. The rate in donors of 20 years and older in the same organization was approximately 7% in female and 5% in male first-time donors[5]. Given the overall higher rate of reactions in these studies, it is possible that additional milder reactions occurred which were not captured by our reporting. In the study by Wiltbank et al., including donors from age 17, the rates of mild and moderate (but not severe) vasovagal reactions tended to be higher in male than in female first-time donors in univariate analysis according to estimated blood volumes, but the differences were not statistically significant; rates were higher in females in other comparisons[6]. Most other studies do not analyze the role of sex as a risk factor separately in the first-time donor population[7,8,12,15].

### Hemoglobin level and vasovagal reactions

The rising trend of vasovagal reactions associated with the hemoglobin level in the first donation cohort after adjustment for sex and age was unexpected. Although the confidence intervals for the odds ratios at some hemoglobin levels cross unity, indicating not statistically

significant, there is a consistent rising trend, robust to adjustment for the other included variables. A similar association was seen in the repeat donors. Preliminary findings of an association with hemoglobin level have been reported by other investigators (Bravo/Tomasulo, oral communication, Montreal April 2012[15]). The observed trend may be due to unmeasured confounding factors. An explanation might be sought in smoking since smokers have higher hemoglobin levels. Recent studies at our blood center have surveyed donor characteristics (including smoking) and donors' attitudes towards returning[11,16]. In a supplementary analysis of study data, no difference was found in the percentage of smokers between donors who reported having had a vasovagal reaction at their last attendance (Veldhuizen, personal communication, 2012). This makes smoking unlikely as an explanatory factor. Dehydration marginally increases the hemoglobin level and is also associated with vasovagal reactions[17]. Newman measured a hemoglobin drop of 0.13 g/dL following a 475 ml water drink so it is conceivable that the effect of hydration state on hemoglobin is large enough to contribute to the observed association[18]. Stress hemoconcentration is a third possible explanation of the association: a reduction of plasma volume and resultant increased hemoglobin level have been described in acutely stressed subjects[19,20] while a contribution of stress in inducing vasovagal reactions is well recognized[21-23]. Further work is needed to examine the association with hemoglobin and possible further confounders.

### Needle-related donor complications, flow problems and failed stab

Female donors were roughly twice as likely as males to be affected by needle-related complications, flow problems or failed stab. The overall higher rate of needle-related complications in first-time donors (both female and male) than in repeat donors is probably explained by selection. For some donors the first attempt at donation is a test of suitability of the venous access and some donors were subsequently deferred; others self-selected and did not return.

### Donor return

Following a vasovagal reaction both male and female donors were less likely to return, the greatest reduction being seen in male donors whose first donation was unsuccessful. Reduced donor return following vasovagal reaction has been previously described[9-11]. Our results make it clear that the reduction is stronger following a vasovagal reaction in combination with an unsuccessful donation, a factor which was also noted by the REDS-II group[24]. It is possible that reactions during collection were more severe and that this led to poorer return. Another likely factor was suggested in the recent study by Veldhuizen et al which indicated that repeat male donors in particular report lower self-efficacy when (self-reported) reactions occur[11].

Donors with venepuncture-related problems at their first donation were also less likely to return, chiefly if the first donation was unsuccessful. The effect of experiencing a failed donation attempt in contrast to a successful donation with a complication (other than a VVR) does not appear to have been systematically examined, although the role of donor motivation and the psychological impact of donation complications has been highlighted[10,11]. Regarding needle-related complications Newman, reporting on a telephone survey in 2006, described an impact of bruises or sore arm which is less strong than vasovagal reactions but can have an additive effect with fatigue following blood donation to reduce return by 65%[9]. In a recent survey of lapsed donors in The Netherlands, fatigue was mentioned among physical reactions after donation which led to donors ceasing to donate[25]. Fatigue is not captured by a collection center-based study such as ours.

Studies are consistent in reporting reduced return following donor reactions but the methods of measuring donor return vary: visits per year[9], return within one year as in this study[10,12], visits within 13 months[26] or one year from eligibility[27]. The baseline rates reported by other authors are generally lower than in our study. For instance France et al reported return rates of 42% for first-time donors and 70% for repeat donors overall. Eder et al found a baseline return rate of 35% following uncomplicated first donation; interestingly this group found – as was the case in our cohort – that donors below the age of 20 years had improved return rates in comparison to older donors with the exception of the top age band. In data from the REDS-II study the return rate for donors without reactions was 60-70% depending on the center[24].

**Strengths and limitations**

Our new coding system has made more detailed analysis of donor complications and of divers collection problems possible. However, a limitation of routinely recorded information is the likelihood of variable and under-reporting. Also the information has little detail and does not allow in-depth analysis of possible causes. In the course of the observation period an increasing tendency was observed in the recorded donation complications and collection problems. There was also a slight increasing tendency of the unsuccessful collections. A small number of serious complications (0.8% of the total) required outside medical care; these were not separately analyzed in this study, however they represent serious morbidity and should be addressed in future work.

As explained above, in the Netherlands all first-time donors have attended for interview and blood testing only prior to the day on which they make their first donation. In the Netherlands there is also a strong focus on donor management and high donor retention with only 5.2% of whole blood donations coming from first-time donors. These aspects may affect generalizability since the occurrence of vasovagal reactions, needle-related complications and

other problems at the first donation may have a greater impact in terms of lost subsequent donations in settings where a higher proportion of collected blood comes from walk-in and/or new donors. Differences in age distribution between our cohort and other countries will also reduce comparability of overall rates which should only be generalized to comparable donor populations; this has been partly addressed by presenting age-stratified analyses.

### What does the study mean for practice?

Blood centers have the opportunity and challenge to move towards interventions to reduce donor complications, based on current knowledge of which donors are at risk. Our study shows that it is worth investing more effort in avoiding venepuncture-related problems at first as well as repeat blood donation. Also there is a need to regard male as well as female first-time donors as "at risk" for vasovagal reactions. A number of interventions have been found effective in reducing the rate of vasovagal reactions, especially in first-time or inexperienced donors. Examples of such interventions are a 500 ml water drink shortly before donation, salt replacement, social distraction, instruction in applied muscle tension and the application of a lower collection volume for young donors with a small estimated blood volume[13,18,21,22,28,29]. The data on recurrence rates for complications provide insights which are relevant for both written and oral information provided to donors.

## CONCLUSION

In conclusion, our analysis of risk factors for vasovagal reactions at first-time whole blood donation, in contrast to repeat donation, showed that male donors were more likely to have a reaction than female donors, although more severe reactions with loss of consciousness revealed only a trend for higher incidence in males. Other risk factors had similar associations with vasovagal reactions among first-time and repeat donors. Female donors were at higher risk of needle-related complications at both first and repeat whole blood donations. Reduced donor return was seen following vasovagal reactions, as well as following venepuncture-related problems leading to unsuccessful collection. Most donors (over 80%) who did come back after complications at their first donation had uncomplicated second donations.

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# CHAPTER 4

# Clinical outcomes after peripheral blood stem cell donation by related donors: a Dutch single-center cohort study.

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## ABSTRACT

### Background

Relatives donating peripheral blood stem cells (PBSC) may be accepted for donation on less strict criteria than unrelated donors. We evaluated the occurrence of adverse events during procedure and follow-up, with a special focus on donors who would have been deferred as unrelated donors.

### Study population and methods

All 268 related PBSC donors at our center (1996-2006) were included. Data were retrospectively collected from medical reports and standard follow-up. Health questionnaires were sent from 2007. Medical outcomes of donors, deferrable or eligible according to international criteria for unrelated donation, were compared.

### Results

Forty donors (15%) would have been deferred for unrelated donation. Short-term adverse events occurred in 2% of procedures. Questionnaires were returned by 162 (60%) donors on average 7.5 years after donation, bringing total person years of follow-up to 1278 (177 in deferrable donors). Nine malignancies and 14 cardiovascular events were reported. The incidence rate of cardiovascular events in eligible donors was 6.5 (95% CI 2.5-12.3) per 1000 person years compared to 44.9 (95% CI 17.4-85.2) in deferrable donors; incidence rates of malignancies were 4.6 (1.4-9.6) and 24.0 (6.0-53.9) per 1000 person years respectively in eligible and deferrable donors. All incidence rates were within the range of age and sex-matched general population. No auto-immune disorders were reported.

### Conclusion

In both the eligible and deferrable related donors treated with G-CSF there are few short-term and long-term problems. Occurrence of post-PBSC cardiovascular events and malignant disease in related donors appears to be within the range of the general population.

## INTRODUCTION

Recombinant human granulocyte colony stimulating factor (G-CSF) is increasingly used to mobilize peripheral blood stem cells (PBSC) from healthy donors for allogeneic haematopoietic transplantation. In The Netherlands, PBSC collection has been performed in related donors since 1995. Counseling, collection and formal follow-up evaluations of unrelated donors conducted since 2004 are performed in accordance with national policies which conform to the World Marrow Donor Association standards.[1] Although related donors are screened by independent physicians not involved in care of the patient, many of these donors are accepted for PBSC donation despite the presence of conditions for which they would be deferred if they were unrelated donors.



There is ample information about the short term effects of the PBSC procedure in related and unrelated donors, indicating an acceptable safety profile in comparison to bone marrow donation under general anaesthetic.[2,3] Nevertheless, some serious and potentially life-threatening complications have been described in allogeneic PBSC donation procedures, including splenic rupture,[4,5] anaphylaxis, vasculitis and acute lung injury.[6] Myocardial infarctions[7], thrombo-embolic events, subarachnoid hemorrhage and cardiac arrests have been reported in at least thirteen cases either during G-CSF mobilization or within 30 days after PBSC harvest.[8,9] Careful donor selection and observation might mitigate but not completely abolish these risks.

Potential long-term complications are however less well known. There are some reports suggesting that administration of G-CSF may enhance malignant transformation in patients.[10-12] Some have reported the occurrence of hematologic and solid malignancies in healthy donors after donation of G-CSF mobilized PBSC. Furthermore, there are concerns about the potential development or exacerbation of auto-immune or systemic inflammatory diseases.[3,8]

These considerations regarding possible long-term effects have stimulated investigators to report on long-term follow-up of PBSC.[13-15] However, long-term data concerning this topic in related donors is relatively scarce. Leitner et al. observed a cohort of 171 related donors.[16] De la Rubia et al. described findings from a voluntary national registry of donation and follow-up of predominantly related donors; Halter et al. reported international survey data from the European Group for Blood and Marrow Transplantation concerning both related and unrelated donors.[17,8] None of these investigators found an increased incidence of malignancies; all authors mentioned the higher age of related donors as a relevant issue and called for systematic long-term follow-up.

Here we report follow-up data concerning a Dutch cohort of related donors. Because of the apparent difference in acceptance of related donors in comparison to unrelated donors, we also separately analyzed the data on the individuals who would not have been accepted under international screening criteria for unrelated donors.

## PATIENTS AND METHODS

### Study population and PBSC procedure

The study cohort consisted of all related donors who underwent G-CSF mobilization and PBSC harvesting in Leiden University Medical Center from May 1996 to May 2006; the recipients were all patients at the hospital's transplantation unit. The study was performed as part of a larger study which also comprised a prospectively enrolled group of donors and for which ethical approval was obtained from the hospital medical ethics committee.

Donor consent and medical clearance were performed by an independent physician. Subject to careful medical assessment, related donors could be accepted without upper age or body weight restrictions and sometimes in the presence of conditions which would constitute contra-indications for unrelated stem cell donation. A short description of the procedures and reference criteria is available as supplementary material with the online version of this article.

Donors received 10 µg/kg of G-CSF (Filgrastim$^{R}$, Amgen Inc., Thousand Oaks, CA, USA) once daily. The white blood cell count was checked on the fourth morning in order for dose adjustment (halving) to take place if there was a rise above 70 x 10^9/L. The fifth dose was administered at the end of the fourth day. PBSC apheresis (Cobe Spectra, Caridian BCT, Lakewood, CO USA) was conducted on the fifth and, if necessary, sixth or subsequent day after an additional dose of G-CSF. If required, calcium was supplemented. Standard procedures allowed re-infusion of autologous platelets prepared from the stem cell product if there was a post-apheresis platelet count below 50 x 10^9/L or if it was below 80 x 10^8/L and a second day of apheresis was needed. After completion of the procedure, follow-up visits were scheduled at both one month and one year after collection.

### Data collection

We extracted data from medical records and hospital information systems concerning predonation examination, donation and follow-up visits. Furthermore, we evaluated findings of medical screening and noted cases of acceptance where the donor would have been deferred under the criteria for unrelated donors. Mobilization and apheresis procedural data were extracted, including data on deviation from standard G-CSF schedule, use of a central venous catheter (CVC), the number of apheresis sessions, PBSC harvest, and reinfusion of autologous

platelets prepared from the stem cell product. We retrieved information on requested target stem cell dose and yield, as well as on second requests for hematopoietic stem cells and donor lymphocyte collections (donor lymphocyte infusion, DLI). Finally, we recorded serious adverse events during follow-up.

In November 2007 we sent all donors a standardized health questionnaire by post. It comprised 14 yes/no questions about medical diagnosis and treatment indicative of health problems since the donation; free text explanation was to be added if there were any "yes" responses. If the information given was not clear, one of the investigators (JW-O) contacted the donor by telephone or e-mail for clarification. When necessary medical details were requested from treating physicians with written consent from the donor. If the questionnaire was not returned, several attempts were made to check the address and find the donor. In January 2011 we accessed the hospital patient database to ascertain whether the recipient was alive or retrieve the date of death.



**Definitions**

Donor eligibility status was retrospectively assessed according to the Assessment Tool at workup from the National Marrow Donor Program (NMDP, 2009 version), Minneapolis, USA,[18] which were applied alongside general blood donation criteria. Broadly, unrelated donors must have no history of cardiovascular, diabetes, systemic auto-immune, eye or thyroid disease; donation is permitted up to age 60 years and a BMI of 40 kg/m$^2$. Donors who would not have been eligible as unrelated donors are referred to as "deferrable donors".

All events requiring unscheduled medical examination or treatment from the start of mobilization until the one-month FU were taken into consideration and categorized as procedure related serious adverse events (SAE).

Follow-up period is defined as the period starting one month after start of G-CSF to the latest contact with the donor. Contacts from 30 up to 100 days were considered as early follow-up and contacts from 100 to 730 days as late follow-up.
The study outcomes were:

1) Any malignancy (basal cell carcinoma excluded)
2) Cardiovascular disease (CVD) after the procedure: a combined outcome of medically diagnosed fatal or nonfatal myocardial infarction, newly diagnosed coronary disease treated by medication or ischemic vascular disease, cardiac intervention or vascular intervention, cerebrovascular event, medically diagnosed transient ischemic attack for which treatment was instituted or venous thromboembolism
3) (systemic) auto-immune disease of any type.

## STATISTICAL ANALYSES

Data for all donors are presented, with comment on completeness of information. Means, medians and inter-quartile ranges (IQR) were calculated as descriptive statistics. For each donor, the number of follow-up years was determined from the time of donation to the latest contact date. Annual disease-specific incidence rates were calculated as the number of events per 1000 person years of follow-up, including all follow-up years until occurrence of the first event or until the latest contact date with donors without events. Confidence intervals are given for the 95% level of statistical significance.

In order to compare incidence rates in our study group with those in the general population, age- and sex-specific incidence rates of cardiovascular disease and for cancer within the Dutch general population were retrieved from the national statistics database (www.statline.cbs.nl/statweb) and from the national cancer registry (www.ikcnet.nl). Using the number of follow-up years for male and female donors in each age band we calculated the numbers of cardiovascular events and malignancies which would be expected in the study population if they had the same rate as in the general population. The standardized morbidity ratio (SMR) was determined, the ratio of observed events to the number expected. (A SMR less than 1 means that there were fewer events in the study cohort than expected). The SMR and 95% CI were calculated for the whole cohort and also separately for the deferrable versus eligible groups.

## RESULTS

### Population characteristics

The 268 related donors had a median age of 43 years (range 14-70) at donation; the demographic characteristics of the cohort are shown in Table 1. Forty donors would have been deferred according to NMDP criteria; the reasons are summarized in Table 2. Apart from age over 60 years, body mass index (BMI) over 40 kg/m$^2$ and hypertension (>160/95 mm Hg), medical contra-indications were present in ten donors: Factor V Leiden and/or previous deep venous thrombosis (n=2), coronary atherosclerosis and medication or revascularization (n=2; stable), aortic valve stenosis (stable), Parkinson's disease, past treatment for breast cancer (more than 5 years previously), diabetes mellitus type 1 or 2 (n=2), low concentration monoclonal (M) protein.

**Table 1.** Donor characteristics and medical history

| Donor characteristics | All donors n=268 | Deferrable n=40 |
|---|---|---|
| Female (n; %) | 115 (43%) | 18 (45%) |
| Age at donation (years; median, IQR*) | 42.8 (34.6-51.2) | 60.4 (46.9-63.5) |
| BMI† (kg/m²; median, IQR*) | 24 (22-28) | 27 (24-30) |

* Inter-quartile range
† Body mass index; known for 242 donors;

**Table 2.** Deferral reasons of 40 deferrable donors*

| Deferral reasons | |
|---|---|
| BMI (>40 kg/m²) | 2 |
| Hypertension (>160/90 mm Hg) | 13 |
| Other medical conditions | 10 |
| Age >60 years | 21 |

* More than one reason may apply



All procedural data were complete for 262 donors. Data on both target and yield of CD34+[1] cells were available for 234 donors. A collection of PBSC which was deemed adequate was achieved in all but three donors (1.1%; one female; two male donors deferrable for age over 60 years).

The collection was completed in one session in 176 donors: 66%; 76% for male and 52% for female donors. Most of the remaining donors underwent two days of aphaeresis; more than two sessions were needed in five (three males). A CVC was used in 22/268 (8%; 16 females). Four females out of these 22 donors were deferrable (two for hypertension, one for age >60 years and one for both BMI >40 kg/m² and hypertension).

Follow-up visits are recorded for 230 donors (86%): 207 (77%) for early follow-up within 100 days and 156 (58%) for late follow-up approximately a year after collection, some because of subsequent donations. There was no correlation between this follow-up attendance and survival of the recipient in the first six months after transplantation. One hundred and twenty-two donors made subsequent donations: 113 donated lymphocytes (DLI) on one or more occasions, 7 donors underwent a second PBSC collection, one donor donated granulocytes and one donor donated bone marrow because of inadequate PBSC yield. The interval for subsequent donations was on average 329 days (inter-quartile range 170-398, median 248 days).

1 Cells with surface marker CD34; these constitute the cell population which is needed for hematopoietic reconstitution

**Procedure-related and short-term events**

G-CSF led to changes in haematological parameters as expected. Eighty donors (30%) received autologous platelets (60 donors once and 20 donors twice or more) separated from the PBSC product. No transfusion reactions to platelets or serious biochemical changes were recorded. All of the mild elevations of LDH[2] and bilirubin normalized within 6 weeks of harvest.

Table 3 shows the serious adverse events, one of which was related to the use of a CVC. In all, five donors (2%) required unscheduled medical attention and/or hospitalization during the period of G-CSF administration, harvest or during the direct follow-up period. We found no correlation between donor's eligibility status and the occurrence of short term procedure-related SAEs. The table also details two potentially serious dosing incidents.

A total of eight donors (3%) reported excessive tiredness in relation to the procedure which lasted for longer than a week, persisting until 6 weeks post donation in three cases.

**Table 3.** Procedure related serious adverse events (SAEs)

| SAEs | Sex (M/F), age (y) | Deferral reason (if present) |
|---|---|---|
| Excessive tiredness, 1 night hospitalization after PBSC | M, 32 | hypertension |
| Chest pain; no explanation | F, 34 | - |
| In-patient opiate pain control; G-CSF stopped day 3 with WBC 59.7 x 10^9/L | M, 39 | - |
| Inguinal venous thrombosis following CVC | F, 45 | - |
| Persistent pain symptoms at injection site | F, 24 | - |
| **Potentially serious dose incidents** | | |
| Received incorrect G-CSF dose; no excessive rise in WBC | F, 36 | Previous DVT |
| No dose reduction day 3 ( WBC was 80 x 10^9/L); pre-collection WBC 107 x 10^9/L. | F, 55 | Previous DVT |

Abbreviations: WBC = white blood cell count; DVT = deep venous thrombosis

*Follow-up*

Figure 1 summarizes the response to the follow-up questionnaire. Of the 268 donors, 162 returned questionnaires giving a response rate of 60%. Responders were more likely to be female and older; there was no difference in proportion of responding donors according to death or survival of the recipient.

The total number of donor follow-up years was 1278. The median follow-up was 4.5 years (range 0-13.6 years, IQR 0.6-8.4). No auto-immune disorders had been diagnosed during the follow-up period.

2 LDH = lactate dehydrogenase

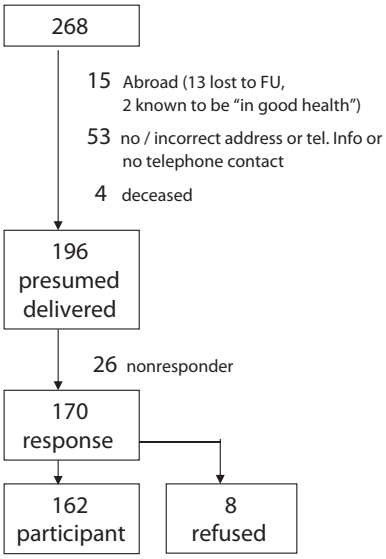


**Figure 1.** Responses to the follow-up (FU) health questionnaire

Table 4 shows the reported long-term morbidity and follow-up outcomes together with the eligibility status of the donors. Fourteen (new) cardiovascular events had occurred and nine malignancies were diagnosed (excluding two donors who had been treated for basal cell carcinoma). In all, four donors are known to have died: one of a cardiovascular event, two from lung cancer while a fourth donor is known to have died but the cause is unknown. Four donors had a new diagnosis of type 2 diabetes and two, previously controlled on diet alone, had started taking oral antidiabetic agents; one of these six donors was in the deferrable group (for age >60 years). A donor who had suffered from persistent pain at the G-CSF injection site continued to be affected by fibromyalgia-like symptoms over five years after donation. The donor who had a femoral venous thrombosis still suffered from functional impairment in the leg and inability to work despite adequate anticoagulant treatment and resolution of the thrombus.

Table 5 (page 53) shows the incidence rates of cardiovascular events and of malignancies in the study cohort and age- and sex adjusted rates in the general population. The incidence rate of cardiovascular events in deferrable donors was 44.9 per 1000 person years (95% CI 17.4-85.2) in comparison to 6.5 per 1000 person years (2.5-12.3) in eligible donors. The rates of cardiovascular events and malignancy in deferrable donors were in the range of the expected rates on the basis of age- and sex-specific rates in the general population; that of cardiovascular events in eligible donors was 0.6 times that of the general population (95% CI 0.2-1.1).

**Table 4.** Follow-up findings in donors

| *Sex (M/F), age (y) at donation* | Interval (y) | Problem during follow-up | Deferral reason (if present*) |
|---|---|---|---|
| F 45 and 24 | - | Persistent symptoms following procedure | - |
| **Cardiovascular total n=14;** interval median 3.5y (range 6w-10.5y) | | | |
| F, 70 | 5.8 | Pacemaker implantation | age |
| M, 37 | 3.2 | Dissecting aneurysm; + | - |
| M, 42 | 4.9 | TIA | - |
| M, 44 | 2.4 | Myocardial infarction | hypertension |
| M, 45 | 6.8 | Myocardial infarction | hypertension |
| M, 47 | 0.6 | DVT | - |
| M, 50 | 3.8 | Peripheral vascular disease | other |
| M, 52 | 3.7 | Myocardial infarction | - |
| M, 54 | 1.4 | Angina pectoris diagnosed | - |
| M, 55 | 4.9 | Myocardial infarction | hypertension |
| M, 57 | 1.5 | Coronary revascularization | - |
| M, 58 | 0.5 | Vascular dementia | - |
| M, 60 | 10.5 | Cardioversion for atrial fibrillation | age |
| M, 62 | 0.2 | Myocardial infarction | hypertension |
| **Malignancies total n=9;** interval median 4.2y (range 3.0-10.1) | | | |
| F, 16 | 4.1 | Hodgkin lymphoma | - |
| F, 46 | 4.2 | Breast cancer | - |
| F, 51 | 7.6 | Bowel cancer | - |
| F, 52 | 7.5 | Lung cancer + | - |
| F, 55 | 8.6 | Breast carcinoma in situ | - |
| F, 70 | 3.9 | Breast cancer | age |
| M, 44 | 10.1 | Glioblastoma | hypertension |
| M, 60 | 3.1 | Rectal cancer | age |
| M, 66 | 3.0 | Lung cancer + | age |

+ Deceased; in addition a female donor in the eligible group, aged 56 at donation, is known to have died but the date and cause are unknown.

## DISCUSSION

In this cohort of related donors, 15% would have not been accepted according to international criteria for unrelated PBSC donation. The likelihood of procedure-related serious adverse events was similar in these deferrable donors compared to donors who would have qualified as unrelated volunteer donors. The overall incidence of 2% short-term procedure-related serious adverse events associated with mobilization and PBSC harvest is consistent with figures

previously reported in larger series. For instance the Center for International Blood and Marrow Transplant Research and European Group for Blood and Marrow Transplantation reported 15 (1.1%) donation-related adverse events among 1337 allogeneic, mostly related PBSC donors, of which five were catheter-related.[19]

**Table 5.** Incidence rates (IR) of cardiovascular events and malignancies in study cohort and comparison to general population rates

| Study population | Events | Person years at risk | Incidence rate* (95% CI) | Comparison with Dutch general population | |
|---|---|---|---|---|---|
| **Cardiovascular disease** | | | | Expected IR† | SMR‡ (95% CI) |
| Eligible | 7 | 1080 | 6.5 (2.5-12.3) | 11.5 | 0.6 (0.2-1.1) |
| Deferrable | 7 | 156 | 44.9 (17.4-85.2) | 33.3 | 1.3 (0.5-2.6) |
| **Malignancy** | | | | Expected IR§ | SMR‡ (95% CI) |
| Eligible | 5 | 1086 | 4.6 (1.4-9.6) | 3.9 | 1.2 (0.4-2.5) |
| Deferrable | 4 | 167 | 24.0 (6.0-53.9) | 10.2 | 2.4 (0.6-5.3) |

*per 1000 person years

† expected rate per 1000 person years on the basis of age- and sex-specific population figures: "Hospital admission for disease of heart or circulation"

‡ SMR = standardised morbidity ratio

§ expected rate per 1000 person years: incident cancer diagnoses

The use of autologous platelet transfusions was implemented in our institution to comply with the guidelines, which do not allow stem cell apheresis if the pre-apheresis count is below 80 x 10^9/L and which require daily monitoring until recovery of platelet counts if the post-apheresis count is below 50 x 10^9/L. The procedure and its effect for the donor as well as for the stem cell product have been validated in our center. No adverse transfusion effects were observed.

In our long-term follow-up, the incidence rate of cardiovascular events in deferrable donors was 45 events per 1000 person years (95% CI 17-85) in comparison to 6.5 per 1000 person years in eligible donors. Rates of malignancy as well as cardiovascular events in both deferrable and eligible donors were in the range of age- and sex adjusted population rates. The point estimate of the standardized morbidity ratio for malignancy in the deferrable group was 2.4, however the 95% CI is very wide and our data cannot exclude an increased incidence up to 5.3 fold.

A theoretical concern has always been that use of G-CSF might favour the development of malignancy which would only become apparent after several years' latency. The overall number of malignancies in our study was relatively high compared to other studies. Halter et al. reported the survey of both related and unrelated donors by the European Group for Blood and Marrow Transplantation which included almost 100,000 person years of follow-up of more than 23,000 PBSC donors. A total of 12 hematological malignancies occurred. While the rate

of hematological malignancy was higher in PBSC donors (1.2 versus 0.4 in 27,770 former bone marrow donors) this is probably explained by the higher age of related PBSC donors. Pulsipher et al. reported on follow-up findings ranging from 2 days to 99 months, median 49 months, on 2408 unrelated donors (9% older than 50 years at donation) for recipients within the NMDP program; there were 21 non-hematologic malignancies excluding basal cell carcinoma, and one case of chronic lymphocytic leukemia. Concerning solid malignancies in former PBSC donors, Hölig et al. reported on 3928 unrelated donors in whom a total of 8 non-hematological and four hematological malignancies occurred. All investigators made comparisons with data for the general population and found no indication of any increase. Our cohort was approximately nine years older than the donors reported on by Hölig et al. who had a median age of 34 years; in our group only 2 malignancies occurred in donors aged below 40 at the time of donation. Although our data give no reason for concern that there might be a relevant increase in rate of malignancy, our cohort is small with a limited follow-up. More person years of follow-up would be needed to reject the possibility even of an implausibly high tenfold increase in rate of malignancies.[20]

The occurrence of auto-immune disease has less frequently been evaluated.[16,21] So far, no investigators have found any indication of an increase of auto-immune conditions. Even if we consider a worsening of pre-existent type 2 diabetes mellitus as a possible effect of G-CSF, the six cases of new or worsened type 2 diabetes in our cohort are not in excess of what would be expected.

Our study benefits from the fact that it describes results from a single center using uniform standard procedures, however the relatively small group of donors remains a limitation. Its retrospective design, in particular the impossibility to trace a large number of donors, is a further limitation. This leads to missing data and a risk of ascertainment bias. The standardized morbidity ratio is calculated using age- and sex-specific population rates and the numbers of follow-up years in females and males in each five-year age band. Hence the result is fully adjusted for the fact that responders tended to be female and older. However any conclusions are based on the assumption that responders and nonresponders do not differ in their rate of the studied outcomes. In the observational setting the validity of this assumption cannot be tested. The difficulty of follow-up of related donors beyond a year after G-CSF exposure is encountered by other investigators.[22,23,16] In The Netherlands, the standard schedule ends after the one-year attendance because the recipient's health insurance only reimburses such follow-up to one year after donation. In our study this lack of routine follow-up was addressed by postal health questionnaires. However, nearly one-fifth of donors could not be traced and the overall response of 60% is suboptimal.

A strength of the study is that it additionally captured data on cardiovascular disease (CVD) in the years following participation in the PBSC procedure. The incidence of late vascular events beyond 4 weeks has to our knowledge never been systematically recorded. The comparison with population data gives no indication of any excess morbidity. However, donors should normally constitute a lower-risk population, which is reflected in the incidence of CVD in the eligible group. Importantly, the incidence rate of approximately 45 per 1000 person years in the deferrable donors suggests that the safety margins in this group are smaller. Vascular disease is an important reason for deferring donors in view of the short-term risk of thrombotic complications. The Halter et al. survey describes clustering of cardiovascular events in the first weeks following the procedure. This was not seen in our study population although three cardiovascular events occurred in the 7 months following the procedure.



Raised and/or drug-controlled blood pressure and age were the most frequent reasons for which the related donors would not have been eligible for unrelated donation. Candidate related donors, most of them being siblings of cancer patients, tend to be older than unrelated donors and age in itself brings increased risks of cardiovascular disease. In our center the donor assessment is performed by a physician who is not involved with the treatment of the patient. While this prevents any conflict of loyalties and minimizes risk, it is not a strict policy to rigidly defer all donors with one or more characteristics, including age, which would have led to deferral of an unrelated donor. Our data are consistent with other observations and show that if screening is performed as for unrelated donation, a population at lower (cardiovascular) risk will be selected. We also found that related donors who do not meet acceptance criteria for unrelated donors have a higher incidence of cardiovascular events, indicating smaller safety margins. Therefore, these criteria – including age – should in our opinion also be taken into consideration in the assessment of related donors. If a family member presents factors which would lead to deferral for unrelated donation because of potential higher risk of the procedure, it should not be assumed these risks may be accepted even if the donor is willing to proceed for the sake of a family member.

Overall our results show acceptable risks of the use of G-CSF in these related donors concerning most important side effects. The long-term occurrence of cardiovascular disease and of malignancy for both eligible and deferrable donors falls within the range reported for the population. However, the small size of the study means that the confidence intervals are wide. There is insufficient information to conclude that there are no relevant long-term increases of cardiovascular or malignant disease. Late medical events will not be systematically captured unless active follow-up extends beyond the first year, not only for unrelated but also for related donors. We therefore strongly support efforts by the international transplantation community to ensure long-term follow-up for unrelated donors and related donors as well.[22,23]

In conclusion, this study gives no indication of long-term increased risks of cardiovascular disease or of malignancies in related donors who have undergone G-CSF mobilization and PBSC apheresis, but cannot exclude this either because of the small size of the cohort.

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**Related donor selection procedures at Leiden University Medical Center, 1996-2006**

Related donor medical clearance G-CSF mobilisation and harvesting in the period 1996-2006 was performed by a physician who was not involved in the treatment of the recipient. This was based on a general medical history, standard hematological and biochemical laboratory tests as well as standard infectious disease marker testing. In addition, bone marrow morphology, ECG, chest X-ray and monoclonal protein analysis were routinely performed.



Concerning the reference criteria, the center used guidelines which were initially based on national blood donation criteria supplemented by tools from the National Marrow Donor Program (NMDP, Minneapolis, USA). In 2004 national guidelines were implemented for unrelated donors as laid down by the national blood service, Sanquin Blood Supply. Of interest, the Dutch unrelated donor criteria are stricter than the NMDP and also stipulate deferral of donors on antihypertensive medication.

In principle these guidelines were used with the following routine deviations regarding donor safety:

- No limit to donor age providing the donor is > 18 years
- No limit to donor weight
- Blood pressure limits 160/100; use of antihypertensive drugs allowed
- Diabetes type 2 allowed if there was no apparent vasculopathy.

In cases of incidental deviations (e.g. previous cardiac stent, bronchial asthma) a consultation of specialists was requested and the conclusions documented.

With respect to patient safety the applicable (national) blood donation guidelines were followed. In cases of deviation from these guidelines, with consent of the transplant centre donors with risk behaviour (chiefly travel risks, body piercing, homosexuality) could be accepted providing mandatory and any necessary additional tests (e.g. malarial antibodies) were negative. In cases of reduced safety for the recipient, the independent physician could release a donor for donation with the agreement of the transplant centre.

# PART 2

## "Recipient" hemovigilance

**Chapter 5**
Clinical predictors of alloimmunization after red blood cell transfusion

**Chapter 6**
Male-only fresh-frozen plasma for transfusion-related acute lung injury prevention: before-and-after comparative cohort study

**Chapter 7**
Variation between hospitals in rates of reported transfusion reactions: is a high reporting rate an indicator of safer transfusion?

# CHAPTER 5

# Clinical predictors of alloimmunization after red blood cell transfusion

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## ABSTRACT

### Background

Development of new red blood cell (RBC) alloantibodies (alloimmunization) is one of the most frequent adverse reactions after an RBC transfusion. Few studies have investigated clinical risk factors for alloimmunization.

### Study design and methods

In this case-control study, the characteristics of all patients in whom alloimmunization occurred for the first time after an RBC transfusion in two hospitals between January 1, 2003, and May 5, 2005, were examined and compared to a randomly selected control group who received RBC transfusions in the same hospitals during the same period without alloimmunization. Odds ratios (ORs) for the association between these characteristics and alloimmunization were calculated and analyzed with a logistic regression model.

### Results

Eighty-seven cases were found, and 101 controls were selected. Female sex (OR, 1.89; 95% confidence interval [CI], 1.05-3.38), diabetes mellitus (OR, 2.15; 95% CI, 0.91-5.05), solid malignancy (OR, 2.07; 95% CI, 1.00-4.30), and previous allogeneic hematopoietic peripheral blood progenitor cell (PBPC) transplantation (OR, 2.24; 95% CI, 0.64-7.81) were associated most strongly with alloimmunization, whereas lymphoproliferative disorders (OR, 0.33; 95% CI, 0.13-0.81) and symptomatic atherosclerosis (OR, 0.52; 95% CI, 0.25-1.08) were associated with the absence of alloimmunization. All of these associations except for female sex became stronger after adjustment for possible confounders.

### Conclusion

Female sex, diabetes mellitus, solid malignancy, and previous allogeneic PBPC transplantation seem to be risk factors for alloimmunization, whereas lymphoproliferative disorders and symptomatic atherosclerosis seem to protect against it. Further studies are needed to confirm these associations and investigate underlying mechanisms.

## INTRODUCTION

Although blood transfusion is generally very safe, adverse reactions to blood transfusions remain an important clinical problem. Since 2002, transfusion reactions in The Netherlands have been reported to the TRIP (Transfusion Reactions in Patients) Dutch National Hemovigilance Office. TRIP captures not only severe transfusion reactions, like Serious Hazards of Transfusions (SHOT) in the United Kingdom, but also nonsevere transfusion reactions. In 2004 and 2005, the most frequent adverse reaction reported to TRIP was the development of new red cell (RBC) antibodies (alloimmunization).[1] Few studies have investigated clinical risk factors for alloimmunization, such as characteristics of the recipient, and previous findings have been inconsistent. Knowledge of clinical conditions that predispose to alloimmunization is important in two ways. First, it may influence the management of a patient. If a certain category of patients has a high risk of alloimmunization, the consequence could be more extensive antigen typing and matching. Second, more knowledge of associations between clinical conditions and alloimmunization may lead to a better understanding of the etiology of this transfusion reaction.



In this case-control study, we examined the case records of patients who developed alloimmunization after a blood transfusion and compared them to patients who never developed such a reaction after a blood transfusion to identify risk factors for alloimmunization. As a secondary objective, we wanted to evaluate whether the TRIP database facilitates the study of such risk factors.

## MATERIALS AND METHODS

### Cases and controls

We examined the case records of all patients in whom alloimmunization was reported in the Leiden University Medical Center and Haga Teaching Hospital in The Hague from January 1, 2003, to May 5, 2005. We chose these two hospitals from the 82 hospitals that reported transfusion reactions to the TRIP organization in 2003 because they are large affiliated hospitals that cooperate on transfusion policy, and both are closely associated with the TRIP foundation. Alloimmunization was defined as the finding of a new antibody against RBC antigens other than Rhesus D and the ABO system. Only first-ever alloimmunizations were taken into account. We were looking for alloimmunization as a result of transfusion, not childbirth, so the patient must have had at least one earlier RBC transfusion to which the alloimmunization could be ascribed. Alloimmunization was ascribed to the last RBC transfusion given before the finding of the new alloantibody. All in-hospital patient records concerning the period around the time of the transfusion event were checked and analyzed by two of us (MB and JW).

The control group for the alloimmunization cases was created by randomly selecting a RBC transfusion administered to a patient in the same hospital on the day after the alloimmunization was reported. Control patients had to fulfill the same criteria as case patients except for the fact that they did not develop an alloantibody. Therefore, the selected RBC transfusion should have been preceded by at least one "type-and-screen" procedure during which no new alloantibody was found. Furthermore, the patient should have received at least one RBC transfusion previously. If a control patient did not meet these criteria, another RBC transfusion was randomly selected from the following day's list. A flow chart of the study design is shown in Fig. 1.

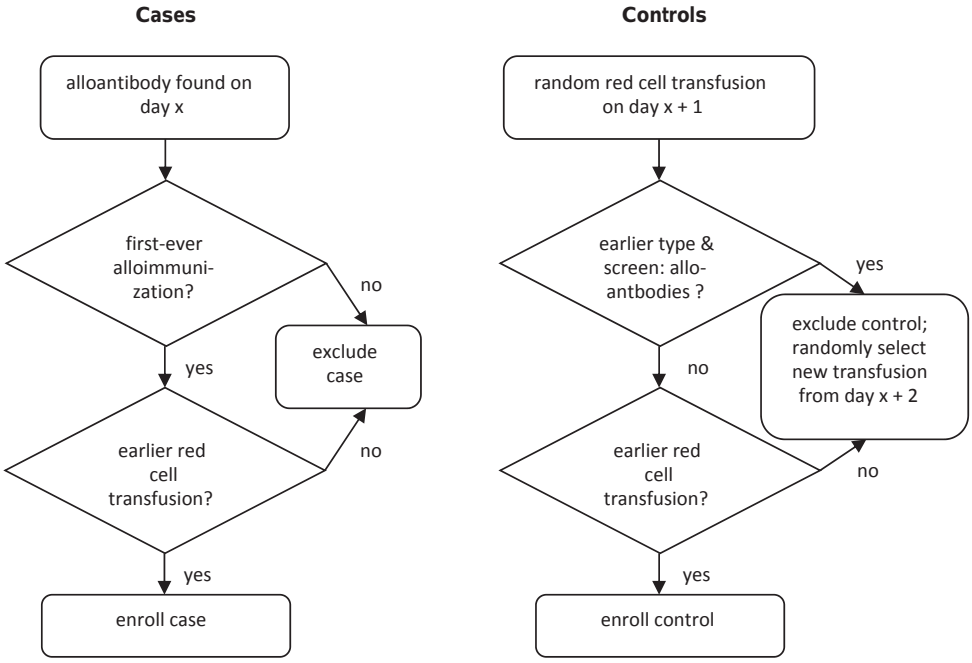


**Figure 1.** Flow chart of study design

## Patient characteristics

Demographic patient characteristics that we recorded were sex, age, and a non-European surname, as a measure of a potential genetic background difference from the main blood donor population, which is known to consist predominantly of non-immigrants in The Netherlands. The clinical characteristics we studied were the indication for the blood transfusion, the reason for the hospital admission during which the blood transfusion took place, previous transfusion reactions, the number of previous transfusions given in the same hospital (including the transfusion to which the reaction was ascribed; only RBC transfusions were counted), the

number of children in the case of women, a history of autoimmunity (defined as any disease in which autoantibodies play a clear etiologic role or any disease of unknown etiology associated with autoantibodies [see Table 1 for list of conditions]), systemic inflammatory diseases without a clear association with autoantibodies, myelogenous marrow disorders (myelodysplasia, myeloproliferative disorders and myelogenous leukemia), lymphoproliferative diseases, a history of an allogeneic hematopoietic peripheral blood progenitor cell (PBPC) transplantation, a history of a solid organ transplantation, chemotherapy before the transfusion, and allergies.

**Table 1.** List of diseases defined as autoimmune

| |
|---|
| Graves' disease |
| Hashimoto's thyroiditis |
| Type 1 diabetes mellitus |
| Autoimmune adrenalitis |
| Autoimmune hemolytic anemia |
| Aplastic anemia |
| Idiopathic thrombocytopenic purpura |
| Thrombotic thrombocytopenic purpura associated with antibodies against ADAMTS13 |
| Acquired hemophilia |
| Antiphospholipid antibody syndrome |
| Pernicious anemia |
| Celiac disease |
| Rheumatoid arthritis |
| Systemic lupus erythematosus |
| Still's disease |
| Felty's syndrome |
| Sjögren's syndrome |
| Systemic sclerosis |
| Polymyositis dermatomyositis |
| Mixed connective tissue disease |
| Autoimmune hepatitis |
| Primary biliary cirrhosis |
| Primary sclerosing cholangitis |
| ANCA-associated vasculitis syndromes |
| Goodpasture's syndrome |
| Relapsing polychondritis |
| Myasthenia gravis |
| Lambert-Eaton syndrome |
| Anti-Hu-associated diseases |
| Multiple sclerosis |
| Vitiligo dermatitis |
| Herpetiformis pemphigus |
| Bullous pemphigoid |
| Lichen sclerosus |
| Vogt-Koyanagi-Harada syndrome |

Abbreviations: ADAMTS13 = circulating protease of the ADAMTS family; ANCA = anti-neutrophil cytoplasmic antibodies; Anti-Hu = antibody directed against neuronal Hu antigen

These are all conditions that could have a plausible relationship with a patient's immune status. Other major disease categories apart from immune disorders that we investigated were a solid malignancy, diabetes mellitus, renal failure (defined as a repeatedly measured serum creatinine concentration of more than 150 mmol/L for at least 1 week; this cutoff level was chosen because it is elevated even for muscular young men and newborns), liver cirrhosis, and symptomatic atherosclerosis. All conditions were only taken into account if they were present at the time of the transfusion. Finally, we examined whether the patient had died since his blood transfusion.

### Blood products

We examined the following characteristics of the blood product to which the transfusion reaction was ascribed: leukoreduction, washing, subtyping (for C, c, E, e, Kell, Duffy (a), Duffy (b), Kidd (a), Kidd (b), M, N, S, and P1 antigens in addition to ABO and Rhesus D) and/or irradiation.

### Analysis

For categorical variables, we calculated Mantel-Haenszel common odds ratio (OR) estimates for the correlation between transfusion reactions and patient characteristics with computer software (SPSS 11.0 for Windows, SPSS, Inc., Chicago, IL). We calculated adjusted ORs with a logistic regression model with the same program. We compared continuous variables with a t test.

## RESULTS

We identified 70 cases of alloimmunization in the Leiden University Medical Center and 31 in Haga Teaching Hospital. Aiming for an equal number of control patients, we selected 101 control patients in both hospitals according to the method described above. Patients who had an earlier alloimmunization episode were excluded from the case group, so that 67 cases from the Leiden University Medical Center and 20 from Haga Teaching Hospital remained. Information on patient and clinical characteristics was obtained from hospital computer files or patient charts. Information on previous childbirths and allergies could not be obtained for all patients. ORs for the association between patient characteristics and alloimmunization are listed in Table 2. A solid malignancy, female sex, and diabetes mellitus seemed risk factors for alloimmunization. A previous allogeneic PBPC transplantation might be a comparable risk factor, although the confidence interval of the OR was wide. Lymphoproliferative disorders and to a lesser extent symptomatic atherosclerosis seemed to protect against alloimmunization. Thirty-six patients in the control group had died since their transfusion versus 23 in the case group; this difference is not significant.

**Table 2.** Mantel-Haenszel adjusted odds ratios (95% confidence intervals) for association between patient characteristics and alloimmunization, stratified by hospital.

| Patient characteristic | Nr in case group (87) | Nr in control group (101) | Odds ratio (95% CI) |
|---|---|---|---|
| **Demographics** | | | |
| Female sex | 51 | 44 | 1.89 (1.05 to 3.38) |
| Non-European surname | 9 | 12 | 0.88 (0.35 to 2.20) |
| Previous childbirth | 25 (n=32)* | 21 (n=23)* | 0.34 (0.06 to 1.82) |
| **Transfusion history** | | | |
| Previous transfusion reaction other than alloimmunization | 7 | 4 | 1.96 (0.56 to 6.93) |
| Number of previous transfusions over 12.5 | 28 | 35 | 0.83 (0.45 to 1.55) |
| **Immunologically mediated diseases** | | | |
| Autoimmune disease | 13 | 11 | 1.38 (0.59 to 3.23) |
| Other systemic inflammatory non-infectious diseases | 7 | 10 | 0.76 (0.28 to 2.11) |
| Allergies | 14 (n=79)* | 18 (n=95)* | 0.92 (0.42 to 1.98) |
| **Haematological disorders** | | | |
| Aplastic anaemia | 3 | 1 | 3.23 (0.33 to 31.89) |
| Myelodysplasia, myeloproliferative disorders, myelogenous leukaemia | 10 | 14 | 0.85 (0.35 to 2.02) |
| Acute myelogenous leukaemia | 5 | 10 | 0.54 (0.18 to 1.64) |
| Myelodysplasia | 2 | 2 | 1.40 (0.20 to 9.80) |
| Lymphoproliferative disorders | 7 | 22 | 0.33 (0.13 to 0.81) |
| Previous allogeneic haematopoietic stem cell transplantation | 8 | 4 | 2.24 (0.64 to 7.81) |
| **Other** | | | |
| Solid malignancy | 23 | 15 | 2.07 (1.00 to 4.30) |
| Chemotherapy within one month prior to alloimmunization | 18 | 24 | 0.84 (0.42 to 1.67) |
| Chemotherapy within six months prior to alloimmunization | 15 (n=67)* | 23 (n=70)* | 0.59 (0.28 to 1.26) |
| Previous solid organ transplantation | 3 | 3 | 1.05 (0.20 to 5.38) |
| Renal failure | 10 | 13 | 0.86 (0.35 to 2.08) |
| Liver cirrhosis | 2 | 2 | 1.16 (0.15 to 8.81) |
| Symptomatic atherosclerosis | 14 | 28 | 0.52 (0.25 to 1.08) |
| Diabetes mellitus | 16 | 10 | 2.15 (0.91 to 5.05) |

Descriptive statistics for the continuous variables in the case group and the corresponding control group are shown in Table 3. The patients in the control group had received slightly more RBC transfusions than those in the case group, although the difference was not significant.

The means of the age and the number of childbirths for the case and control group were not significantly different either.

**Table 3.** Means and 5th and 95th percentiles (p5 and p95) for continuous variables for the alloimmunization cases and corresponding controls

| | | Median | p5 | p95 |
|---|---|---|---|---|
| Age (years) | Cases | 56.5 | 12.8 | 84.2 |
| | Controls | 56.0 | 8.1 | 84.3 |
| Nr of previous red blood cell transfusions | Cases | 6.0 | 1.0 | 40.0 |
| | Controls | 9.0 | 1.1 | 65.2 |
| Number of childbirths* | Cases | 2.0 | 0.0 | 4.0 |
| | Controls | 2.0 | 0.0 | 4.0 |

* women for whom information on childbirths was available

To correct the ORs for potential confounders, we performed logistic regression analysis. Given the relatively small numbers of cases, we only entered three or four variables together in a single model. We selected confounders that have an obvious relationship with certain risk factors. For example, allogeneic PBPC transplantation is usually used to treat lymphoproliferative or myelogenous marrow disorders and is obviously associated with previous chemotherapy. The results are listed in Table 4.

**Table 4.** Crude and adjusted odds ratios (OR; 95% confidence intervals) for association between patient characteristics and alloimmunization

| Patient characteristic | Crude OR | Confounder | Adjusted OR |
|---|---|---|---|
| Female sex | 1.89 (1.05 to 3.38) | Diabetes mellitus; symptomatic atherosclerosis | 1,74 (0.96 to 3.16) |
| Lymphoproliferative disorders | 0.33 (0.13 to 0.81) | Chemotherapy within one month prior to alloimmunization; previous allogeneic haematopoietic stem cell transplantation | 0.26 (0.09 to 0.71) |
| Previous allogeneic haematopoietic stem cell transplantation | 2.24 (0.64 to 7.81) | Lymphoproliferative disorders; myelogenous marrow disorders; chemotherapy within one month prior to alloimmunization | 3.70 (0.94 to 14.63) |
| Solid malignancy | 2.07 (1.00 to 4.30) | Chemotherapy within one month before alloimmunization | 2.13 (1.02 to 4.44) |
| Symptomatic atherosclerosis | 0.52 (0.25 to 1.08) | Diabetes mellitus; female sex | 0.46 (0.21 to 0.99) |
| Diabetes mellitus | 2.15 (0.91 to 5.05) | Female sex; symptomatic atherosclerosis | 2.66 (1.07 to 6.63) |

The associations between alloimmunization and solid malignancy and diabetes mellitus became stronger after correction. Female sex was slightly less strongly associated with alloimmunization after correction. Strikingly, previous allogeneic PBPC transplantation seemed a much stronger risk factor after correction for lymphoproliferative disorders, myelogenous marrow disorders, and previous chemotherapy. The protective effects of lymphoproliferative disorders and atherosclerosis seemed stronger after correction. The number of patients with female sex was not significantly different between patients with and without a lymphoproliferative disease. There were slightly more women among the patients with a solid malignancy than without a malignancy, but regression analysis did not influence the ORs much. The number of previous RBC transfusions was not a confounder.

## DISCUSSION

In this exploratory study, we found a number of associations between patient characteristics and alloimmunization. Our data suggest that solid malignancy, previous allogeneic PBPC transplantation, diabetes mellitus, and female sex are risk factors for alloimmunization against RBC antigens, whereas lymphoproliferative disorders and symptomatic atherosclerosis protect against it. All these associations except for female sex were stronger after correction for possible confounders.



The main weakness of this study is the relatively small number of patients, which limits the power to detect small differences. This project, however, has demonstrated the usefulness of identifying side effects in databases like TRIP's for etiologic studies and future studies can be undertaken with a larger number of participating hospitals.

The way in which the control patients were selected resulted in an overrepresentation of patients who had received many RBC transfusions. For that reason, the number of previous transfusions could not be evaluated as a risk factor. This ensures, however, that controls had enough exposure to develop antibodies. Certain RBC antibodies become undetectable within months after their development.[2] Therefore, alloantibodies that have developed may be missed if a type and screen procedure is performed a long time after the RBC transfusion that caused their development. Owing to the fact that control patients received more RBC transfusions, the transfusion intervals in the control group, that is, the intervals between the last RBC transfusion and the transfusion for which a new type-and-screen procedure was performed, were usually shorter than the transfusion intervals in the case group, so that short-lived antibodies had a larger chance to be detected in the control group than in the case group. Therefore, differences found between cases and controls cannot be caused by confounding by the duration of the transfusion interval.

In contrast, it is possible that patients with slowly forming alloantibodies are still in the control group because their antibodies are not yet apparent. If the risk factors for slow-forming alloantibodies are the same as those for early alloantibodies, this means that any associations found between alloimmunization and possible risk factors would be weakened because cases with an excess of risk factors are hidden in the control group. Therefore, if an association is found, it can only be stronger than suggested by the present data, a phenomenon called nondifferential misclassification. Furthermore, we judge the chances of slowly forming antibodies being missed in the control group to be small due to the large number of transfusions the control group received and the inherently high frequency of screening for alloantibodies.

The case-control design is a powerful tool for the detection of several risk factors at the same time. This design has rarely been applied in studies investigating risk factors for transfusion reactions.

Part of our findings are consistent with earlier studies. Female sex has been indicated as a risk factor.[3-6] This is biologically plausible, because women are exposed to alloantigens during pregnancy and childbirth. Earlier studies suggested that chronic lymphocytic leukemia, a lymphoproliferative disorder, protects against alloimmunization.[3,7] Our study found lymphoproliferative disorders as a group to be protective. This is also biologically plausible, because the malignant clone may displace functional T and B cells. Moreover, most of the patients with lymphoproliferative disorders receive intensive chemotherapy, which suppresses immunity. A protective effect of intensive chemotherapy has been suggested in an earlier study.[8] Our study suggests a slightly protective effect of chemotherapy. Aplastic anemia has been suggested to be a risk factor.[3] Our data are consistent with this, although the numbers are very small.

Some of our findings are inconsistent with earlier studies. In a number of studies, alloimmunization seemed to be associated mainly with racial differences between donor and recipient populations and the number of previous blood transfusions.[10-13] We found no indications for this with our rather crude method of comparing surnames. Furthermore, an association between alloimmunization and autoimmune diseases has been reported,[14] which we did not find either. One study found liver cirrhosis and myelodysplastic syndromes to be risk factors,[3] which we could not confirm, possibly due to the very low frequency of these conditions in our study population. Finally, splenectomy was found to be a risk factor in one study.[12] In our study population, only one control patient had had a splenectomy.

Finally, we found associations that have not been reported earlier. A new finding is the increased risk of alloimmunization in patients with solid malignancy, in spite of the fact that

many of them were receiving chemotherapy. A possible mechanism for this is a state of increased immune activation. A recent animal model suggests that alloantibodies are formed more easily in the context of an inflammatory state.[15] Another finding that has not been published earlier to our knowledge is the increased risk of alloimmunization after an allogeneic PBPC transplantation. There are several reports on hemolysis due to alloantibodies after an allogeneic PBPC transplantation, however. The development of these antibodies might have a relationship with major and minor incompatibility between donor and recipient and the persistence of mixed chimerism. This might play a direct role because part of the recipient's immune system might recognize the transfused antigens as foreign, or an indirect, role — again in the context of an inflammatory state. Also, a passenger lymphocyte mechanism has been implicated.[9] Surprisingly, we found diabetes mellitus to be a risk factor. For this finding we have no pathogenetic explanation. We also found symptomatic atherosclerosis to protect against alloimmunization, although we have no theory for a possible underlying biologic mechanism. Obviously, we do not know whether these findings are the result of an unknown pathophysiologic mechanism or the association is caused by random variation in the small numbers.



In conclusion, female sex, diabetes mellitus, solid malignancy, and previous allogeneic PBPC transplantation seem to be risk factors for alloimmunization against RBC antigens, whereas lymphoproliferative disorders and symptomatic atherosclerosis seem to protect against it. Further studies are needed to confirm these associations and investigate their possible underlying mechanisms. For this goal, databases such as TRIP can be very useful.

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1 Reference incorrect in the published version. The reference should be to TRIP Report 2005, The Hague 2006, ISBN 978-90-78631-01-9.

# CHAPTER 6

# Male-only fresh-frozen plasma for transfusion-related acute lung injury prevention: before-and-after comparative cohort study

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## ABSTRACT

### Background

TRALI is one of the most serious complications of blood transfusion. It can be caused by incompatible leukocyte antibodies in transfused plasma. The objective of this study was to quantify the reduction of TRALI following introduction of male-only plasma for transfusion as a preventive measure, which took effect in 2007.

### Study design and methods

In The Netherlands all cases of TRALI are reported to the national hemovigilance office. All reported cases of TRALI from 2002 to November 2009 were considered for inclusion. Those meeting the Canadian consensus clinical definition were included and subdivided according to whether or not the patient had received quarantine FFP (Q-FFP) in the six-hour period before the reaction. The numbers of TRALI cases involving plasma donated before the measure and of those involving plasma donated after the measure were compared to TRALI cases that did not involve Q-FFP in order to adjust for reporting bias.

### Results

110 cases were included in the analysis. Of 68 cases before the measure, 36 involved Q-FFP. 31 cases occurred after the measure of which 8 involved Q-FFP. Eleven occurred in the transitional period, of which 4 involved Q-FFP. The population attributable risk of pre-measure plasma among TRALI cases occurring before the measure was 0.33 (95% CI 0.09 to 0.51).

### Conclusion

In The Netherlands the male-only Q-FFP measure was associated with a 33 percent reduction of TRALI cases.

## INTRODUCTION

Transfusion-related acute lung injury (TRALI) is one of the most serious transfusion reactions and one of the top three causes of transfusion-related mortality in most hemovigilance registries.[1,2] According to the Canadian consensus criteria, respiratory distress, hypoxia, increased airway resistance and frothy sputum in ventilated patients arise within six hours of transfusion and are associated with (new) infiltrates showing on X-ray. This is assumed to be due to neutrophils entering the pulmonary interstitium and fluid loss into the alveoli.[3,4] TRALI has been attributed to incompatibility between donor leukocyte antibodies (HLA class I and II antibodies as well as anti-granulocyte antibodies) in transfused plasma and recipient leukocytes.[5,6] However, in many cases no leukocyte incompatibility is found. In the postulated two-hit mechanism of TRALI, a first hit consists of neutrophil priming or initial triggering of endothelium in the pulmonary vascular bed. The second hit can be the transfusion of leukocyte antibodies incompatible with the recipient or other factors that arise during storage of blood products.[4]

The proportion of TRALI cases which are deemed to be caused by leukocyte incompatibility has been estimated at up to 89%.[3] Leukocyte antibodies are mainly induced by pregnancy or blood transfusion.[7] Therefore several countries where fresh frozen plasma (FFP) is used for transfusion have introduced FFP preferentially or exclusively derived from male donors who have never received a blood transfusion with the aim to reduce the number of TRALI cases. In the UK, analysis of ten years of TRALI registration within "SHOT" (Serious Hazards of Transfusion) the national hemovigilance office shows that implementation of preferential male-only FFP has led to a near-disappearance of TRALI associated with leukocyte incompatibility following plasma transfusion.[2] However this may be partly a consequence of the SHOT method of assessing "imputability", the likelihood that the clinical picture of TRALI is related to transfusion. SHOT grades imputability of TRALI reports higher in the presence of patient-incompatible leukocyte antibodies. The international consensus definition for TRALI does not include leukocyte incompatibility as a criterion.[8,9]

The male-only measure became effective in The Netherlands for all quarantine plasma (Q-FFP; henceforth in this article we will refer simply to "plasma") distributed to hospitals since 1st July 2007. The aim of the present study was to quantify the reduction of TRALI cases, as defined by the international consensus definition, following implementation of male-only plasma.

## METHODS

### Design and study setting

We performed a cohort study among all patients who had a diagnosis of TRALI in The Netherlands from 2002 to 2009 with the aim of comparing the incidence of TRALI before and

after the male-only plasma measure became effective. In The Netherlands all suspected cases of TRALI are reported to TRIP (Transfusion Reactions in Patients), the national hemovigilance system which became fully operational in 2003. The reports are submitted on a paper or digital reporting form; additional information is requested from hospitals if necessary for standardized classification. TRIP also receives information on reported TRALI cases from the blood service. Inclusion was terminated on 15th November 2009, when a further measure was introduced in the production of platelet concentrates.

## Patients

*TRALI case definition*

TRALI cases had to conform to the criteria of the international consensus definition of TRALI: a patient was included in the cohort if there were clinical findings of hypoxia with bilateral infiltrates on the chest X-ray, starting within 6 hours of the transfusion of a labile blood component; circulatory overload had to be excluded as a (more likely) cause.[8,9] Information on the clinical condition of the patient was evaluated for known risk factors for acute lung injury or other possible causes of hypoxia with a temporal relationship to the respiratory distress.

All reports were reviewed by a panel of transfusion experts and assessed on clinical information without considering results of leukocyte serological investigation, which in most cases were not available to the reviewing committee. If the patient had a risk factor for acute lung injury (e.g. aspiration, toxic inhalation, lung contusion, near-drowning, cardiopulmonary bypass, pneumonia, acute pancreatitis, sepsis) the case was flagged as a "possible TRALI" according to the consensus definition.[8,9] Cases were excluded if there were other more likely causes for the respiratory problems. All blood components received by the patient up to 6 hours before onset of respiratory symptoms were recorded.

*Transfusional setting and analysis periods*

In The Netherlands plasma for transfusion is prepared from apheresis plasma which is released after the donor has been retested for infectious diseases after a minimum of six months. From October 2006 all plasma collected for Q-FFP and from July 2007 onwards all plasma distributed to the hospitals was from male never-transfused donors. Units distributed before 1st July 2007 were not recalled from the hospitals and were transfused from the hospital inventory over the following months. Cryosupernatant plasma is occasionally used for refractory TTP[1] and prepared on demand from Q-FFP.

1 Thrombotic thrombocytopenic purpura

Since 1988 all platelet products and since 2002 all red cell components have been leukoreduced by prestorage filtration (<1x 10^6 leukocytes per unit). Plasma for transfusion meets the same specification. Red blood cell concentrates are stored in SAGM additive solution and contain less than 20 ml of residual donor plasma. Over 90% of platelet concentrates are prepared from five pooled buffy coats and resuspended in either 200 ml of plasma from one of the donors (approx. 70% of total platelet units) or platelet additive solution with residual circa 85-100 ml plasma consisting of <20 ml of plasma from each buffy coat. Apheresis platelets are collected in a volume of 150 to 400 ml donor plasma and are used for special indications such as HLA-matched platelets, Parvo B19 or CMV-safe products[2]. During the study years the total number of blood components distributed to the hospitals annually was approximately 700,000 units.

For TRALI cases reported after July 07 the donation date of transfused plasma was checked. Reports where any plasma had been transfused were classified according to the donation date of the plasma as occurring with products from before or after the measure. TRALI cases involving no plasma were assigned to the same period as any plasma-associated TRALI in that month. The three analysis periods were: before the measure (2002 – June 2007), the transitional period during which cases were associated with plasma both from before and after the measure (July – November 2007) and after the measure (December 2007 – 15 November 2009). Plasma-associated cases during the transitional period were assigned according to the date of donation of the plasma and the cases without plasma were assigned half to before and half to after the male-only measure for purposes of calculation.



*Statistical analysis*

We compared the number of reported TRALI cases from before introduction of the male-only measure with the number after it had become effective. If the measure was effective a reduction will be seen in the number of TRALI patients who received one or more units of plasma, with or without other blood components, when only male plasma was available for transfusion. The number of reported cases where the patient had not been transfused with plasma reflects the overall sensitivity of TRALI detection and reporting in any period. This number was used to correct for changes in this sensitivity.

We expected that after the measure became effective there would be a drop in the proportion of TRALI reports after transfusion of plasma against the total number of reported TRALI cases. The drop represents the population attributable risk (PAR) for female plasma as available prior to the measure, and corresponds to the fraction of TRALI prevented by the implementation of male-only plasma. An additional sensitivity analysis was performed, calculating the PAR separately for the ramp-up phase of reporting to TRIP (2002–4) and for the plateau phase

2 HLA=human leukocyten antigen; CMV = cytomegalovirus

(from 2005 – mid 2007). The main result was recalculated with the omission of reports from the interim period as an additional verification.

The formula used is:
$PAR = (R - R_0)/R = 1 - \text{risk after/risk before}$
with R the risk of TRALI in transfusion recipients before the measure and $R_0$ the risk in transfusion recipients after the measure.
During the reporting period there was little change in numbers of blood components distributed in The Netherlands,[10] so stable proportions of patients transfused with different types and combinations of types of blood component are assumed. The number of TRALIs (N) reported in a given period is
$N = X * f * Y$
in which X is the "true" incidence rate of TRALIs (number per year), f is the proportion detected and reported and Y the follow-up period (years).
$PAR = 1 - (\text{risk after/risk before}) = 1 - X_A/X_B = 1 - (N_A/(Y_A * f_A))/(N_B/(Y_B * f_B))$
For TRALIs where no plasma was transfused the "true" rate cannot have changed since the measure was introduced so
$X_{B, \text{no plasma}} = X_{A, \text{no plasma}}$
Since we collected TRALIs with and without plasma concurrently we can also assume that f at any time is the same for TRALI with and without plasma. This allows the proportion $Y_A * f_A/(Y_B * f_B)$ (for all cases) to be estimated by $N_{A, \text{no plasma}}/N_{B, \text{no plasma}}$. Thus the PAR was calculated as
$PAR = 1 - ((N_A/N_B) * (N_{B, \text{no plasma}}/N_{A, \text{no plasma}}))$
simply using the observed numbers of reported TRALIs.
A confidence interval for the PAR was calculated using
$\text{Var}[\ln(1-PAR)] = 1/N_{B,\text{no plasma}} - 1/N_B + 1/N_{A, \text{no plasma}} - 1/N_A$.[11]

## RESULTS

### Characteristics of the study population

The study population comprised 110 patients with TRALI approved by expert review as complying with the TRALI definition. Figure 1 shows the numbers of all suspected TRALIs per year from 2002 to 2009 according to the types of blood component(s) received by the patient.

### TRALI before and after the male-only plasma measure

The earliest TRALI involving one or more plasma units from after the measure occurred in July 2007, the last case where one or more plasma units dated from before the measure occurred in November 2007. Thirty-one of the TRALI cases were designated as "possible TRALI" according to the consensus definition because one or more other risk factors for acute lung injury (ALI) were present.

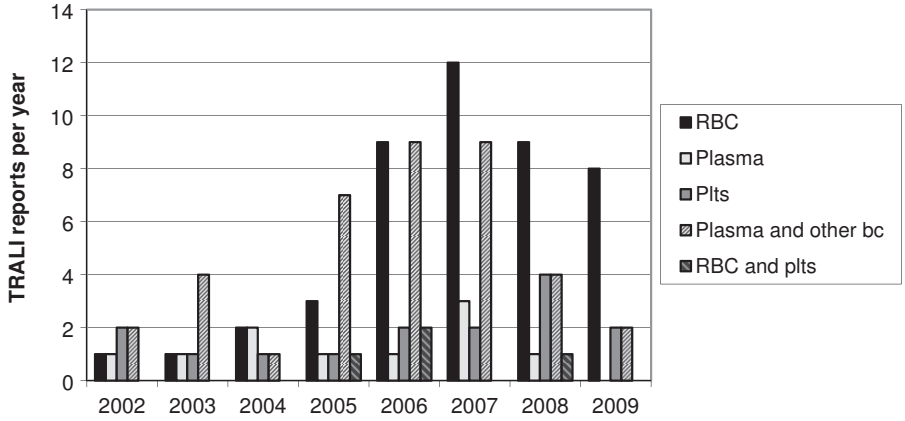


**Figure 1.** Reports of suspected TRALI and associated blood components, 2002-2009
bc = blood component(s)

## Outcomes and estimation

The annual number of reports of TRALI rose for all types of blood component between 2002 and 2007, which can be attributed to increased awareness of TRALI. The initial rise in total annual number of reports to the new hemovigilance reporting system had levelled off in 2005. A total of 68 cases of TRALI occurred before the male-only plasma measure of which 36 involved plasma, with or without other types of blood components. From December 2007 there were 31 cases of which 8 involved plasma. Four of the eleven cases in the transitional period were associated with plasma, two with plasma donated before the measure. Table 1 summarizes the numbers of reports with and without plasma per analysis period.



**Table 1.** TRALI cases and transfused blood components per analysis period

| TRALI | Before the measure 1 Jan 2002 – 1 July 2007 | Transitional period* 1 July 2007 – 1 Dec 2007 | After the measure 1 Dec 2007 – 15 Nov 2009 | Total | PAR $1 - ((N_A/N_B) * (N_{B,}$ no plasma / $N_{A,}$ no plasma)) |
|---|---|---|---|---|---|
| **All TRALI** | 68 | 11 | 31 | 110 | 1-((36.5/73.5)*(35.5/26.5)) = 0.33 (95% CI 0.09-0.51) |
| with plasma | 36 | 2 before 2 after | 8 | 48 | |
| without plasma | 32 | 7 | 23 | 62 | |
| **TRALI, excluding cases of "possible TRALI"** | 48 | 8 | 23 | 79 | 1-((27/52)*(22.5/18.5)) = 0.37 (95% CI 0.06-0.58) |
| with plasma | 28 | 2 before 1 after | 7 | 38 | |
| without plasma | 20 | 5 | 16 | 41 | |

* If cases in the interim period are left out of the calculation the PAR becomes 1 – ((31/68)*(32/23)) = 0.37 (0.12-0.54) and 0.40 (0.08-0.61) excluding "possible TRALI".

The overall PAR was 0.33 (95% CI 0.09-0.51) for all TRALI. After exclusion of "possible TRALI" it was 0.37 (0.06-0.58). In the sensitivity analysis comparing the separate periods of 2002–4 and 2005 – mid 2007 to that after the measure the PAR was comparable though with a wider confidence interval: PAR 0.41 (95% CI –0.07 to 0.67); and 0.31 (–0.02 to 0.54) respectively.

## DISCUSSION

The male-only plasma measure was associated with a 33 percent reduction of TRALI in The Netherlands, a reduction totally driven by lower numbers of cases where plasma had been transfused in combination with red blood cells and/or platelets. The finding implies that against the average number of approximately 20 reports per year before the measure, some 7 of the previously reported cases annually may have been avoided by the measure. Moreover, since the plasma measure can only prevent TRALI caused by plasma, this size of effect means that the majority of TRALI cases where plasma had been transfused prior to the measure were in fact caused by female plasma. The figures in Table 1 show that TRALI cases where plasma had been transfused are in the majority in the period before the measure and that this is reversed after the measure. (See also supplementary figure 2 at the end of this article, not published.)

We observed a higher attributable risk when cases of "possible TRALI" were excluded. In some cases where other risk factors for ALI were present, ALI was probably not induced by the transfusion. Inclusion of some such cases leads to dilution and underestimation of the effect of the measure. The higher attributable risk after exclusion of "possible TRALI" is probably more valid and provides further support that there is a true reduction.

### Strengths and limitations

The strength of this analysis lies in its inclusion of all reported patients meeting the standardized criteria for TRALI in a whole country, with as little as possible interference from awareness of the results of leukocyte serology testing. Reporting of such a serious complication as TRALI to TRIP and/or the blood service is expected to be nearly complete. An important advantage is that we use the number of TRALIs not associated with plasma to correct for variability in detection and reporting behavior. The fact that a similar effect is found in the sensitivity analyses of the sub-periods supports our use of these cases as a comparator.

A limitation of the study is its observational nature and reliance on spontaneous reporting of cases. A recent analysis has shown that bias may operate in the decision whether to report a reaction as suspected TRALI.[12] If any interpretation bias operated it could be expected to favor reports of TRALI associated with FFP and to have most strongly influenced TRALIs where FFP was the sole product transfused. However the present findings do not support this. Also,

since most clinicians in The Netherlands are not aware of the plasma measure this reporting preference is unlikely to have changed and therefore could not have biased our analyses.

The overall blood use and the proportions of type of blood component remained largely stable over the study period, except for a slight (less than 10%) drop in the number of both RBC and plasma units distributed to the hospitals between 2002 and 2004 (see Table 2). Thus a relative reduction of the use of plasma as compared to cellular blood components has not contributed to a lower incidence of TRALI. The assumption of unchanged risk associated with RBC and platelet transfusion could also be challenged if female plasma donors returned to whole blood donation. In fact however female donors continued to donate plasma for fractionation.

**Table 2.** Annual blood use (to nearest 1000) and rate of reported TRALI

| Blood components distributed (to nearest 1000 units) | | | | Total number of TRALI and overall rate per 100,000 units distributed | |
|---|---|---|---|---|---|
| Year | RBC | Plasma | Platelets | | |
| 2002 | 630 | 105 | 50 | 6 | 0.76 |
| 2003 | 617 | 112 | 48 | 7 | 0.90 |
| 2004 | 585 | 97 | 53 | 6 | 0.81 |
| 2005 | 568 | 92 | 51 | 13 | 1.83 |
| 2006 | 556 | 92 | 51 | 23 | 3.29 |
| 2007 | 555 | 93 | 54 | 26 | 3.71 |
| 2008 | 554 | 98 | 51 | 19 | 2.70 |
| 2009 | 564 | 90 | 49 | 12 | 1.70 |



The overall incidence of reported TRALI appears to show a downward trend after the year 2007 (figure 1). Analyses by TRIP show that there have been increased reports of transfusion-associated circulatory overload and other transfusion reactions, suggesting that the diagnosis of TRALI is assigned more critically.[1] As explained above the calculated drop in TRALI is based on the ratio of TRALI cases where plasma was (one of blood components) transfused, to cases without plasma, and would be valid despite a reduced trend in the overall level of TRALI detection and reporting.

### Consistency with prior findings

A reduction by 33% is slightly higher but in the same order of magnitude as suggested by the findings of leukocyte serology as reported recently from our country.[13] The reduction is comparable to observational pre- and post intervention data on ALI in ruptured abdominal aneurysm repair from a single UK center (0.39, 95% CI 0.16-0.90).[14] An American study of TRALI fatalities in 2003–5 found that 18 out of 38 probable TRALI fatalities (47%) were associated with female antibody-positive fresh frozen plasma and might be avoided by limiting transfusion of leukocyte antibody-containing FFP.[15] This proportion is again similar although the relative

contribution of alloimmune-mediated TRALI associated with FFP would not necessarily be the same among cases with fatal outcome. A recent overview of probable TRALI (including nonfatal cases) reported by the American Red Cross describes a drop from 30 cases associated with plasma transfusion in 2006 to 10 cases in 2008 after implementation of male-predominant plasma for transfusion.[16]

In the United Kingdom reports to SHOT of TRALI associated with FFP containing patient-incompatible leukocyte-reactive antibodies dropped from 10 in 2003 to none in 2004–7 since implementation of preferential use of male plasma. This suggests that, if supply of exclusively male plasma is achieved, this measure could prevent most or all TRALI caused by plasma. As explained above, SHOT assesses the likelihood that a suspected TRALI is indeed transfusion-related partly on the basis of the finding of concordant HLA antibodies in the transfused unit(s). The overall rate of reported TRALI (assessed as highly likely, probable or possible) before the change in the UK was 1.9 per 100,000 units, compared with 2.6 per 100,000 in 2005-6 in our registry. In The Netherlands, the expert assessors were blinded to the results of this investigation from 2007 onwards. Prior to that year they were not consistently blind to the results but these were not used for the clinical definition of TRALI. The calculated reduction in The Netherlands is remarkably similar to the effect in the UK despite the important difference in the assessment of cases; this is in line with the hypothesis of TRALI cases having being prevented by elimination of patient exposure to incompatible leukocyte antibodies in plasma from female donors.

**Meaning of the study, implications for clinicians and policymakers**

Not in all countries are donors excluded if they have been recipients of transfusion. Plasma from male donors who have (ever) been transfused should logically also be excluded, although it has been established that pregnancy-related HLA antibodies persist for longer than antibodies developed following blood transfusion. In The Netherlands it was possible to implement the measures for no significant costs and without serious threat to the blood (plasma) supply. We adopted the use of male-only plasma for the plasma added to platelet pools in mid November 2009. A further safety improvement will be obtained if this achieves a comparable risk reduction for the platelet concentrates preserved in plasma.

Some blood services have implemented antibody screening for all female donors, with repetition of the screening following pregnancy.[17] This should have comparable efficiency in preventing TRALI, while resulting in fewer donor deferrals, but is associated with increased costs. Other countries (e.g. France, Ireland, Norway, Finland) use pooled solvent-detergent (SD) virally inactivated plasma and report that TRALI is not seen in association with this product. Reduction in non-infectious transfusion complications (both TRALI and allergic reactions) was included as an important aspect in a recent review of cost-effectiveness aspects of this product.[18]

## CONCLUSION

In conclusion, our findings suggest that in The Netherlands the male-only plasma measure has led to a reduction of TRALI cases of about 33 percent.

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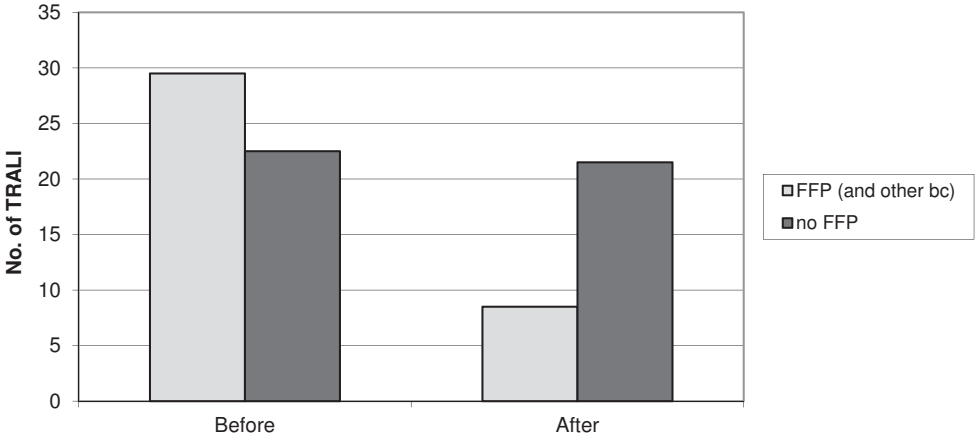


**Figure 2.** (not published with article) Numbers of reported TRALI, excluding cases of "possible TRALI", before and after the measure

# CHAPTER 7

# Variation between hospitals in rates of reported transfusion reactions: is a high reporting rate an indicator of safer transfusion?

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## ABSTRACT

### Background and objectives

It has been suggested that the rate of reported transfusion reactions is positively correlated with safety of the transfusion chain in a hospital. We evaluated this assumption in the TRIP Dutch National Hemovigilance Office database taking reported incorrect blood component transfused as a proxy for unsafe transfusion.

### Methods

Reports from 2006-2010 and annual numbers of transfused blood components from the 103 hospitals were analysed. The rate of transfusion reactions per 1000 blood components was calculated per hospital. Logistic regression analysis was performed between reporting of at least one incorrect blood component and tertile of transfusion reaction rate.

### Results

Out of the 103 hospitals, 101 had complete data in some and 93 in all five years. In all, 72 had reported at least one incorrect blood component transfused; this was associated with blood use level and also with rate of reported transfusion reactions: odds ratio 4.2 (95% confidence interval 1.3-13.7) in the highest vs. the lowest tertile after adjustment for blood use level.

### Conclusion

Hospitals in The Netherlands which report more transfusion reactions per 1000 units are also more likely to have reported incorrect blood component transfused. The data do not support that hospitals with a higher rate of transfusion reaction reports are safer.

## INTRODUCTION

Blood transfusion is an essential part of modern health care without which many advances in medical and surgical treatment would not have been possible. Nevertheless, there is always the risk of an adverse reaction or of patient harm resulting from an error or other type of incident. Since the high-profile blood scandals of the 1980s and 1990s, national haemovigilance systems have been put in place to receive, register and analyse reports of transfusion reactions and adverse incidents in the blood transfusion chain from donor to recipient.[1-3] In the European Union, legislation requires member states to have a haemovigilance system to collate mandatory reports of serious adverse reactions and serious adverse events which may be associated with the quality or safety of blood or blood components for transfusion.[4]

The work of haemovigilance registries serves to document the occurrence of transfusion reactions as well as of errors and incidents in the transfusion chain. Haemovigilance systems highlight the risks associated with the transfusion of labile blood products, make recommendations for changes in practice and can trigger research. Some registries have presented evidence of decreases in reports of a particular type following interventions. Any decline in voluntary spontaneous reports must however be examined critically against other information, e.g. a different type of report which has remained static or increased.[5,6] The SHOT (Serious Hazards of Transfusion, the UK haemovigilance system) 2009 annual report comments: "….. the hallmark of an effective vigilance system, in that the participation in the scheme, and thus total reports, increases as users become engaged with the process while the number of serious incidents declines."[2] This suggests that reporting of non-serious events could be used as an indicator of transfusion safety when serious events are simultaneously declining, assuming that better reporting is associated with safety awareness and good surveillance of patients, thus a lower actual risk.

We studied whether the reports to the Dutch national haemovigilance system over a number of years support the assumption that a relatively high number of reported transfusion reactions in a hospital is associated with a lower likelihood of incorrect blood transfused (IBCT), taking this as a proxy for unsafe transfusion. We examined the outcome of the reporting of incorrect blood component transfused and analysed its associations with the rates of reporting transfusion reactions and different types of incidents.

## MATERIALS AND METHODS

### Study design

We performed a nationwide study using data that had been reported by the 103 Dutch hospitals to the TRIP (Transfusion Reactions in Patients) Dutch National Hemovigilance Office

(see below). From the database we extracted figures of reported transfusion reactions and incidents in 2006-2010. For each hospital the reported transfusion reactions and incidents were analysed in relation to the annual numbers of transfused blood components (red blood cells, platelet concentrates and fresh frozen plasma).

### Transfusion setting

In The Netherlands there is a national blood service, Sanquin Blood Supply. In all but a few hospitals the blood transfusion laboratory holds a blood stock and performs blood grouping, immunohaematological investigations, blood component selection and compatibility testing, which may be in the form of electronic crossmatch.

### Haemovigilance reporting

TRIP Dutch National Hemovigilance Office has been operational since 2003. Each hospital has a designated haemovigilance officer, who is generally a chief biomedical scientist or consultant haematologist. Hospitals submit reports either electronically or using a paper reporting form. Each year hospitals are asked for data on numbers of transfused blood components, at which time hospitals also confirm whether reports for the previous year are complete. Haemovigilance reporting to TRIP covers all types and levels of severity of transfusion reactions as well as errors and incidents within the transfusion chain. These are collected using standard definitions which are similar to the international definitions as developed by the International Haemovigilance Network and the haemovigilance working party of the International Society of Blood Transfusion (see Table A in the web version of this article).[7,8] The definitions for bacterial complications and that for severity grade 2 were modified slightly in 2008. Serious reactions are defined as those which are life-threatening or fatal or which cause long-term morbidity or (prolongation of) hospital admission/morbidity.

Participation in haemovigilance reporting is regarded as the professional standard both in the national transfusion guideline and by the Healthcare Inspectorate.[9] Participation by the hospitals has been approximately 95% each year from 2006. Since 2008, in accordance with European legislation, the reporting of serious adverse reactions and serious adverse events in parallel to the Healthcare Inspectorate as competent authority has been mandatory. Hospitals are also mandated to have a patient safety management system. TRIP publishes annual reports which are publicly available on the website (www.tripnet.nl). Annually there is considerable variation in the rate of reports in relation to the number of blood components transfused in a hospital.[10]

Reporting of transfusion reactions, errors and incidents occurs in three broad domains: the clinical/ward domain, the hospital transfusion laboratory and the patient safety domain. There is variation between hospital protocols regarding investigation. Notably some but not all hospitals go beyond the minimum requirements of the national guideline and perform investigations for mild non-haemolytic febrile reactions (temperature rise >1<2 °C without chills or rigors) and (mild) allergic transfusion reactions.

**Study outcome measures and statistical analysis**

We used submission to TRIP of one or more reports of incorrect blood component transfused by a hospital as a proxy for poor safety. Incorrect blood component transfused is defined as any case where the patient is transfused with a blood component which did not meet all the requirements according to the hospital protocol for a suitable transfusion for that patient, or that was intended for another patient. As a secondary outcome measure we analysed the reporting by a hospital of at least one unintentionally ABO-incompatible transfusion.

As reporting parameters for each hospital we calculated the rate of all reported transfusion reactions per 1000 blood components and defined tertiles of the reporting rate. We also calculated the rates per 1000 blood components of non-haemolytic transfusion reactions (≥ 2°C and/or rigors), of mild febrile reactions (>1<2°C) and of all other reported transfusion reactions with the exception of new erythrocyte allo-antibodies. Yes/no variables were defined for reporting of new allo-antibodies, of near miss and of other incidents. The presence of a transfusion safety officer was classified as none, 1-4 years or all years. We further defined four levels of annual total blood use: <3000, 3000-6000, 6000-13000 and >13000 units and three levels of the proportion of platelet units out of total blood use: <2.5%, 2.5-5% and >5%. For an assessment of any changes in absolute rates of reports we analysed 2006-8 and 2009-10 separately, including all hospitals with at least four years of data.

Statistical analyses were performed using PASW Statistics 18.0.0 (SPSS inc., part of IBM Corporation, New York). The consistency of the rate of reported transfusion reactions in a hospital from year to year was assessed by performing linear regression of the rate of transfusion reactions in 2010 with that in 2009 and 2006-9 for all hospitals with four or five years of complete data, adjusting for the level of blood use. This was repeated without the adjustment but with exclusion of the hospitals transfusing fewer than 3000 units per year, as verification that the result was not driven by the smallest hospitals being least likely to have reported incorrect blood component transfused. To study the associations between reporting parameters and incorrect blood component transfused as well as reported ABO-incompatible transfusion we performed logistic regression with adjustment for blood use levels (categorical).

## RESULTS

Information on both transfusion reactions and total transfused units was available from 101 of the 103 hospitals for one or more years in 2006-10, covering approximately 95% of national blood use. Table 1 summarises key figures about reporting according to the hospitals' total blood use level.

**Table 1.** General characteristics of blood use and reporting, 2006-10

| Hospital blood use level[a] | Number of hospitals (n=101) | Total number of units transfused | Total reports[b]; rate per 1000 units | Interquartile range of hospital rates | IBCT[c] reports; rate per 1000 units | ABO-incomp. reports; rate per 1000 units |
|---|---|---|---|---|---|---|
| <3000 | 34 | 336,087 | 1141; 3.39 | 1.35-4.32 | 36; 0.11 | 4; 0.012 |
| 3000-6000 | 21 | 630,605 | 2047; 3.25 | 1.76-4.56 | 51; 0.08 | 9; 0.014 |
| 6000-13000 | 32 | 993,668 | 3351; 3.59 | 2.14-4.73 | 74; 0.07 | 9; 0.010 |
| >13000 | 14 | 1,384,157 | 4611; 3.33 | 2.21-4.74 | 144; 0.10 | 16; 0.012 |

[a] Average total units of blood components per year (red blood cells, apheresis or 5-donor pooled buffy coat platelets, fresh frozen plasma)
[b] Total of reported transfusion reactions, new allo-antibodies, errors and incidents
[c] Incorrect blood component transfused

### Hospitals' consistency from year to year

Ninety-nine hospitals had four (n=6) or five (n=93) years of data and were included in this analysis. Table 2 presents the explained variance in individual hospitals' rates of reported reactions in 2010 in comparison to rates of preceding years. Hospitals' previous rates were good predictors of the 2010 transfusion reaction rate. Comparing the 2010 to the 2009 rate and that in 2006-8 with adjustment for blood use level gave a value of $R^2$ of 0.55, indicating that approximately 55% of variance in the rate of reporting transfusion reactions is explained by the rates in the previous years. A similar result was obtained if only the hospitals transfusing over 3000 units per year were included.

**Table 2.** Consistency of transfusion reaction reporting rate in hospitals

| Linear regression with rate of transfusion reactions in 2010 | All hospitals (n=99) | | Hospitals transfusing >3000 units p.a. (n=66) | |
|---|---|---|---|---|
| | $R^2$ | Significance | $R^2$ | Significance |
| 2009 rate | 0.509 | P<0.001 | 0.301 | P<0.001 |
| 2006-2008 | 0.377 | P<0.001 | 0.481 | P<0.001 |
| 2009, 2006-2008 | 0.553 | P<0.001 | 0.498 | P<0.001 |
| 2009, 2006-2008 and blood use level | 0.553 | P<0.001 | | |

### Trends in time

The total rate of reports to TRIP rose from 3.20 to 3.82 per 1000 blood components transfused from 2006-8 to 2009-2010, with the total number of transfusion reactions rising from 2.81 to

3.34 per 1000 units (Table 3). This is partly explained by increased reports of allo-antibodies (from 0.93 to 1.20 per 1000 units). There were nonsignificant rising trends for reporting febrile reactions and for the total of transfusion reactions in other categories (data not shown). The overall rate of incorrect blood component transfused remained similar from 2006-8 to 2009-2010 (0.096 and 0.092 per 1000 units in 2006-2008 and 2009-2010 respectively), as did that for ABO-incompatible transfusion (0.011 and 0.013 per 1000 units respectively). There was a rising trend of the rate of incorrect blood component transfused and unintended ABO-incompatible transfusion in the hospitals with the lowest rate of reported transfusion reactions and a declining trend in those with the highest rate (Table 3).

**Table 3.** Rates of reported transfusion reactions per period according to level of transfusion reaction reports

| Level of hospital total transfusion reaction reporting[a] | 2006-8 | 2009-10 | Difference in rate (95% confidence interval) | |
|---|---|---|---|---|
| Lowest (<1.8/1000 units; n=28) | | | | |
| Total transfusion reactions | 1.19 | 1.32 | 0.13 | (–0.05-0.30) |
| Incorrect blood component transfused | 0.053 | 0.075 | 0.022 | (–0.018-0.062) |
| ABO incompatible | 0.011 | 0.019 | 0.008 | (–0.011-0.027) |
| Middle tertile (1.8 - 3.7/1000 units; n=37) | | | | |
| Total transfusion reactions | 2.36 | 3.14 | 0.78 | (0.60-0.95) |
| Incorrect blood component transfused ABO | 0.090 | 0.080 | –0.010 | (–0.040-0.020) |
| incompatible | 0.011 | 0.015 | 0.004 | (-0.008-0.017) |
| Highest tertile (>3,7/1000 units; n=34) | | | | |
| Total transfusion reactions | 4.38 | 4.87 | 0.49 | (0.23-0.76) |
| Incorrect blood component transfused | 0.129 | 0.119 | –0.011 | (–0.053-0.032) |
| ABO incompatible | 0.011 | 0.007 | –0.004 | (–0.015-0.007) |
| Overall (n=99) | | | | |
| Total transfusion reactions | 2.81 | 3.34 | 0.53 | (0.40-0.65) |
| Incorrect blood component transfused | 0.96 | 0.92 | –0.004 | (–0.026-0.018) |
| ABO incompatible | 0.011 | 0.013 | 0.002 | (–0.005-0.010) |

[a] Rate of reports per 1000 blood components transfused; hospitals are classified according to the average rate of transfusion reaction reporting in 2006-2010

## Whole period: odds of incorrect blood component transfused

The odds ratio for at least one report of incorrect blood component transfused rose with hospitals' annual blood use level and increased independently with higher levels of total transfusion reaction reports. The odds ratio (OR) was 4.2 (95% confidence interval (CI) 1.3-13.7) for the highest vs. the lowest tertile after adjustment for blood use level (Table 4). Reported incorrect blood component transfused was also significantly associated with the highest tertile of mild non-haemolytic febrile reactions (>1 <2°C) and with a hospital's reporting of allo-antibodies, near miss and/or other incidents. There was no association with platelet use level or with the proportion of serious reactions.

**Table 4.** Hospital reporting parameters and odds ratio (OR) of reported incorrect blood component transfused

| Parameter (no. of hospitals; total n=101) | | Incorrect blood component transfused (IBCT; ≥ 1 per hospital) | | | | | |
|---|---|---|---|---|---|---|---|
| | | No (%) with IBCT | | Crude OR (95% confidence interval) | | Adjusted OR[b] (95% confidence interval) | |
| Blood use level[a] | | | | | | | |
| <3000 | (34) | 19 | 56% | 1 | (0.9-8.0) | N.A. | |
| 3000-6000 | (31) | 24 | 77% | 2.7 | (0.8-9.0) | | |
| 6000-13000 | (22) | 17 | 77% | 2.7 | (0.9-24.5) | | |
| >13000 | (14) | 12 | 86% | 4.7 | | | |
| Total transfusion reaction reporting level[c] | | | | | | | |
| <1.8 | (30) | 16 | 53% | 1 | | 1 | |
| 1.8-3.7 | (37) | 28 | 76% | 2.7 | (0.96-7.7) | 2.5 | (0.8-7.3) |
| >3.7 | (34) | 28 | 82% | 4.0 | (1.3-12.7) | 4.2 | (1.3-13.7) |
| NHTR reporting level[c,d] | | | | | | | |
| <0.52 | (32) | 20 | 63% | 1 | | 1 | |
| 0.52-0.80 | (35) | 27 | 77% | 2.0 | (0.7-5.9) | 1.6 | (0.5-4.8) |
| >0.80 | (34) | 25 | 74% | 1.7 | (0.6-4.7) | 1.7 | (0.6-5.0) |
| Mild febrile reaction[c,e] | | | | | | | |
| <0.25 | (34) | 19 | 55% | 1 | | 1 | |
| 0.25-0.66 | (31) | 24 | 77% | 2.7 | (0.9-8.0) | 2.6 | (0.8-8.3) |
| >0.66 | (36) | 28 | 80% | 3.3 | (1.1-9.5) | 4.7 | (1.5 - 15) |
| Transfusion reactions excluding allo-antibodies and febrile reactions[c] | | | | | | | |
| <0.37 | (30) | 20 | 66% | 1 | | 1 | |
| 0.37-0.73 | (37) | 24 | 65% | 0.9 | (0.3-2.5) | 1.0 | (0.3-2.8) |
| >0.73 | (34) | 28 | 82% | 2.3 | (0.7-7.5) | 2.3 | (0.7-8.1) |
| Serious-nonserious ratio | | | | | | | |
| 0-0.04 | (49) | 32 | 65% | 1 | | 1 | |
| 0.04-0.08 | (32) | 26 | 81% | 2.3 | (0.8-6.7) | 1.8 | (0.6-5.5) |
| >0.08 | (20) | 13 | 70% | 1.2 | (0.4-3.8) | 1.1 | (0.3-3.7) |
| Reporting of near miss | | | | | | | |
| No | (62) | 35 | 57% | 1 | | 1 | |
| Yes | (39) | 37 | 95% | 14.3 | (3.2-65) | 14.2 | (3.0-66) |
| Reporting of other incident | | | | | | | |
| No | (47) | 22 | 47% | 1 | | 1 | |
| Yes | (54) | 50 | 93% | 14.2 | (4.4-46) | 15.4 | (4.2-56) |
| Allo-antibody reporting | | | | | | | |
| No | (27) | 11 | 41% | 1 | | 1 | |
| Yes | (74) | 61 | 82% | 6.8 | (2.8-16) | 5.8 | (2.1-16) |
| Transfusion safety officer | | | | | | | |
| No | (23) | 13 | 57% | 1 | | 1 | |
| 1 -4 years | (15) | 12 | 80% | 3.1 | (0.7-13) | 2.8 | (0.6-13) |
| All years | (63) | 47 | 75% | 2.3 | (0.8-6.1) | 2.2 | (0.8-6.1) |

[a] Average total units of blood components per year (red blood cells, platelets, fresh frozen plasma)
[b] Odds Ratio adjusted for blood use in four levels
[c] rate of reports per 1000 blood components transfused
[d] non-haemolytic transfusion reaction (≥ 2°C and/or chills/rigors); see definitions in Table A
[e] >1<2 °C; see definitions in Table A

In a multivariable logistic regression model which included blood use level, the presence of a transfusion safety officer and the reporting variables, reported incorrect blood component transfused remained independently associated with reporting of allo-antibodies, with near miss, and with other incidents; it was also associated with mild febrile reaction reporting (OR 2.2, 95% CI 1.0-5.1; data not shown). Independently of the reporting of incorrect blood component transfused, the parameters representing a relatively high rate of reports tended to be associated with each other as well as with the presence of a transfusion safety officer.

Reported ABO-incompatible incorrect transfusion showed similar but weaker associations compared to all reported incorrect blood component transfused, both with and without adjustment for hospital blood use level (data shown in Table B in the web version of this article); because of the lower number of these reports the confidence intervals are wider.

## DISCUSSION

In this study we first examined the consistency of hospitals' rates of reported transfusion reactions. It was found that approximately 55% of the variation could be explained from the rates in earlier years thus there is considerable consistency from year to year. This probably reflects hospitals' stable patient mix, transfusion reaction protocols and other factors relevant for reporting practice, e.g. safety awareness in the blood transfusion laboratory, nurse alertness and organisational safety culture. The consistency supports our pooling of each hospital's data over several years.



As our main study question we investigated the hypothesis that higher numbers of less serious reports are an indicator for fewer very serious adverse transfusion reactions and events, as proposed in the 2009 SHOT Annual Report. We examined the reporting of incorrect blood component transfused as a proxy for unsafe transfusion and observed that this is more likely in hospitals which have a relatively high rate of reported transfusion reactions or which report to TRIP on allo-antibodies, on near miss or other incident(s). The breakdown of "total transfusion reactions" given in Table 4 shows that the positive association of reported incorrect transfusions with level of reports of transfusion reactions may be driven more by the reports of mild non-hemolytic transfusion reactions than by those of non-hemolytic transfusion reactions. None of the associations is negative, i.e. none supports the hypothesis. While we cannot exclude the possibility that the hospitals with a higher rate of transfusion reactions may have more incorrect transfusions to report, a more likely explanation is that reporting of incorrect blood component transfused is more reliable in hospitals with strong awareness and reporting culture in the clinical areas, in the blood transfusion laboratory and in the domain of patient safety. In any case the data do not provide evidence that hospitals with higher rates of reported transfusion reactions are safer. The most serious incorrect transfusion events, those where

an ABO-incompatible unit is transfused, showed similar but non-significant associations. We observed no change in the overall rate of reported incorrect blood component transfused or of ABO-incompatible transfusions, nor was this demonstrated in the subgroup of hospitals with higher rates of reported transfusion reactions. The suggestive declining trend in the group with most transfusion reactions (Table 3) is driven by a small number of hospitals and should be interpreted with extreme caution.

The SHOT comment refers to trends noted at the national level and could be explained by increased reporting by some hospitals coinciding with national improvement from adoption of recommendations. The question posed in this study examines whether the trend holds at the hospital level: if improvements are detectable, is it in the hospitals where rates of reported transfusion reactions are higher, where one regards this as an indicator that haemovigilance reporting is functioning well. What can explain our failure to demonstrate this – plausible and attractive – trend described by SHOT? Firstly, national haemovigilance reporting is a tool for monitoring events and not a direct means of improving safety. The Dutch system, launched in 2003, is relatively young and to date, neither the occurrence of the most serious reactions (Grade 3 and 4) nor that of ABO incompatible transfusions has shown any decline in the TRIP data. With the exception of TRALI following the male-only plasma intervention[6] there has not yet been any improvement as regards the occurrence of serious transfusion reactions, but more notably also not of errors.

The SHOT haemovigilance system was launched in 1996 and the declining trend of the proportion of transfusion-related serious morbidity and deaths has only gradually become apparent: the number of ABO incompatible red blood cell transfusions has dropped since approximately 2004 compared to the preceding eight years. The apparent improvement is ascribed chiefly to better application of safety procedures and recommended practices as laid down in national guidelines.[11] Similarly the French haemovigilance system, active since 1994, reports that the rate of ABO-incompatible transfusions leading to reactions was lower in 2006-2010 than in 2000-2005, although the difference does not reach statistical significance.[12] In France the bedside ABO compatibility check by the transfusing nurse has been in place since 1985 and the bedside verification of patient and unit identity was designated as a distinct mandatory task by a ministerial circular in 2003. The trend of reduction of the most serious events in the world's two oldest haemovigilance systems would be consistent with the explanation that it takes time for improved transfusion safety awareness, extra training and gradual implementation of recommended practices to lead to such improving trends.

The Dutch figures in absolute terms show that we must not seek the explanation in a greater safety level from the outset. The rate of total reported incorrect blood component transfused

(2010 data) is 6.9 per 100,000 units distributed in the United Kingdom,[13] probably similar in France (total of "serious adverse events with transfusion of LBP declared on the AR as Grade 0" and "serious adverse events with transfusion of LBP that caused an RAE of a grade >0" is 5.6 per 100,000 units[12]) and 8.3 in The Netherlands. Ireland to our knowledge has the highest national rate of reported incorrect blood component transfused at 45 per 100,000 units[14] (number of "SAE/IBCT" minus unnecessary transfusions and storage/expiry problems). The rates of ABO incompatible transfusion over the last four years are 0.38 in the UK, 0.36 in France, 1.13 in Ireland and 1.11 in The Netherlands (rates calculated from the annual reports [2,9,11,12]). Of all events, the ABO-incompatible incorrect transfusions are among the most serious so should be least subject to under-reporting. The cited figures make it likely that reporting of incorrect blood component is not exhaustive in The Netherlands and secondly that there is room for improvement in the avoidance of ABO incompatible transfusions. We are not of the opinion that variation in reporting level could be reduced by regulatory requirements. In The Netherlands the overall rate of reports in 2006-10 ran at approximately 3 per 1000 blood components transfused, which is similar to or slightly above that in France with its mandatory system for reporting all transfusion reactions as well as serious adverse events in the transfusion chain. Regional variation in the rate of reporting has been noted both in the UK with reporting of only serious events but comparable regulations to The Netherlands, and France.[12,13]

A strength of this study is that it reviews several years of data in a haemovigilance system with near-complete participation. To our knowledge it is the first thorough analysis by a haemovigilance system of whether having more reports of transfusion reactions is an indicator for better hospital-level transfusion safety. It suggests greater reliability of reporting incorrect blood component transfused in hospitals with high levels of reports in various domains. In so far as success for a haemovigilance system depends on capturing information which will provide relevant signals to the transfusion professionals, this is in line with the statement that a successful haemovigilance system receives increasing numbers of less serious reports.

The study is limited by the fact that we lacked knowledge of what specific hospital factors influenced reporting on the one hand, and transfusion safety on the other. A further possible limitation is the change of definitions in the course of the study period, however this did not affect the specific categories from which the analysed parameters were calculated.

The cited comment in the SHOT 2009 report referred to the ratio of reports of very serious morbidity or death to the less serious events, as well as to a progressive (absolute) decline of ABO incompatible red cell transfusions. Our use of reported incorrect blood component transfused as an indicator for unsafe transfusion is a slightly different approach. These events (and among them, the ABO incompatible transfusions) constitute the most clearly

avoidable transfusion hazards, but are only one way in which transfusion can be unsafe. Avoidable transfusion reactions as another possible indicator merit future study, however only a minority of transfusion reactions (e.g. transfusion-associated circulatory overload) are currently avoidable by improvements in the clinical part of the transfusion chain. Avoidance of unnecessary transfusions represents a third dimension of safety with potential for improving patient outcomes and saving money. Reports of errors and incidents involving unnecessary transfusion are captured by some haemovigilance systems. Our haemovigilance system is soon to collaborate with hospitals to collect and provide benchmarking of basic indicators on observance of transfusion triggers.

## CONCLUSION

In conclusion, a high reporting rate of transfusion reactions is associated with increased odds of reporting incorrect blood component transfused. This may be explained by better surveillance and more complete reporting, although it cannot be excluded that hospitals with higher rates of transfusion reactions may have more incorrect transfusions to report. The data do not support the hypothesis that a higher rate of reporting transfusion reactions is an indicator for greater safety in the transfusion chain.

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**Table A.** TRIP (2008) definitions of transfusion reactions and incidents (published online only)

**Nonhaemolytic transfusion reaction (NHTR)**

Rise in temperature of ≥ 2°C (with or without rigors/chills) during or in the first two hours after a transfusion, with no other relevant symptoms or signs; OR rigors/chills with or without a rise in temperature within the same time limits. No evidence (biochemical or blood group serological) for haemolysis, and no alternative explanation.

**Mild (nonhaemolytic) febrile reaction**

Rise in temp. >1°C (<2°C) during or in the first two hours after a transfusion with no other relevant symptoms or signs; optional reporting to TRIP. Haemolysis testing and bacteriology negative if performed.

**Acute haemolytic transfusion reaction**

Symptoms of haemolysis occurring within a few minutes of commencement of until 24 hours subsequent to a transfusion: one or more of the following: fever/chills, nausea/vomiting, back pain, dark or red urine, decreasing blood pressure or laboratory results indicating haemolysis within the same period.

Biochemical haemolysis testing positive; blood group serological testing possibly positive; bacteriology negative.

**Delayed haemolytic transfusion reaction**

Symptoms of haemolysis occurring longer than 24 hours after transfusion to a maximum of 28 days: unexplained drop in haemoglobin, dark urine, fever or chills etc.; or biochemical haemolysis within the same period. Biochemical testing and blood group serology confirm this.

If new antibodies are found without biochemical confirmation of haemolysis, report as new allo-antibody.

**TRALI (Transfusion-related acute lung injury)**

Dyspnoea and hypoxia within six hours of the transfusion; chest X-ray shows bilateral pulmonary infiltrates.

There are negative investigations (biochemical or blood-group serological) for haemolysis, bacteriology is negative and no other explanation exists. Depending on the findings of tests of leukocyte serology, report is classified as immune-mediated or unknown cause.

**Transfusion-associated circulatory overload (TACO)**

Dyspnoea, orthopnoea, cyanosis, tachycardia >100/min. or raised central venous pressure (one or more of these signs) within six hours of transfusion, usually in a patient with compromised cardiac function. Chest X-ray consistent.

**Anaphylactic transfusion reaction**
Rapidly developing reaction occurring within a few seconds to minutes after the start of transfusion, with features such as airway obstruction, in and expiratory stridor, fall in blood pressure ≥ 20 mm Hg systolic and/or diastolic, nausea or vomiting or diarrhoea, possibly with skin rash.

Haemolysis testing and bacteriology negative, test for IgA and anti-IgA.

**Other allergic reaction**
Allergic phenomena such as itching, redness or urticaria but without respiratory, cardiovascular or gastrointestinal features, arising from a few minutes of starting transfusion until a few hours after its completion. Haemolysis testing and bacteriology negative if performed.

**New allo-antibody**
After receiving a transfusion, demonstration of clinically relevant antibodies against blood cells (irregular antibodies, HLA or HPA antibodies) that were not present previously (as far as is known in that hospital).

**Post-transfusion bacteraemia/sepsis**
Clinical symptoms of bacteraemia/sepsis arising during, directly after or some time subsequent to a blood transfusion, for which there is a relevant, positive blood culture of the patient with or without a causal relation to the administered blood component.

**Post-transfusion viral infection**
A viral infection that can be attributed to a transfused blood component as demonstrated by identical viral strains in donor and recipient and where infection by another route is deemed unlikely.

**Haemosiderosis**
Iron overload induced by frequent transfusion with a minimum ferritin level of 1000 micrograms/l, with or without organ damage.

**Post-transfusion purpura (PTP)**
Serious self-limiting thrombocytopenia possibly with bleeding manifestations (skin, nose, gastrointestinal, urinary tract, other mucous membranes, brain) 1-24 days after a transfusion of a red cell or platelet concentrate, usually in a patient who has been pregnant. Investigations: HPA antibodies and HPA typing of patient.

**Transfusion-associated graft versus host disease (TA-GvHD)**
Clinical features of graft versus host disease such as erythema which starts centrally, watery diarrhoea, fever and rise in liver enzymes 1-6 weeks (usually 8-10 days) after transfusion of a T-cell containing (non-irradiated) blood component. Skin (and liver) biopsies can support diagnosis.

**Other transfusion reaction**
Transfusion reaction which does not fit into the categories above

**Incorrect blood component transfused (IBCT)**
All cases in which a patient was transfused with a component that did not fulfil all the requirements of a suitable component for that patient, or that was intended for a different patient. TRIP requests institutions to report these cases, even if there are no adverse consequences for the patient.

**Positive bacterial screen**
The blood service reports a positive bacteriological screen, but bacterial contamination of the relevant material is not confirmed by a positive culture result on the same material or other products made from the same donation

**Bacterial contamination of a blood component**
Relevant numbers of bacteria in a (remnant of) blood component or in the bacterial screen bottle of a platelet component, or in material from the same donation, demonstrated in the approved way with laboratory techniques, preferably including typing of the bacterial strain or strains.

**Look-back by the supplier**
Retrospective notification of a possibly infectious donation, leading to investigation of the recipient for that infection, but where no infection is demonstrated in the recipient.

**Viral contamination of blood component**
Retrospective analysis by Sanquin demonstrates viral contamination of an already administered blood component, previously screened and found negative.

**Near miss**
Any error that, if undetected, could have led to a wrong blood group result or issue or administration of an incorrect blood component, and which was detected before transfusion.

Please indicate where the error arose, any further errors or failed checks, and how the error was discovered.

**Haemolysed product**
Occurrence of clinical signs / symptoms in a patient associated with the presence of free haemoglobin in a transfused product (from recovered blood).

**Heparinisation**
Clotting problems associated with incomplete removal of added heparin during automated blood recovery method.

**Other incident**
Error or incident in the transfusion chain that does not fit into any of the above categories, for instance patient transfused whereas the intention was to keep the blood component in reserve, or transfusing unnecessarily on the basis of an incorrect Hb result or avoidable wastage of a blood component.

**Table B.** Hospital reporting parameters and odds ratios (OR) of ABO incompatible transfusion report(s) (published online only)

| Parameter (no. of hospitals) | | ABO incompatible transfusion reported (≥ 1 per hospital) | | | | | |
|---|---|---|---|---|---|---|---|
| | | No (%) with ABO-incompatible Tf | | Crude OR (95% CI) | | Adjusted OR[#] (95% CI) | |
| Blood use level* | | | | | | | |
| <3000 | (34) | 3 | 9% | 1 | | N.A. | |
| 3000-6000 | (31) | 8 | 26% | 3.6 | (0.9-15.1) | | |
| 6000-13000 | (22) | 5 | 23% | 3.0 | (0.6-14.3) | | |
| >13000 | (14) | 9 | 64% | 18.6 | (3.7-93) | | |
| Total transfusion reaction reporting level[c] | | | | | | | |
| <1.8 | (30) | 6 | 20% | 1 | | 1 | |
| 1.8-3.7 | (37) | 11 | 30% | 1.7 | (0.5-5.3) | 1.4 | (0.4-4.9) |
| >3.7 | (34) | 8 | 24% | 1.2 | (0.4-4.1) | 1.1 | (0.3-4.0) |
| NHTR reporting level[c, d] | | | | | | | |
| <0.52 | (32) | 7 | 22% | 1 | | 1 | |
| 0.52-0.80 | (35) | 11 | 31% | 1.6 | (0.5-4.9) | 0.89 | (0.26-3.0) |
| >0.80 | (34) | 7 | 21% | 0.93 | (0.28-3.0) | 0.67 | (0.18-2.5) |
| Mild febrile reaction[c,e] | | | | | | | |
| <0.25 | (34) | 5 | 15% | 1 | | 1 | |
| 0.25-0.66 | (31) | 13 | 42% | 4.2 | (1.3-13.7) | 5.1 | (1.3-19.9) |
| >0.66 | (36) | 7 | 19% | 1.4 | (0.4-14.9) | 2.8 | (0.7-12) |
| Transfusion reactions excl. allo-antibodies and febrile reactions[c] | | | | | | | |
| <0.37 | (30) | 4 | 13% | 1 | | 1 | |
| 0.37-0.73 | (37) | 11 | 30% | 2.8 | (0.8-9.8) | 2.8 | (0.7-10.6) |
| >0.73 | (34) | 10 | 29% | 2.7 | (0.7-9.8) | 1.8 | (0.4-7.8) |
| Serious-nonserious ratio | | | | | | | |
| 0-0.04 | (49) | 8 | 16% | 1 | | 1 | |
| 0.04-0.08 | (32) | 10 | 31% | 2.3 | (0.8-6.8) | 1.7 | (0.5-5.4) |
| >0.08 | (20) | 7 | 35% | 2.8 | (0.8-9.1) | 2.6 | (0.7-10.2) |
| Reporting of near miss | | | | | | | |
| No | (62) | 11 | 18% | 1 | | 1 | |
| Yes | (39) | 14 | 36% | 2.6 | (1.0-6.5) | 2.0 | (0.7-5.6) |
| Reporting of other incident | | | | | | | |
| No | (47) | 6 | 13% | 1 | | 1 | |
| Yes | (54) | 19 | 35% | 3.7 | (1.3-10.3) | 2.7 | (0.9-8.4) |
| Allo-antibody reporting | | | | | | | |
| No | (27) | 2 | 7% | 1 | | 1 | |
| Yes | (74) | 23 | 31% | 5.6 | (1.2-25.9) | 4.3 | (0.8-21.7) |
| Transfusion safety officer | | | | | | | |
| No | (23) | 3 | 13% | 1 | | 1 | |
| 1 or more years | (15) | 6 | 40% | 3.6 | (1.2-10.5) | 4.4 | (0.8-24.6) |
| Yes | (63) | 16 | 25% | 1.8 | (0.8-4.0) | 2.0 | (0.5-8.4) |
| Period (n=99) | | | | | | | |
| 2008-8 | (99) | 16 | 16% | 1 | | 1 | |
| 2009-10 | (99) | 15 | 15% | 0.9 | (0.4-2.0) | 0.9 | (0.4-2.1) |

[a] Average total units of blood components per year (red blood cells, platelets, fresh frozen plasma)
[b] adjusted for blood use in four levels
[c] rate of reports per 1000 blood components transfused
[d] NHTR-non-haemolytic transfusion reaction
[e] >1 <2 °C

# Conclusion

**Chapter 8**
Final discussion: Is hemovigilance making a difference to transfusion safety?

# CHAPTER 8

General discussion:
is hemovigilance making a difference
to transfusion safety?

## GENERAL DISCUSSION

The chapters in this thesis concern various parts of the transfusion chain. In this general discussion we return to the main study question: is hemovigilance making a difference to safety in the transfusion chain? Hemovigilance is defined as "a set of surveillance procedures covering the whole transfusion chain from the collection of blood and its components to the follow-up of its recipients, intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence and recurrence".[1] There is considerable variation between hemovigilance systems and other players – notably hospitals, blood supply organisations and regulators – in the types of events examined, as well as in the inclusion of other activities focused on monitoring and improving safety in the chain. Since the impact of hemovigilance must vary according to what is done, we have listed components of hemovigilance in Table 1. The key component of hemovigilance is the collecting and analysing of reports of adverse reactions and adverse events with a view to making recommendations for improving safety. This will be the focus in the reflections which follow.

In this discussion we will consider the following four aspects of transfusion safety, which are of immediate relevance to donors on the one hand and to patients on the other.

1. Transparency and knowledge of risks
2. Avoidance of preventable adverse reactions
3. No mistakes
4. Appropriate blood use: sufficient and timely use of blood components according to current evidence, but only if truly indicated.

### 1. Transparency and knowledge of risks

It was the perceived lack of transparency and insight that triggered the move towards centralised hemovigilance data collection. This insight into transfusion risks is of value and a relevant part of transfusion safety when reporting of reactions and incidents is in place and the findings public. If there is failure to reduce hazards, this would not be a reason to cease collecting data - on the contrary the data are all the more essential in order to demonstrate the areas where action is needed.

In chapter 1 it was seen that the European Union legislation (mandating data collection on blood product-related adverse reactions and adverse events from 2007) led to the introduction of national hemovigilance reporting in nine member states which did not previously have such a system. Patients can be assured that harms which have occurred are reported so lessons may be learned. If previously unknown adverse reactions occur, there is now a mechanism for these to be recognised and this opens possibilities for timely investigation and implementation of measures.

**Table 1.** Components of hemovigilance activity and remarks on the situation in The Netherlands

| Activity | Remarks | TRIP Dutch national Hemovigilance office | Relevance of chapters |
|---|---|---|---|
| **Collecting and analysing reports**[1] | Serious reactions / suspected transfusion-transmitted infections (co)investigated by Sanquin[2] as indicated | Primary process | |
| Serious transfusion reactions<br>Incl. TRALI | Only fatalities collected by the FDA, US | Yes | Chapter 1, 7<br>Chapter 6 |
| Non-serious transfusion reactions | | Yes | Chapter 7 |
| Transfusion-transmitted infection, confirmed | (Co)investigated by Sanquin | Yes | Chapter 1 |
| Previously unrecognised (serious) transfusion reaction | | Yes | |
| New allo-antibody formation (after transfusion) | | Yes | Chapter 4 |
| Incorrect blood component transfused, serious reaction | Requirement to report to Healthcare Inspectorate because of care quality issues | Yes | Chapter 7 |
| Incorrect blood component transfused, mild or no reaction | Hospitals: role of patient safety committee[2] | Yes | Chapter 7 |
| Near miss | | Yes | Chapter 7 |
| Patient outcomes following transfusion | | No | |
| Divers incidents in hospital<br>e.g. avoidable unit wastage | | Yes | |
| Post-donation information<br>Look-back investigation<br>Recall re pos. bacterial screening | Sanquin | Reports as submitted by hospitals; summary data from Sanquin | |
| **Special areas** | | | |
| Anti-D | | No | |
| Blood salvage techniques | | Yes | |
| Benchmarking information to hospitals re hemovigilance reports | | Yes | Chapter 7 |
| Traceability | | No | |
| Blood use<br><br>Monitoring appropriate blood use | | Info requested from hospitals<br>Previously no; now piloting indicators recommended in national guideline | |

**Table 1.** Components of hemovigilance activity and remarks on the situation in The Netherlands *(Continued)*

| Activity | Remarks | TRIP Dutch national Hemovigilance office | Relevance of chapters |
|---|---|---|---|
| Education/certification: | | | |
| Hemovigilance staff | | Yes | |
| Nurses | Hospitals: yes (some) | No | |
| (Junior) doctors | | No | |
| Blood donor adverse reactions, serious | Sanquin | Yes (as submitted to Inspectorate) | |
| Non-serious | Sanquin | No | Chapters 2,3 |
| Long-term outcomes/ safety for donors | | No | Chapter 4 |
| Post-marketing surveillance of new blood component type | Producer's responsibility | Currently standard reporting only | |

[1]Non-exhaustive list
[2]Sanquin Blood Supply, national blood service in The Netherlands
[3]Patient safety committee

Hemovigilance fulfils the function of surveillance of blood components after their authorisation and the formal post-marketing (Phase 4) study. Interestingly, all but one of the 23 responding countries include reporting about serious adverse reactions in blood donors, although this is not strictly required in law. Nevertheless the usefulness of collecting – and publishing – hemovigilance data depends on the validity of the collected information. Several European Union member states were found to have seriously incomplete or undocumented coverage of reporting organisations. The European (non-binding) guidance document provides definitions for types of transfusion reactions, based on those of the International Society of Blood Transfusion (then still in draft form) and the SHOT definition for transfusion-transmitted infection. The survey showed that half of the countries did not receive supporting information with all the serious reports thus were not able to consistently validate them against the internationally adopted definitions.

In The Netherlands the TRIP reports largely meet the objective of transparency. There is high participation by hospitals (though not 100%) and a policy of expert review of serious transfusion reactions. Concern regarding uniformity of data collection still exists, however. In the assessment of complex cases discussion frequently arises between experts about the most likely diagnosis of a transfusion reaction, for instance a suspected TRALI, even though a definition exists and when sufficient clinical information is available.[2,3] The rating of the severity of a reaction and its imputability to the blood transfusion can capture some of the variation between cases – as well as give rise to further debate between hemovigilance professionals. Such detailed assessment of reports is chiefly relevant for

serious reports, as opposed to non-serious ones which are less likely to trigger major preventive measures.

Chapter 3 provided insight into the complications of whole blood donation in The Netherlands and is the first published large-scale analysis of the national donor complication data. In the blood supply organisation there is full participation by collection centres, which use standard operating procedures. Despite the limitations of routinely – perhaps variably – recorded data, the data give real-life information which was not previously available.

The primary result of central reporting of adverse reactions and incidents is to obtain a picture of what the short-term hazards are. This can show up the types of reaction which are causing a heavy burden of harm or demonstrate a previously unknown or less common problem. Attention can be drawn specifically to those reactions which can be prevented, as well as to the types and causes of errors and incidents. In order to progress beyond the stage of merely counting events additional information, either captured by the hemovigilance system or obtained from other sources, is needed. Areas to be considered are denominator data regarding donations or transfusions without adverse reaction or mishap; characteristics of donors and patients, component production parameters and specifications, information about hospital laboratory and clinical transfusion practices.

Meanwhile, the specifications of the system vary considerably between countries (chapter 1, annexes) and with them, the scope and level of detail of the insights which can be obtained. The system must be appropriate to the setting, for instance a low human development index country where women die from peripartum blood loss should first ensure availability of tested blood and only then set up a basic hemovigilance system to capture just the serious reactions and errors. In a country with adequate resources there is a lack of evidence to guide the decision of which areas to include. While there is wide consensus about capturing serious reactions, some professionals would question the nationwide collecting of reports of known minor side effects of blood transfusion such as febrile or allergic reactions. Others believe in the value of these reports as an indication that the system is working or as a comparator category to support interpretation of a decline of another category as a true improvement.[4] It is clear that minor reactions have a practical and economic impact in the hospitals – TRIP is currently performing a cost analysis of the reported reactions. An incremental cost-effectiveness analysis of collecting additional types of reports at national level is impossible to perform: any improving trends generally cannot be ascribed to the reporting activity.

**2. Avoidance of preventable adverse reactions**

The objective is to reduce those adverse reactions which are amenable to prevention. This could be through general measures or through targeted precautions in donors or patients who have risk factors for harm. The findings of chapter 3 are relevant for counselling donors who faint or experience a venepuncture-related problem at their first donation, who wish to know how to avoid having the same problem next time. A general intervention could be to develop improved donor information material using the results of the study, providing tips for preventing possible complications and discussing the (increased, but still low) risk of recurrence at the next donation. Provision of such information can already reduce the occurrence of complications and improve donor retention.[5] The routinely recorded complications will be useful for monitoring the rates following the intervention.

Chapter 4 describes the only study in this thesis which actively investigated long-term outcomes. It was started in 2004 at the time when Sanquin Blood Supply and the donor registry Europdonor Foundation authorised the use of granulocyte colony stimulating factor (G-CSF) for mobilisation and harvesting peripheral blood stem cells in healthy unrelated donors. This guideline lays down several precautionary restrictions for exposure to G-CSF, e.g. an upper age limit of 55 years. The study, conducted among related donors, specifically examined whether such restrictions enhance safety. Reassuringly there was no suggestion of long-term increased risks of malignancy or cardiovascular disease but the number of follow-up years was (far) too small to exclude an increase. International collaboration in capturing donor follow-up data will be necessary to come nearer to an answer to these theoretical concerns. The results of our study highlighted the fact that the donor screening criteria for unrelated donors effectively select those at lower cardiovascular risk, which led us to recommend following the same criteria for related donors. We also found that female donors were more likely to require two days of apheresis or a central venous catheter: an aspect which can be weighed in selecting a preferred donor for the procedure, obtaining the best balance between the burden to the donor and prospect of benefit to the patient. The study is part of an investigative protocol which also evaluates the donation procedure and its acceptability for prospectively included unrelated and related donors. Recruitment of donors to the study has been concluded and analyses are to be performed in 2013 after the 1-year follow-up.

The pilot case-control study described in Chapter 5 suggested a number of risk factors for the development of red cell antibodies, including the presence of solid malignancy which had not previously been implicated. This study required laborious collection of additional clinical patient information. A limitation of the routine hemovigilance reports is that they capture very little patient data: in The Netherlands chiefly the specialty of the prescribing doctor and the indication (e.g. chronic symptomatic anemia or clotting

factor deficiency) while free text information can be added on main clinical diagnosis and clinical condition. Scope for future studies would be greatly increased by making use of other routine sources of data, such as hospital treatment episode administration. For the present, risk factors for the development of allo-antibodies have become one of the ongoing areas of investigation for the research departments at Sanquin Blood Supply and Leiden University Medical Center.[6,7]

Chapter 6 demonstrated the improvement in safety following a measure to reduce the risk of Transfusion-related acute lung injury (TRALI). It was partly through hemovigilance worldwide that there was an increase of awareness and research on mechanisms of this previously described transfusion complication. Based on the role of anti-leukocyte (HLA and HNA) antibodies many countries have introduced measures to reduce the risk of TRALI. In The Netherlands this was the male-only plasma measure, effective from mid-2007 (quarantine fresh frozen plasma being the type of plasma product used in this country from 2002 to 2012). This gives an example of using hemovigilance data to complete the quality cycle: a problem is noted, a measure is taken and the ongoing reporting monitors the effects of change. A caveat exists, however. Hemovigilance reporting is essentially a form of spontaneous reporting as opposed to active monitoring as in clinical trials. Spontaneous reporting is subject to inconsistency and incompleteness so a change of rates must always be analysed, as we did in chapter 6, against comparison cases in order to plausibly take account of possible shifts in reporting tendencies.

**3. No mistakes**

Has hemovigilance activity in The Netherlands been associated with a reduction of transfusion errors? This was examined in chapter 7. Hospitals with a high rate of reported transfusion reactions were found to also have a greater likelihood of having reported an incorrect blood component transfused. This would be consistent with not all errors being detected or reported in hospitals with a less strong reporting culture, which could partly arise from differences of interpretation about what types of event are reportable errors, despite the availability of definitions.[8] The Dutch data showed no decline in the numbers of reported incorrect transfusions or of the most serious subgroup, that of the ABO-incompatible transfusions. This is in contrast to the United Kingdom and to France where there have been declining trends of the reported ABO incompatible transfusions. (Note however that the number was again higher in the recently published SHOT 2011 report, though the rate in the UK remains lower than in The Netherlands.) No country has seen widespread introduction of electronic technology for the prevention of errors so any improvements are the result of less specific changes in practices.[1]

It must be appreciated that hemovigilance reporting serves for surveillance of adverse reactions and of errors and incidents. The act of reporting is not an intervention to actually reduce risks, although the assumption is that feedback to the transfusion professionals on what is happening, combined with recommendations for practice, may lead to improvements in safety. A priori it cannot be assumed that the hospitals which detect and send in higher numbers of reports of febrile and other reactions should make less mistakes in sample collection, component selection or identifying patients at the bedside. Even so it was disappointing that we failed to demonstrate better safety in the supposedly vigilant hospitals with higher rates of reported transfusion reactions. Maybe there truly is no association between the rate of reported transfusion reactions and the level of the vigilance or adherence to protocols in the hospital. Or was the reporting of incorrect blood component transfused not an appropriate proxy for unsafeness of transfusion, perhaps because reporting is indeed inconsistent? Avoiding incorrect transfusions is highly important but only part of transfusion safety. For now it remains an unanswered question whether certain hemovigilance data (preferably easy to collect) are usable as an indicator of safe practice.

**4. Appropriate blood use**

Sparing use of blood transfusion is important for both for donors and for patients. Donors have no demonstrated health benefit from their donation. The national burden to donors should be limited to the lowest which is compatible with the "good" for which they accept the inconveniences and small risks of donation: the availability of a safe, effective transfusion service. For patients, numerous studies have shown better outcomes when a restrictive transfusion policy is in place. It is also clear that adverse reactions and incidents in the transfusion chain will be immediately avoided by reducing blood use.

In the era of hemovigilance, capture of national figures on blood transfusion by international bodies including the Council of Europe has highlighted large differences in the number of components used, a twofold difference in the consumption of red blood cell concentrates per 1000 in the population being apparent between countries with well-developed healthcare systems.[9] Table 2 summarises the data for a number of countries with Ireland, France and The Netherlands showing the lowest consumption in western Europe. Interestingly, the rate was lowest in France in 2002, when a study of anesthetic-related mortality from that country reported 200 deaths per year from delayed blood transfusion or failure to transfuse.[10] The cause was related to delay in requesting and logistic problems but not to the transfusion triggers which were applied. Since then there has been an increase in the parameter in France. In Denmark, the country with the highest consumption in 2003-4, nationwide actions have brought about a noteworthy decrease in blood use.[9,11] In the years to come, through growth in the numbers of elderly people in populations, increasing blood requirements are to be expected even with thrifty use.[12]

**Table 2.** Numbers of units of red blood cell concentrate distributed per 1000 inhabitants (source: see ref. 9)

| | UK | France | Ireland | Netherlands | Denmark |
|---|---|---|---|---|---|
| 2001 | 46.2 | 33.0 | 30.1 | 37.7 | 62.3 |
| 2002 | 45.1 | 31.8 | - | 39.2 | - |
| 2003 | 43.7 | 32.4 | - | 37.6 | 70.8 |
| 2004 | 41.4 | 32.8 | 34.8 | 36.6 | 72.9 |
| 2005 | 39.5 | 32.1 | 32.9 | 35.5 | 63.5 |
| 2006 | - | 33.1 | 32.7 | 34.0 | 67.0 |
| 2007 | 35.8 | - | 35.3 | 33.8 | 64.0 |
| 2008 | 36.3 | - | 31.8 | 34.2 | 60.0 |

Although hospital hemovigilance staff are very much implicated in the area of auditing the appropriateness of prescribed blood transfusions it is not currently within TRIP's mandate (or that of other hemovigilance systems) to analyse data on blood use except as a denominator for the reports. However it is known from analysis of reports of transfusion reactions that sometimes the actual prescription of the transfusion was debatable or incorrect according to accepted transfusion indications.[13,14] Also some reports to TRIP concern incidents which led to inappropriate or unnecessary transfusion or avoidable component wastage. These incidents are captured in the category of other incident and have been highlighted in recent TRIP reports. The (2011) revised national transfusion guidelines include recommended quality indicators for blood transfusion.[15] The guideline development group has requested TRIP to evaluate these in collaboration with the hospitals. Although still under development they can potentially provide a tool for hospitals to monitor their own practice against that of other hospitals. For this work, the strength of a national office with an established network of contacts within hospitals is self-evident.

In conclusion, we have shown that hemovigilance reporting is improving knowledge about the occurrence of adverse reactions and incidents in the transfusion chain. Demonstration of actual safety improvement since TRIP started at the end of 2002 has been limited to the effect of the male-only plasma measure for TRALI reduction. The observational data are bound by limitations of data quality and variable reporting and do not capture longer-term outcomes. After ten years of national hemovigilance reporting in The Netherlands we do not know whether capturing hemovigilance data by a hospital or a country contributes to obtaining more favourable patient outcomes, or which form of data collection is most effective. It is timely to consider possible future developments.

## WHERE NEXT?

### International tools, data sharing and comparisons

Internationally recognised instruments are necessary for classifying data in a harmonized way. The International Haemovigilance Network and the Haemovigilance working party of the International Society for Blood Transfusion (ISBT) have usefully published surveillance definitions for donor complications and non-infectious transfusion reactions.[16] Definitions for infectious transfusion complications have proved more intractable (these are being developed by the ISBT working party on transfusion-transmitted infections) but work is progressing. Comparison of rates of reported errors and incidents is seriously hampered by differences in classifications between countries. (This includes the mandatory EU reporting, where the definitions and guidance document are not uniformly interpreted). The ISBT hemovigilance working party should continue its project of drawing up definitions for surveillance of sentinel types of errors. The ISBT working party on clinical blood use has assumed the task of developing an agreed and validated way of classifying patients' medical conditions and of indications for blood transfusion. Such international groups should make strong statements about the need for monitoring data quality.

Under the auspices of the International Haemovigilance Network a reporting database for aggregate national hemovigilance data has been launched: the International Surveillance database for Transfusion Adverse Reactions and Events, ISTARE.[17] Currently the first year of digitally captured data is being analysed. In the pilot phases there were wide variations between countries' data. The ISTARE steering group envisages taking up data quality issues with the participating countries and planning more in-depth analyses. The differences between countries in donation volumes and in blood component types will constitute a limitation. Such international comparisons are likely to encourage gradual harmonisation of categorisation and trigger further specific research projects by (groups of) participants. A future development may be sharing line-by-line data between donor or recipient HV systems so that specific questions can be investigated.

### Making data more accessible

As stated, hemovigilance reporting is not in itself a direct means to improve safety. It can only contribute to improvements if information is made available to those who organise or perform tasks in the transfusion chain. In the short term, effort is needed to make information accessible, e.g. turning routinely collected donor complication information into "dashboard" information for blood collection centre managers. TRIP hopes to develop interactive features in the online reporting database so that hospitals can generate graphs showing their own rate of certain types of complications against national figures.

Currently it cannot be said whether there is an optimal rate of a particular type of reports which is associated with transfusion safety, so the time is not ripe for hemovigilance data to be used as performance indicators which might be made public.

TRIP could perform more analyses if better "denominator" information were available about transfusion recipients who do not suffer from adverse reactions. Different groups have an interest in transfusion-related research and reported transfusion reactions. For instance, Sanquin must conduct post-marketing surveillance of newly introduced component types. Linking of transfusion data to patient survival using population mortality data (with encryption mechanisms to meet privacy requirements) was employed in the PROTON study[18] and a larger follow-on study is in preparation. It is essential to collaborate so that – while guaranteeing donors', patients' (as well as practitioners' and hospitals') privacy – duplication is avoided and effort invested in collecting data leads to the best possible returns. Types of routinely collected data which have recently been explored (but not yet in The Netherlands) are those of hospital episode statistics and health care insurance claims data.[19,20] Appropriate mechanisms will be needed, while protecting individuals' privacy, to enable healthcare professionals and organisations to harness information on transfusion practice and link this with extended donor and product data for studying and improving donor and patient outcomes.

**Patient outcomes**

At present hemovigilance reporting only covers the occurrence of transfusion reactions or incidents. What matters more are patient outcomes following transfusion. The literature on effects of the removal of white blood cells (leukoreduction) from transfused blood components was recently reviewed.[21] While it is clear that febrile reactions, formation of HLA antibodies and the risk of cytomegalovirus transmission are all reduced when leukoreduced blood components are transfused, the review questions the possible effects of leukoreduction on postoperative infections, aggravation of multi-organ failure or cancer recurrence, the only exception being a demonstrated 50% reduction of short-term mortality from leukoreduction of blood components in cardiac surgery. It remains far from clear what transfusion practices are best for patient outcomes and a matter of speculation whether there are links between occurrence of transfusion reactions and patients' longer-term immunological status and health. Studies of relevant outcomes are needed in different groups of patients in order to investigate the impact of transfusion reactions and monitor the effect of changes in practice.[22]

**Links to vigilance in other domains**

Numerous stakeholder organisations in hemovigilance, which in The Netherlands include TRIP, the Healthcare Inspectorate and Sanquin Blood Supply, are also involved with activity and vigilance in the domain of human tissues and cells. The overlap of interests concerns the types of hazard, the donors who may make different types of donations and the common methodology for hemovigilance and tissue and cell vigilance. At the time of writing it is not clear how The Netherlands will ensure links between vigilance and surveillance procedures relating to organs for transplantation as required under the European Directive 2010/53/EU (formerly Directive 2010/45/EU; to be transposed into European Union member states' national legislation by 27th August 2012). This will clearly require new loops in the network of collaboration between relevant stakeholder organisations.

While links between hemovigilance for blood and biovigilance for tissues, cells and organs have obvious relevance, it is no less relevant to create or strengthen links with pharmacovigilance and the "vigilance" of medical devices. In many countries the competent authority responsible for hemovigilance also deals with biovigilance as well as medicines, however the expertise may lodge in different departments with little contact between them. In The Netherlands TRIP initiated an agreement for collaboration with the Dutch medicines adverse reaction agency, Lareb, because of areas of common interest regarding plasma-derived medicines and medicines used in patient blood management. When SD-plasma (solvent-detergent treated plasma) is reintroduced (as is likely to happen in 2013) this collaboration will be the basis of the reporting instructions communicated to the hospitals for adverse reactions or incidents which may arise with its use. Information from medical device vigilance reporting is currently not accessible to the hemovigilance office, but the possibility of links should be explored. Such collaboration could lead to speedier results, as for instance in promoting design modification of apheresis devices for improving donor safety,[23] and improve information and transparency about recipient adverse reactions from use of autologous drain blood reinfusion devices or new technologies.

**Hot or cold hemovigilance?**

Some reporting systems require timely reporting of certain types of event, notably where speedy corrective action can prevent or reduce harm. This is the case for cases needing investigation and/or look-back by the blood service. In The Netherlands early reporting to the inspectorate is mandatory in cases of very serious patient harm from safety incidents. TRIP, a passive reporting system, has politely but repeatedly requested hospitals to submit their reports more promptly. Regrettably, on a number of occasions the response to

queries about serious reports only reached TRIP in the form of publications. TRIP has so far failed to present its annual report earlier than October or November of the following year and this means the information and recommendations are always retrospective. For hemovigilance and the link with other types of vigilance to have more practical relevance, TRIP should explore ways of maintaining its role as a safe, professionally based agency but becoming an active partner with other organisations, contributing its expertise in looking for and promoting ways to improve safety for donors and patients.

**Polder model vigilance, "we do it together"**

As discussed above, hemovigilance reporting does not in itself improve transfusion safety. The collating of transfusion reaction and incident reports can primarily be used to improve transparency and make professionals more aware of what is going on. Top-down mandatorily imposed data capture by no means always achieves even that. Evidence is largely lacking to state criteria for a hemovigilance system which will be "effective" for reliably providing insights on which to base recommendations. We are equally uncertain about the most effective ways of disseminating the basic data and recommendations of hemovigilance, in order to trigger change.

For the time being, the TRIP system – launched at the end of 2002 on the basis of expert opinion and subsequently essentially unchanged – should critically review its methods. It is essential to look for the most efficient methods of data collection to minimise the burden of reporting for hemovigilance staff and combat the risk of reporting fatigue, particularly at a time of cutbacks in healthcare. For TRIP, it will require both creativity and extra work to actively pursue optimisation of the system.

Hemovigilance should be considered in the broader sense of surveillance and promoting quality of the transfusion chain. The stakeholders range from senior blood service quality staff who pursue the results of look-back investigations to donor attendants who provide social distraction to inexperienced and fearful blood donors so that they have a relaxed, successful donation experience. They include hospital managers who back the work of transfusion safety officers in monitoring blood utilisation, Healthcare Inspectorate staff who can mete out "push" to those who would otherwise place requirements of hemovigilance to the bottom of their priority list, professionals who prescribe blood components and nurses who administer them. Hemovigilance should be seen as an activity and a focus, rather than an end in itself. All stakeholders should play their part while respecting other people's roles and responsibilities. Then we will be able to progressively develop hemovigilance in the fashion of a polder model so that we achieve the greatest likelihood of effective interventions and improved patient outcomes.

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## SUMMARY

Hemovigilance has been widely introduced and promoted. By collecting reports of adverse transfusion reactions and of transfusion errors or incidents, it aims to conduct surveillance of transfusion safety, make recommendations and bring about improvements in safety of blood components and practice in the transfusion chain. In the European Union (EU), member states are mandated to have a hemovigilance system for reporting of serious adverse reactions and events which might have links with the component quality or safety. Nine out of 23 countries responding to a descriptive minisurvey set up new systems to compliance with this legislation (chapter 1). At present completeness and quality of the data are uncertain in some countries.

Data on donor adverse reactions is an integral part of hemovigilance (chapter 2). Though not part of mandatory EU reporting, it is collected by nearly all national hemovigilance systems in the EU. In The Netherlands, Sanquin Blood Supply now analyses and for the first time has published findings from the routinely collected donor adverse reaction data (chapter 3). Analysis of procedural and follow-up data in a cohort of related peripheral blood stem cell donors raised no concern of unacceptable safety but highlighted the fact that the donor screening criteria for unrelated donors effectively select those at lower cardiovascular risk (chapter 4), which led us to recommend following the same criteria for related donors.

In the domain of recipient hemovigilance, an exploratory case-control study found previously undescribed associations of reported new allo-antibody formation following transfusion with patient characteristics (chapter 5). As well as generating hypotheses for larger studies, this demonstrated the usefulness and feasibility of using hemovigilance data in conjunction with more extensive patient data. The ongoing national hemovigilance registration was directly employed to calculate the reduction in risk of TRALI following a change of blood component specifications, viz. the implementation of male-only plasma (chapter 6). This analysis employed the reported cases not associated with transfusion of plasma to adjust for reporting trends. It was estimated that the total burden of reported TRALI was reduced by approximately one third. Since the launching of Dutch national hemovigilance reporting this is the only area where a reduction of risk has been demonstrated. It has been postulated that a successful hemovigilance system sees more non-serious reports while the reports of serious harm go down. In The Netherlands, an analysis of hospital-level data found that hospitals reporting a relatively large number of mainly non-serious transfusion reactions do not appear to be safer for transfusion, as measured by the fact that they also were more likely to have reported a transfusion error (chapter 7). Also the TRIP data up to and including 2010 show no tendency of reduction of either serious transfusion reactions or of errors.

Overall, the hemovigilance activity described in this thesis has provided increased insight in the

adverse reactions and incidents regarding both donors and recipients of blood components. Donor and patient care can now benefit from knowledge of Dutch data, however hemovigilance itself has not brought about any reduction of risks. Longer-term risks are not addressed by standard hemovigilance data collection. Collaboration and combining hemovigilance data with further data sources on donors, blood collection and component parameters, patient characteristics, hospital practices and relevant outcomes are needed to realise more of the potential for study and for safety improvement.

## SAMENVATTING

Hemovigilantie is in veel landen ingevoerd en gepromoot. Het doel is om door het verzamelen van meldingen van ongewenste transfusiereacties en van fouten of incidenten in de transfusieketen de veiligheid van bloedtransfusie te monitoren, en aanbevelingen te doen voor verbetering van de veiligheid van bloedproducten of van praktijken in de transfusieketen. In the Europese Unie (EU) moeten lidstaten een systeem hebben voor het melden van ernstige ongewenste reacties of van incidenten die mogelijk een relatie hebben met kwaliteit en/of veiligheid van bloedproducten. Negen van 23 Europese landen die respondeerden op een korte descriptieve survey hadden een nieuw systeem opgezet om aan de wetgeving te voldoen. Momenteel zijn de mate van volledigheid en de kwaliteit van de gegevens in sommige landen onduidelijk.

Informatie over nadelige reacties bij bloeddonors maakt deel uit van hemovigilantie (hoofdstuk 2). Ondanks dat het niet valt onder de EU meldverplichting, worden deze gegevens verzameld door bijna alle landelijke meldsystemen in de EU. In Nederland worden de routinematig vastgelegde gegevens over donorcomplicaties nu door de bloedvoorzieningsorganisatie Sanquin geanalyseerd en er is voor het eerst over gepubliceerd (hoofdstuk 3). Een analyse van procedureproblemen en follow-up informatie in een cohort van verwante perifere bloed stamceldonors gaf geen aanwijzing voor onaanvaardbare risico's. De studie maakte duidelijk dat de donor screeningscriteria voor onverwante stamceldonatie effectief zijn in het selecteren van donors die een lager cardiovasculair risico hebben (chapter 4), hetgeen reden was om aan te bevelen deze criteria ook te volgen bij de keuring van verwante donors.

In het domein van hemovigilantie bij ontvangers van bloedtransfusies toonde een verkennende case-controlestudie associaties tussen gemelde nieuw gevormde antistoffen en bepaalde patiëntkarakteristieken die niet eerder waren beschreven (hoofdstuk 5). Naast het genereren van hypotheses voor grotere studies, bewees deze studie het nut en de haalbaarheid van gebruik van hemovigilantie in samenhang met uitgebreidere patiëntgegevens.

De doorlopende nationale registratie van hemovigilantiegegevens werd direct toegepast om de afname van het risico op TRALI te berekenen na een wijziging in de specificaties van een bloedproduct, t.w. de implementatie van vers bevroren plasma afkomstig van mannelijke, nooit getransfundeerde donors (hoofdstuk 6). In deze analyse werden de gemelde TRALI's waarbij geen plasma was getransfundeerd, gebruikt om te corrigeren voor wijzigingen in het melden van deze complicatie. De afname van het totale aantal gemelde TRALI's bedroeg volgens deze methode ongeveer éénderde. Sinds het begin van het Nederlandse hemovigilantiesysteem is dit het enige voorbeeld van afname van het risico op een type bijwerking. Men heeft gesteld dat een succesvol hemovigilantiesysteem te herkennen is aan toename van niet-

ernstige meldingen terwijl de ernstige meldingen dalen. In Nederland toonde een analyse van meldingen aan TRIP in 2006 – 2010 op ziekenhuisniveau dat ziekenhuizen met een relatief groot aantal van voornamelijk niet-ernstige meldingen van transfusiereacties ook meer kans hadden om een of meer transfusiefouten te hebben gemeld (hoofdstuk 7). Het melden van een transfusiefout kan beschouwd worden als teken van onveiligheid in de transfusieketen. Het is op dit moment onbekend of ziekenhuizen met meer meldingen van transfusiereacties ook meer fouten te melden hadden, of dat de fouten beter gedetecteerd en doorgemeld werden aan TRIP. Er was in de TRIP gegevens tot en met 2010 geen dalende tendens van fouten, noch van ernstige transfusiereacties met uitzondering van TRALI.

Over de hele linie genomen, heeft de hemovigilantie aktiviteit die in dit proefschrift beschreven is, inzicht gegeven in het optreden van transfusiereacties en van incidenten zowel bij bloeddonors als bij ontvangers van bloedproducten. Er zijn aanbevelingen gedaan voor verbeteringen in selectie van bloedproducten, in monitoring van patiënten en organisatie van de transfusieketen. De zorg van donors en van patiënten kan nu mede gebaseerd worden op Nederlandse gegevens. Echter het is niet aangetoond dat door hemovigilantie de risico's zijn afgenomen. Langere-termijn risico's worden niet in kaart gebracht door de standaard dataverzameling van hemovigilantie. Meer samenwerking en het combineren van hemovigilantiedata met aanvullende bronnen van gegevens over donors, bloedafname en bloedproduct, over patiënt eigenschappen en relevante patiëntuitkomsten en over werkwijze in ziekenhuizen, zijn noodzakelijk om vooruitgang te boeken met studies en met veiligheidsverbetering.

## GLOSSARY

| | |
|---|---|
| Afssaps | Agence française de sécurité sanitaire de produits de santé |
| ALI | acute lung injury, acute longschade |
| ANSM | Agence nationale de sécurité du médicament et des produits de santé (France) |
| Bc | blood component |
| BE, blood establishment | organisation which performs collection, testing and/or processing of blood or blood components |
| BMI | Body mass index |
| CBO | CBO quality organisation in healthcare (Netherlands) |
| CI | confidence interval |
| Competent authority | National regulatory authority for blood and blood components |
| CVC | central venous catheter |
| CVD | cardiovascular disease |
| EFS | Établissement Français du Sang |
| EU | European Union |
| FDA | Food and Drug Administration (United States) |
| FFP | fresh frozen plasma |
| FU | follow-up |
| G-CSF | granulocyte colony stimulating factor |
| Hb | hemoglobin |
| HLA | human leukocyte antigen |
| IBCT | incorrect blood component transfused |
| IGZ | Inspectie voor de Gezondheidszorg (Healthcare Inspectorate, Netherlands) |
| IHN | International Haemovigilance Network |
| IQR | inter-quartile range |
| ISBT | International Society for Blood Transfusion |
| ISTARE | International Surveillance Database for Transfusion-Associated Reactions and Events |
| MHRA | Medicines and Healthcare Products Regulatory Agency (United Kingdom) |
| NHTR | non-hemolytic transfusion reaction |
| NMDP | National Marrow Donor Program (United States) |
| OR | Odds Ratio |
| PAR | population attributable risk |
| PBPC, PBSC | peripheral blood progenitor cells, peripheral blood stem cells |

| | |
|---|---|
| Plts | platelets, platelet concentrate |
| PTP | post-transfusion purpura |
| Q-FFP | quarantine fresh frozen plasma |
| RBC | red blood cell concentrate |
| SAE | serious adverse event |
| Sanquin | Sanquin Blood Supply Foundation |
| SAR | serious adverse reaction |
| SD | solvent detergent (virus-reducing treatment) |
| SHOT | Serious Hazards of Transfusion (United Kingdom Hemovigilance scheme) |
| SOP | standard operating procedure |
| SMR | standardized morbidity ratio |
| Tf | transfusion |
| TR | transfusion reaction |
| TRALI | Transfusion-related acute lung injury |
| TRIP | TRIP Foundation (Transfusion Reactions In Patients) |
| VVR | vasovagal reaction |

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Moge dit proefschrift verder onderzoek naar hemovigilantie inspireren!

## CURRICULUM VITAE

Jo (Johanna) Wiersum-Osselton werd geboren op 4 december 1956 in Southampton, Engeland. Toen zij 12 jaar was verhuisde het gezin naar Leiden, waar zij haar schoolopleiding vervolgde aan het Stedelijk Gymnasium en in 1974 het eindexamen behaalde. In hetzelfde jaar ving zij de geneeskundestudie in Leiden aan; het doctoraalexamen werd in 1980 en het artsexamen in 1981 (cum laude) gehaald. Hierna werkte zij enkele jaren in Engeland, eerst als artsassistent in de spoedeisende hulp, interne geneeskunde en dermatologie. Na haar huwelijk en tussen de geboorten van de kinderen in 1984 en 1986 werkte zij parttime als polikliniekarts (clinical assistant) dermatologie tot 1988. Hierna werkten zij en haar echtgenoot Tim ruim vijf jaar in Conakry in de republiek Guinée in west-Afrika. Samen met Guineeërs zette zij een eerstelijns gezondheidsheidszorgpost op, die nog steeds draait. In 1996 trad zij in dienst bij Bloedbank Leidsenhage als donorarts en zij doet dit werk nog steeds, nu bij Sanquin Bloedvoorziening. De opleiding tot sociaal geneeskundige, tak algemene gezondheidszorg, werd in 2000 voltooid. Haar hoofdfunctie vanaf eind 2002 is die van coördinator van het TRIP (Transfusie Reacties in Patiënten) Landelijk Hemovigilantie Bureau.

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