Conclusion

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

CHAPTER 8

General discussion:
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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 Incl. TRALI	Only fatalities collected by the FDA, US	Yes	Chapter 1, 7 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 e.g. avoidable unit wastage		Yes	
Post-donation information Look-back investigation 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 Monitoring appropriate blood use		Info requested from hospitals 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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