Introduction

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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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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.

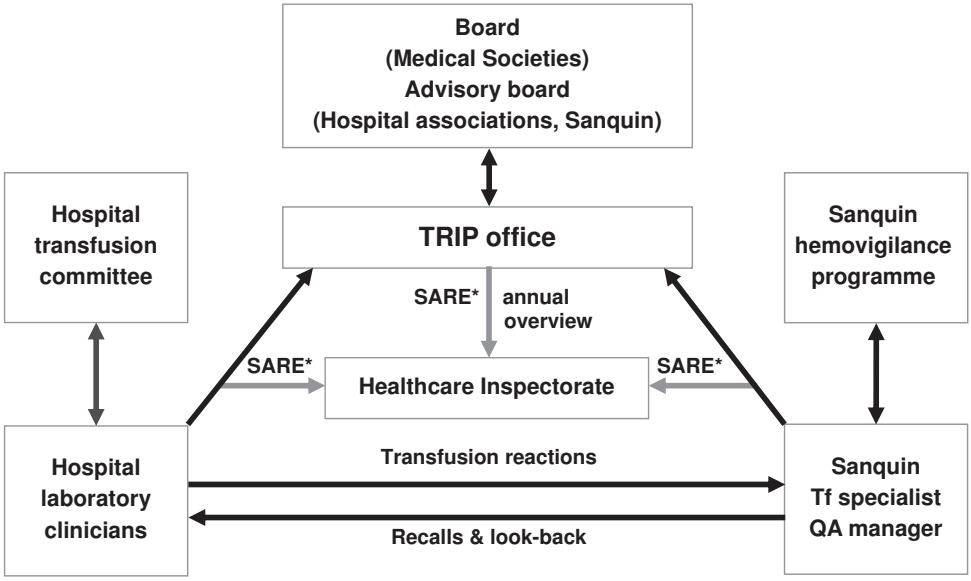
ANNEX 3 TRIP DUTCH NATIONAL HEMOVIGILANCE OFFICE (WWW.TRIPNET.NL)

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

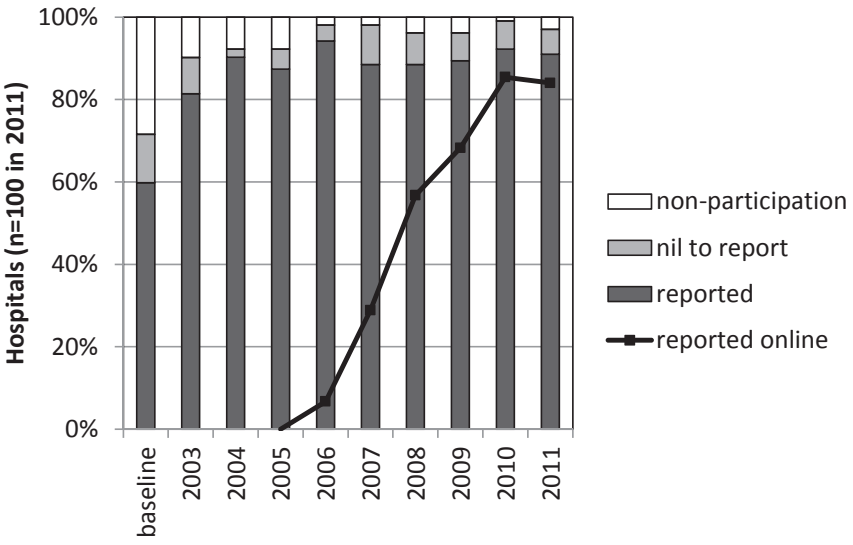


Figure 2. Participation in reporting to TRIP