2006 Annual Report

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FOREWORD

This, the 2006 and fourth TRIP annual report, has been translated into English so that its description of hemovigilance in the Netherlands will be more accessible to professionals the world over. TRIP (Transfusion Reactions in Patients) Foundation for Hemovigilance launched its Dutch National Hemovigilance Office at the end of 2002 and has reported on transfusion safety since 2003. Readers of this report will see how the system has become a well-established part of the Dutch transfusion scene, and I wish to acknowledge the enthusiasm of the hemovigilance officers and hemovigilance assistants in the 100 or so Dutch hospitals as well as the TRIP office staff in achieving this.

The number of reports, particularly in the categories of non-serious reactions, errors and near misses, has increased each year and this indicates an increase in vigilance. In 2006 there was a slight increase in the number of serious reactions, chiefly owing to a modification of the definition of severity grade 2 to bring this in line with the definition of 'serious' in European Directive 2002/98/EC. I believe that the calculated incidence of serious reactions, at 1 per 5600 transfused labile blood components, is close to the 'true' incidence. This means that blood components and receiving transfusions in Dutch hospitals are to be regarded as very safe in comparison to other products and treatments.

An important conclusion is that only about a third of the serious reactions could have been prevented. Hemolytic transfusion reactions and transfusion-associated circulatory overload are amenable to preventive measures. However, most of the serious reactions constitute a (small) "calculated risk". The patient should be closely observed particularly during the first 5 to 10 minutes of transfusion and receive prompt treatment for any untoward reaction. The most important types which cannot be prevented are the serious allergic or anaphylactic reactions and TRALI.

Setting up a vigilance system for transplantation of human tissues and cells is a new challenge. TRIP is among the forerunners in Europe in this activity and thus able to assume a role in shaping the implementation of the European legislation in this area.

What has come of the recommendations which TRIP made in earlier reports? I will start with the only poor result: as far as I know there has been no work done in response to the recommendation in our 2005 report calling for research in the area of the serious allergic and anaphylactic reactions. There remains a need for work on this problem and for trialling of blood components which might be less likely to provoke serious allergic reactions.

The other recommendations have led to relevant activities: TRALI research, development of protocols for bacteriological investigation following transfusion reactions, comparative studies of the various current and possible future types of platelet concentrates delivered by Sanquin, an online reporting system which has improved the submission and feedback time for reports, and last but not least educational sessions for health care professionals who are involved in the practice and safety monitoring of blood transfusion.

I will conclude by highlighting three of the recommendations in the 2006 report. Firstly, we recommend reporting and analysis of adverse reactions and incidents in the use of blood management techniques (pharmacological as well as autologous transfusion methods) so that these may be compared to those of allogeneic blood transfusion. Secondly, we call for more awareness of the risk of circulatory overload since simple preventive measures are available. Finally, as hospitals introduce overarching safety management systems there is a need for awareness and reinforcement of existent reporting systems in hospitals and most notably that for reporting of transfusion reactions and errors.

I hope that you will enjoy reading this report and find aspects which are relevant and profitable for the improvement of transfusion safety wherever you work.

Prof. Dr. René R.P. de Vries
President, TRIP Foundation

Executive summary

TRIP Dutch National Hemovigilance Office

The objective of TRIP (Transfusion Reactions In Patients) Dutch Foundation for Hemovigilance and its National Hemovigilance Office is to receive reports on side effects and incidents associated with blood transfusion in the Netherlands and to report publicly on transfusion safety. Since August 2006 TRIP has also run a pilot reporting system for adverse reactions and events involving human tissues and cells (see the closing paragraph of this summary).

Reports on transfusion reactions are submitted using a national reporting form by the contact persons (hemovigilance officers) in the Dutch hospitals. Reports to TRIP are voluntary and anonymous. Participation is however regarded as the standard in the national blood transfusion guideline as well as by the Dutch Health Care Inspectorate. TRIP also receives information from the national blood service Sanquin concerning adverse effects and incidents involving blood components delivered to hospitals. By arrangement with the Health Care Inspectorate and the Ministry of Health, TRIP provides the scientific analysis and annual overview of serious adverse reactions and adverse events as required by the European Union Directives (2002/98/EC and 2005/61/EC).

Reports are initially examined by the TRIP office medical staff and if necessary further information or clarification is requested. An 'Expert Committee' appointed by the TRIP steering group reviews the reports before the data are accepted and included in the annual report.

2006 findings

Participation

Ninety-eight (94%) of the 104 Dutch hospitals participated in the TRIP data collection in 2006. Ninety-four hospitals submitted reports on transfusion reactions and four indicated that they had nil to report in the TRIP categories. Two hospitals sent in reports to TRIP for the first time in 2006.

The reports

A total of 2030 reports about transfusion side effects and incidents in 2006 were received by the closing date for the annual report (1st April 2007), in comparison to 1840 reports concerning 2005 at the closing date last year. Of the total, 1776 concerned clinical transfusion side effects and 254 were incidents in the transfusion chain. 509 of the reports were in optional reporting categories. TRIP wishes to collect information on a number of types of less serious event but does not need all hospitals to take on the extra work. Hospitals may decide for themselves whether to send in these optional reports.

Severity of the events

In accordance with international practices the reports are graded as to severity. 1856 (91.4%) of the 2006 reports were rated for severity by the reporter. Of these reactions 1732 (93.3%) were rated as grade 0-1 (no or only minor morbidity), 91 (4.9%) as grade 2 (serious), 29 (1.26) as grade 3 (life-threatening) and 4 (0.2%) as grade 4 (death following a transfusion reaction).

Rating of the imputability

Symptoms or signs in a transfused patient may be related to numerous factors other than the actual transfusion. The reporting form requests an assessment of the imputability, i.e. whether the observed effects can be ascribed to the transfusion. In 2006, 1646 (81.1%) of the transfusion reactions were rated for imputability. Out of these 1646, 387 (23.5%) were judged to be 'certainly' related to the transfusion, 562 (34.1%) 'probably', 538 (32.7%) 'possibly' and 159 (9.7%) 'unlikely' or certainly not'.

Types of reactions and incidents

The following types of reports were received: non-hemolytic transfusion reaction 463, acute hemolytic transfusion reaction 17, delayed hemolytic transfusion reaction 14, transfusion-related acute lung injury (TRALI) 23, anaphylactic reaction 18, other allergic reaction 208, circulatory overload 34, viral infection 7, bacterial contamination 7, hemosiderosis 5, other reaction 55, new allo-antibody 603 and mild febrile reaction (>1<2^{o}C, optional category) 322. Among the incidents there were 64 reports of transfusion of an incorrect blood component (product intended for another patient or not meeting appropriate requirements for that patient) with clinical consequences in 14 cases (two reactions rated as grade 2 or higher). TRIP received 85 reports of other incidents, 76 reports of near accidents and 27 reports from hospitals on

cases where a blood component had been transfused and the bacteria screening at the Sanquin blood bank later gave a positive result (optional categories). Sanquin also contributed an summary of transfused blood components (57) with positive bacteria screening; overlap with the hospital information may be presumed although this has not been formally confirmed.

Number of reports in relation to the number of blood components

In 2006 the blood supply organisation Sanquin delivered a total of 699,904 labile blood products to the hospitals. The total number of reports was 2030. This gives an average of 2.9 reports per 1000 blood components nationally, compared to 2.6 per 1000 in 2005 (2.8 including reports which were received after the closing date for the 2005 report). In 2006 the reactions rated as grade 2 or worse totalled 124, or 0.18 per 1000 blood components (1 in 5600). This represents an increase of over 20% in comparison to 2005. The increase is explained by a modification of the definition of Grade 2 to include reactions where hospital admission was necessary or was prolonged: this modification was adopted as per 1st January 2006 so that TRIP Grades 2 – 4 include all reactions which are 'serious' according to the European Union definition. Most of the increase in the Grade 2 - 4 reactions consists of low-imputability reports.

Discussion and conclusions

Participation and reports in 2006 compared to 2005

Participation by 94% of the hospitals, with reports coming from 90%, is as high as in 2005. All hospitals have participated in the system by now, although year by year a number fail to submit information in time for their data to be included in the report. There was a slight increase in the number of reports in comparison to 2005 and this increase occurred mainly in the categories of non-serious reactions. As in previous years there was considerable variation between hospitals in the ratio of reports to blood use.

Types of reports and relevance for improving transfusion safety in the Netherlands

Among the serious types of transfusion reaction the number of reports increased (slightly) in the categories of TRALI and circulatory overload, probably because of increased awareness of TRALI. An increase in these categories was noted in 2005 and in 2006 they constitute the largest categories among the serious reports. In 2006 Sanquin decided to change to supplying plasma from non-transfused male donors as a preventive measure against TRALI (this will take effect in the course of 2007). Continued vigilance for TRALI is essential and more research is needed into the pathogenesis of TRALI and effectiveness of possible preventive measures.

In 2006 investigation following seroconversion of a blood donor revealed that two recipients of blood components from the previous donation had been infected with hepatitis B. Despite state of the art tests there remains a risk of failure to detect viral infectivity shortly after infection: 'window donation'. The other reports concerning possible viral transmission were only of 'possible' or lower imputability. Likewise none of the reports of bacterial contamination was judged to be of a high imputability, that is supported by finding the same bacterial type on culturing the remnant of the unit as in the patient blood culture. Thus in 2006 the risk of bacterial or viral infection from receiving a blood transfusion is low, as in previous years.

The number of reports of transfusion of an incorrect blood component, near accidents and of other incidents was higher in 2006 than in 2005. The number is still lower than in the United Kingdom or Ireland (for instance). It is likely that there is underreporting. In 2006 there were seven reports of AB0-incompatible transfusions (five units of red blood cells) with two acute hemolytic transfusion reactions and three delayed hemolytic reactions in consequence but no deaths. Failure to observe the preventive Kell-negative transfusion policy for women under 45 again accounted for several reports. Among the near accidents, as in previous years the largest group is that of errors in patient identification at various stages in the transfusion chain. Many of these are detected at the compulsory confirmatory blood grouping (on second sample) of new patients or by checks against the previously confirmed blood group.

The reports of new allo-antibody formation in 2006 are roughly at the same level as in 2005; as before not all hospitals are reporting this category. The reports underline the importance of national recommendations on blood component selection for prevention of allo-immunisation. 285 reports of c and E antibodies included 20 in women younger than 45. Transfusion of Rhesus phenotype compatible blood to women of child-bearing potential should be recommended in order to prevent hemolytic disease of the newborn.

Tissue vigilance: method and findings of a pilot reporting system

After a preparatory period and in agreement with the Ministry of Health, Welfare and Sports, TRIP introduced a voluntary pilot system for reporting serious adverse reactions and incidents in the production and clinical application of human tissues and cells. TRIP will fulfill the same role for tissues as in hemovigilance, i.e. receiving the reports, providing scientific analysis and reporting publicly on the safety of these transplantations. This will ensure compliance with the European Union Tissue directives, which have been implemented in Dutch legislation. The system was launched on 1st August 2006. As for hemovigilance, TRIP focuses not just on the supply side, but particularly aims to involve the health care professionals. A committee of representatives from the professional bodies involved in transplantation of human tissues and cells has been convened. This group will be responsible for steering the implementation of tissue vigilance in the Netherlands.

During the initial pilot phase eight reports were received, involving bone, cardiac valve tissue, cornea and hematopoietic stem cells. In view of the hitherto voluntary nature of reporting, it is likely that these reports are incomplete. Four of them were 'serious' according to the definition given in the Directive; one of the four was clearly product-related. This report concerned tuberculosis which was transmitted by a bone transplant; the (living) donor had responded in the negative to the question about ever having had tuberculosis. In the Netherlands an imputability assessment has been added to the minimum reporting requirements. The other three serious reports were of unlikely or possible imputability.

1. Introduction

TRIP Dutch national hemovigilance system

A thorough knowledge of the types and rates of side effects of blood transfusion is necessary for the timely recognition of known as well as hitherto unknown adverse reactions associated with transfusion of currently available or new types of blood components. Centralised (national) reporting of transfusion reactions (TR) makes it possible to monitor safety in the transfusion chain, discover weak links and pinpoint areas for improvement.

TRIP (Transfusion Reactions In Patients) Foundation was created in 2001 by representatives of the various societies of professionals active in the domain of blood transfusion. After the granting of an initial subsidy by the Ministry of Health in 2002, TRIP Dutch National Hemovigilance Office was launched early in 2003. It runs a national hemovigilance reporting system in collaboration with regular contact persons in the hospitals and in Sanquin, the national blood supply foundation. Reporting to TRIP is anonymous and in principle voluntary. However participation is regarded as the norm in the 2004 national transfusion guideline as well as by the health care inspectorate.

In the Netherlands the standard blood components are supplied to the transfusion laboratories of the hospitals, which perform the necessary laboratory testing and issue the components according to hospital protocol. Blood components are universally leukodepleted; most platelets are buffy coat-derived pooled products, with either plasma or platelet additive solution. Special products, transfusion advice and reference laboratory services are also provided by Sanquin, which in addition has divisions for diagnostic investigations (including infectious disease testing), research and fractionation of plasma.

Besides reporting to TRIP, provision of care and investigation of TR remain the responsibility of the hospitals. It is also mandatory to refer serious errors and incidents to the hospital's "MIP" committee (Meldingen van Incidenten in de Patiëntenzorg, reports of incidents in patient care). The European blood directive 2002/98/EC lays down a requirement for reporting of serious adverse reactions and incidents which may affect the quality and/or safety of blood components. TRIP provides the analysis and reports on these events (grade 2 or higher) on behalf of the competent authority, the Health Care Inspectorate (Inspectie voor de Gezondheidszorg, IGZ). Hospitals themselves submit these reports in parallel to the IGZ, which can thus exercise its supervisory responsibility.

In the course of 2006 a secure online reporting system was launched for the hemovigilance reports, initially with a small group of pilot hospitals. This system has performed satisfactorily, opening the way for gradual expansion of the number of users in the course of 2007. The system will incorporate a facility for reporters to electronically submit relevant reports to the IGZ.

In August 2006 TRIP launched a pilot of a national reporting system for serious adverse reactions and events which are associated with the use of human tissues and cells and which may affect the quality or safety of the products, in compliance with the disuse directive 2004/23/EC and its daughter directive. More can be read about this in Chapter 3 of this report. A digital reporting system is under development.

The hemovigilance and tissue definitions can be found on the TRIP website www.tripnet.nl. Reporters are asked to specify the clinical severity of reactions. In addition the imputability is assessed, i.e. the level of certainty with which a reaction can be ascribed to a transfusion or transplantation. Where necessary TRIP requests further details from the reporter. All reports are reviewed by an 'expert committee' (EC) nominated by the TRIP board prior to inclusion in the annual report.

2. Hemovigilance

2.1 Participation

The number of actively participating hospitals and the quality of the information sent in determine the value of national registration and evaluation of transfusion reactions. Ninety-eight of the 104 (94%) of the hospitals took part in the registration in 2006. Of the 98, 94 hospitals reported transfusion reactions and four indicated they had no transfusion reactions to report. In principle, participation is now complete, in the sense that all hospitals have reported information about transfusion reactions or have reported that no reactions took place for one or more of the years studied. There is a number of hospitals each year that do not send in reports by the closing date: the status of these hospitals in the final summary is 'no information'. The final date for sending in information covering 2006 was 1 April 2007.

Additionally, central Sanquin departments made available to TRIP summaries of serious adverse events and of administered blood components which subsequently showed positive bacteria screening results (for further information see 2.3). TRIP also received a number of reports from contact persons in Sanquin's regional blood bank divisions.

In 2006, after the closing date for the 2005 report, TRIP received a further 144 reports covering 2005. The EC has now assessed these formally. In general, the late reports were less complete than those sent in on time. All the figures and tables of this report include the late reports from previous years where relevant.

Figure 1 shows degrees of participation for the years 2002 (the zero reference point) up to and including 2006, as of the reference date 1 April 2007. As of this same date, *Table 1* shows participation in terms of hospital type (university, teaching, other).

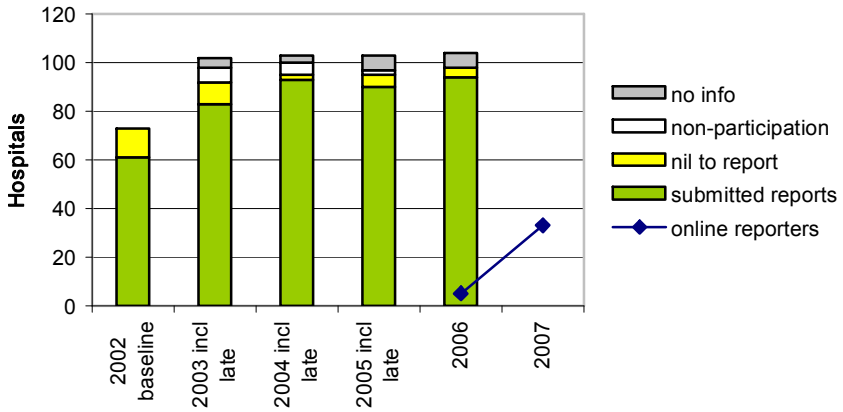

Figure 1 Annual participation

Table 1 Participation per hospital type 2003 - 2006

	University	N	Teaching	N	Other	N	Total	N
2003	9 (100%)	9	12 (71%)	17	61 (80%)	76	82 (80%)	102
2004	8 (89%)	9	19 (90%)	21	68 (93%)	73	95 (92%)	103
2005	8 (89%)	9	20 (95%)	21	69 (95%)	73	97 (94%)	103
2006	9 (100%)	9	20 (91%)	22	69 (95%)	73	98 (94%)	104

2.2 Hemovigilance reporting in 2006

At the beginning of 2006, with a view to implementing the European Directive 2002/98/EC and the accompanying technical specifications, the definition of severity grade 2 was amended somewhat, such that all reporting that must be classified 'serious' according to the Directive would be TRIP grade 2 or higher. Grade 2 applies if there is prolongation of illness or hospitalisation, even if the reaction did not lead to serious morbidity clinically. Additionally, it was made explicit that cases of chronic morbidity or disability had to be classified as grade 2. In practice, this will lead to a slight increase (estimated in advance at 5 to 10 annually) in the number of grade 2 reports.
See www.tripnet.nl under publications (*publicaties*) for definitions.

Reports received

TRIP received a total of 2030 reports of transfusion reactions and incidents in 2006; these came from 94 hospitals. Some non-serious categories count as optional categories when reporting. TRIP sees it as useful to register data about these elective categories, but does not necessarily need all the hospitals to cooperate in reporting these. Of the total, we received 512 elective reports from 75 hospitals. Numbers of reports have increased somewhat in 2006 compared to 2005.

Following the EC evaluation, supplementary questions were asked to the reporter in a number of cases (31 times). Sometimes (ten times, 32%) this led, after consultation with the reporter, to amending the category of type of transfusion reaction or of the relationship of the reaction to the transfusion: seven times category, three times severity and/or imputability level. In other cases, this further questioning elicited relevant supplementary information.

Table 2 (transfusion reactions, TR) and *Table 3* (incidents) show the number of reports per category in the years 2002 - 2006. Transfusion reactions following incidents are discussed in chapter 2.3 in the relevant paragraphs. As in previous years, TRIP discusses all reports (full categories and reports in optional categories collectively) given the large numbers of reports submitted in elective categories. In calculating the number of reports in relation to the number of blood components, we deal with all submitted reports collectively as well.

Table 2 Transfusion reactions reported to TRIP, 2002 - 2006

Reaction	2002	2003	2004	2005	2006	Hospitals (2006)
Non-hemolytic TR	240	318	344	435	463	79
Acute hemolytic TR	12	8	14	9	17	12
Delayed hemolytic TR	21	19	14	12	14	11
TRALI	7	6	9	17	23	12
Anafylactic reaction	13	8	21	26	18	12
Other allergic reaction	98	132	171	219	208	49
Transfusion-associated circulatory overload	1	7	6	27	34	23
Bacterial contamination	12	9	5	10	7	5
Viral infection	1	5	7	8	7	3
Post-transfusion purpura	1	0	0	0	0	0
Transfusion-associated GVHD	0	0	0	0	0	
Hemosiderosis	0	0	0	3	5	2
New allo-antibody	117	244	428	571	603	47
Other reaction	48	54	64	67	55	26
Mild febrile reaction (optional category)	247	326	341	375	322	71
Total TR	**818**	**1136**	**1425**	**1779**	**1776**	**94**
Total reports	**862**	**1267**	**1548**	**1984**	**2030**	**94**

Table 3 Annual incidents, 2002 - 2006

Incident	2002	2003	2004	2005	2006	Hospitals (2006)	Hospitals (2002-2006)
Incorrect blood component transfused	17	34	37	60	64	38	65
Other incident (optional category)	5	5	14	53	85	21	30
Near miss (optional category)	12	31	62	79	76	18	27
Virally infected blood component					2		
Pos. bact. screening of transfused product (optional category)	10	61	10 **	13 **	27 **	11	27
Total	**44**	**131**	**123**	**205**	**254**	**48**	**74**

** Additional information received from Sanquin, see chapter 2.3

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Severity of TR

Severity level	*Definition*
Grade 0	*No morbidity*
Grade 1	*Minor morbidity, no threat to life*
Grade 2	*Moderate to serious morbidity, with or without threat to life, and/or leading to hospitalisation or prolongation of illness, or accompanied by chronic invalidity or disability*
Grade 3	*Serious morbidity, directly life-threatening*
Grade 4	*Mortality following a transfusion reaction*

In conformance with international practice, the transfusion reactions are classified according to their grade of severity. Of the reports submitted in 2006, the 91.4% (1856 reports) were rated by the reporting hemovigilance officer for their severity level. This percentage has increased from year to year. Of the 1856, 848 (45.7%) are grade 0; 884 (47.6%) are grade 1, 91 (4.9%) are grade 2, 29 (1.6%) are grade 3, and 4 (0.2%) are grade 4. One thousand seven hundred and fifteen reports, 96.5% of the 1776 reports of clinical transfusion reactions (i.e. excluding the categories of incidents), recorded the severity.

Figure 2 below shows the distribution of severity level for the clinical transfusion reactions from 2002 - 2006. Last year (2005), we noticed a slight shift from grade 0 to grade 1, which can be explained by the fact that the TRIP office has consistently voiced the point of view that if clinical signs are present the report must be at least grade 1. This shift has continued to a slight extent in the percentage of the 2006 reports of clinical reactions. Additionally, there is ongoing improvement in the percentage of reports which are rated for severity level.

The number of serious reports (grades 2 - 4) was 124, an increase compared to 2005. The extension of broadening of the definition of grade 2 in connection with the European Directive partly responsible for this increase. The increase is most pronounced in reports of low imputability (see 2.4). We discuss differences in comparison to 2005 under the categories in question (see 2.3).

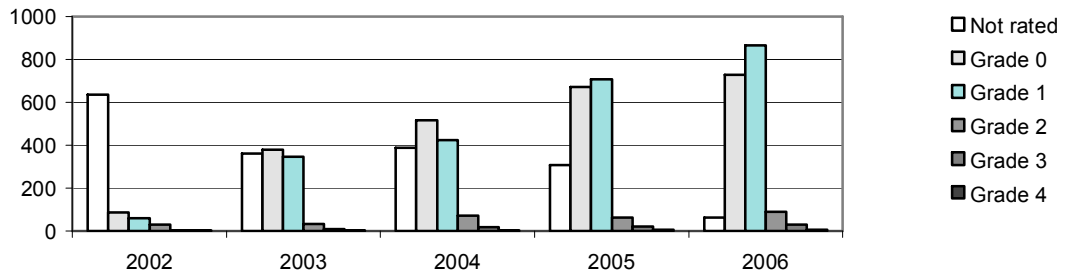


Figure 2 Severity of clinical TR, 2002 - 2006

Relationship to the blood transfusion (imputability)

Imputability	*Definition*	
Solely applicable to clinical transfusion reactions		
Certain	*clinical symptoms present, and*	• *clear course of events, temporally related to the transfusion, and* • *confirmed by laboratory findings, and* • *other causes excluded*
Probable	*clinical symptoms present, but*	• *no clear course of events or not temporally related to the transfusion, or* • *not confirmed by laboratory findings, or* • *other possible cause present*
Possible	*clinical symptoms present, but*	• *not temporally related to the transfusion, and* • *not confirmed by laboratory findings, and* • *other possible cause present*
Unlikely	*clinical symptoms present, but*	• *not temporally related to the transfusion, and* • *not confirmed by laboratory findings, and* • *another more probable explanation present*
Excluded	*clearly demonstrable other cause*	

In addition the reports are assessed for the imputability level, the likelihood with which the reaction can be ascribed to transfusion.

In 2006, reporters rated 1646 (81.1%) of the transfusion reactions for imputability. Of these, 387 reports (23.5%) were judged as having a 'certain', 562 (34.1%) a 'probable', 538 (32.7%) a 'possible', and 146 (8.9%) an 'unlikely' relationship to the transfusion, while 13 (0.9%) were 'excluded' from being related to the transfusion. These percentages are practically identical to those found in 2004 and 2005. *Figure 3* shows imputability for the 1776 clinical transfusion reactions in 2006 compared to previous years; of these, imputability was recorded for 1593 (89.3%).

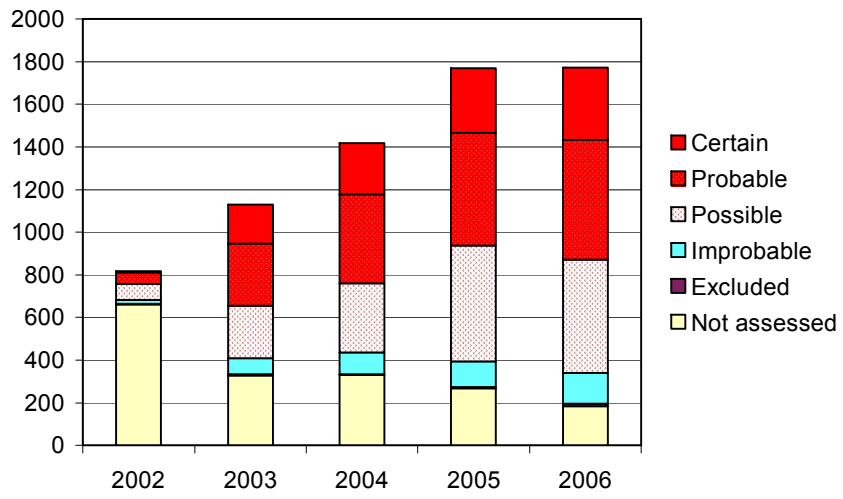


Figure 3 Imputability of the clinical TR, 2002 - 2006

Number of transfusion reactions in relation to number of supplied blood components

Numbers of blood components supplied by Sanquin in 2006 (with the exception of special components such as peripheral blood stem cells and granulocytes) total 699,904 units. The countrywide number of reports over 2006 is 2030. This is an average of 2.9 reports per thousand supplied blood components (in 2005: 2.6 at the time of writing the report, 2.8 including late reports). The number of blood components distributed to the hospitals functions here as an approximation of the number of units administered.

Table 4 shows the national incidence of transfusion reactions in 2005 and 2006 per type of blood component. The type of blood component is not recorded in 200 reports (11%) and for 65 other reports (3.5%) the patient received different types of blood components, making it impossible to attribute the reaction with certainty to one component type. This means that the calculation in the table underestimates the actual number of reactions per 1000 blood components. For some types of reports (such as blood group discrepancies in the category of 'near miss'), the type of blood component is irrelevant. Totals include all reports.

Table 4 Reports in 2005 and 2006, per blood-component type

Type of Blood component	Reports in 2005	No. distributed in 2005	Reports / 1000 in 2005	Reports in 2006	No. distributed in 2006	Reports / 1000 in 2006
Red blood cells (RBC)	1370	567,472	2.41	1393	556,293	2.46
Platelets	239	51,264	4.66	242	51,015	4.74
Fresh frozen plasma	84	92,442	0.90	87	92,380	0.94
Autologous (RBC, predeposit)	1	280 (donations)	3.57	1	216 (donations)	4.63
Other components#	6			4		
Autologous, perioperative	2			4	Denominator not known	
Combinations	82			82		
Not specified	202			222		

The 'other components' in 2006 were two units of autologous perioperatively salvaged blood, one exchange blood unit and one unit of granulocytes. In this report, reactions and incidents concerning hematopoietic stem cell transplantation (cord blood or peripheral blood stem cells) are discussed under tissue vigilance (Chapter 3).

There is a slight general increase in the number of reports per blood component type in 2006 compared to 2005. *Table 5* shows the distribution of types of blood components per reaction category. Reactions that occurred after an incident (for instance, hemolysis as a consequence of an ABO-incompatible unit) are counted solely under the causal incident in question.

Table 5 Distribution of reporting categories per blood-component type in 2006

Reaction	RBC	Platelets	Plasma	Combi	Other	Not specified
Non-hemolytic TR	370 (27.0%)	60 (24.8%)	7 (8.0%)	15		11
Acute hemolytic TR	16 (1.2%)	1 (0.4%)	-	-	-	-
Delayed hemolytic TR	12 (0.9%)	-	-	2	-	-
TRALI	8 (0.6%)	2 (0.8%)	1 (1.1%)	12	-	-
Anafylactic reaction	4 (0.3%)	5 (2.1%)	7 (8.0%)	2	-	-
Other allergic reaction	44 (3.2%)	97 (40.1%)	51 (58.6%)	13	1	2
Transfusion-associated circulatory overload	23 (1.7%)	2 (0.8%)	3 (3.4%)	5	-	1
Bacterial contamination	5 (0.4%)	-	-	2	-	-
Viral infection	3 (0.2%)	1 (0.4%)	-	3	-	-
Hemosiderosis	1 (0.1%)	-		2		2
New allo-antibody	477 (34.3%)	11 (4.5%)	-	15	-	100
Other reaction	40 (2.9%)	9 (3.7%)	3 (3.4%)	1	1	1
Mild febrile reaction	269 (19.3%)	13 (5.4%)	6 (6.9%)	6	1	28
Incident						
Incorrect blood component transfused	50 (3.6%)	4 (1.7%)	3 (3.4%)	1	1	5
Other incident	52 (3.7%)	15 (6.2%)	6 (6.9%)	2	-	12
Near miss	13 (0.9%)	1 (0.4%)	-	1	-	61
Pos. bact. Screening of transfused blood component	6 (0.4%)	21 (8.7%)	-	-	-	-
Total	**1393** (100%)	**242** (100%)	**86** (100%)			

Variation among hospitals

The number of transfusion reactions per 1000 blood components per hospital varies from 0 to 28.37 (the maximum in 2004 was 10.53 and in 2005 13.64). One hospital sent in one or more reports for the first time in 2006.

Once again, there was remarkable variation among hospitals in the number of reports per 1000 blood components. *Figure 4* shows the distribution of the number of reports per hospital with regard to the ad-

ministered number of blood components.
The hospital with 28.37 reports per 1000 blood components is an institution making very little use of blood: this means that this number actually lies within the boundaries of the statistical variation. Two hospitals making extensive use of blood lie under the 95% confidence interval for this trend line. These hospitals informed TRIP orally that they only sent in reports of serious adverse reactions or events in 2006. TRIP regrets this approach. Selective reporting clearly decreases the value of the national reporting system.

Table 6 below shows the number of reports per 1000 blood components in relation to the type of hospital.

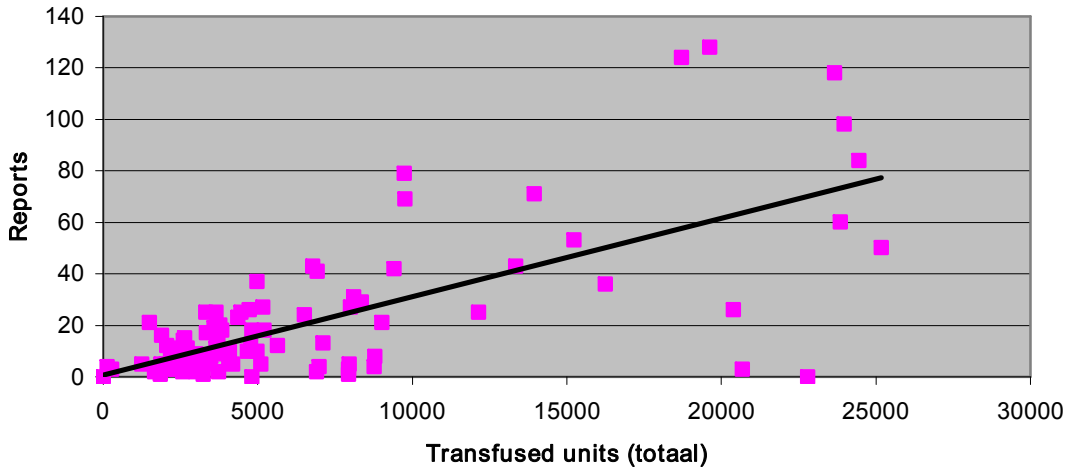


Figure 4 Number of reports per hospital in 2006 compared to numbers of blood components transfused

Table 6 Reports per 1000 blood-components per hospital type in 2006

Type of hospital (n per type)	No. (%) which also supplied data on transfused units	Reports /1000 blood units (range per hosp.; median)	2005 (% with full data)
University (9)	9 (100%)	2.94 (0.00 – 6.62; 3.44)	3.52 (67%)
Teaching (22)	19 (86%)	3.80 (0.29 – 8.11; 3.47)	3.16 (86%)
Other hosp. (73)	68 (93%)	2.86 (0.00 – 28.37; 2.45)	2.48 (84%)
Total (104)	**95 (90%)**	**2.88 (0.00 – 28.37; 2.74)**	**2.94 (83%)**

2.3 Discussion of the categories of reports

Non-hemolytic transfusion reactions (NHTR) and mild febrile reactions

NHTR:
Rise in temperature ≥ 2oC (with or without rigors) during or in the first two hours after a transfusion, with no other relevant symptoms or signs;
or rigors with or without a rise in temperature within the same time limits.
No evidence (biochemical or blood-group serological) for hemolysis, bacteriology negative, and no alternative explanation.
Mild febrile reaction:
Rise in temp. >1oC (<2oC) during or in the first two hours after a transfusion with no other relevant symptoms or signs; optional reporting to TRIP.
Hemolysis testing and bacteriology negative if performed.

The percentage of NHTR is as high in 2006 as it was in 2005, amounting to almost a quarter (22.8%) of reactions. With reported mild febrile reactions added in, these reports make up 38.7% of the total.

Twenty-six reactions were recorded as being grade 2 or higher; the reporter judged nine of these as 'probably' related to the transfusion. In these categories reporters several times indicated that the reaction had led to prolongation of hospitalisation or to hospitalisation after day case transfusion. This group of reactions is responsible for the largest increase in the number of grade 2 reports in 2006 in comparison with 2005.

As in other years, most non-hemolytic transfusion reactions occur after the use of RBC concentrates: 79.9% of the NHTR and 83.5% of the mild febrile reactions. Nationally, the percentage of RBC concentrates approximates 80% of all distributed blood components, and is therefore a comparable percentage. Approximately as many male as female patients suffer these reactions. We would need information about the 'denominator' of all transfused patients in order to establish the risk to an individual.

Thirty-seven patients (n=37) suffered several NHTR or mild febrile reactions after transfusion in 2006.

Acute hemolytic transfusion reaction (AHTR)

Symptoms / signs of hemolysis occurring within a few minutes of starting to 24 hours after a transfusion: rise in temperature / rigors, nausea/vomiting, backache, dark or red urine, fall in blood pressure ≥ 20 mm Hb systolic and/or diastolic (one or more of these); or laboratory results indicating hemolysis within the same time limits
Biochemical hemolysis testing positive; blood-group serological testing possibly positive; bacteriology negative.

Seventeen AHTR were reported, including reactions upon administering an incorrect blood component or an other incident. Of the seventeen, five were deemed grade 2 or more serious. Acute hemolysis is consequently a relatively rare reaction (2.4 reports per 100,000 supplied blood components in 2006). The number is slightly higher than in 2005 and 2004. As in previous years, pathogenesis was not extensively investigated for a number of the reports, and in a small number of cases (n=3) incomplete information or lack of testing in the hospital makes it impossible to confirm or exclude hemolysis.

Three patients (one of whom had a number of irregular antibodies) with increased hemolysis parameters prior to transfusion suffered a total of five hemolytic transfusion reactions following which no specific

blood-group serological cause could be determined.

One report, where symptoms were typical of hemolysis, but for which hemolysis was solely corroborated by increased LDH, was associated with an A-negative platelet transfusion given to an O-positive recipient with a high titre of anti-A (anti-A [IgM] 1:32, anti-A incomplete 1:4000). Once symptoms of hemolysis occurred upon administrating autologous blood via a cell saver; see the paragraph on incidents for further discussion of this report.

The paragraph on transfusion of an incorrect blood component discusses four more cases of acute hemolysis – two as a result of ABO-incompatibility (one was plasma) and two whose cause was not immunologic.

Delayed hemolytic transfusion reaction (DHTR)

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

The number of reports in this category in 2006 is 14; in addition, four reports recorded delayed hemolysis following an incident. The number has been stable since 2004. It is worthy of note that the number does not differ much from the number of acute hemolytic reactions, while the literature states that delayed hemolysis is more common by a factor of five to ten.

All reports were associated with transfusion of RBC concentrates (two of them involved another type of blood component as well); eight of the total were judged to be of severity grade 2. The reports of delayed hemolysis, as in previous years, are better substantiated than reports of acute hemolysis. One case was 'unlikely', one was 'possible', and the others were 'probable' or 'certain'. The antibodies present in these eight cases were anti-Co(a), anti-Jk(a), anti-Jk(b), anti-M, anti-Kell, anti-S and HTLA, anti-S and anti-C, anti-K and anti-Bg(a), respectively. In three cases, it was impossible to establish a blood-group serological cause. In two cases, there was chronic hemolysis in addition to an allo-antibody (anti-K; anti-E and anti-Jk(b)): one of these was sickle-cell anaemia and the other incipient autoimmune hemolysis. It is known that blood transfusion can exacerbate hemolysis in the presence of auto-immune hemolysis. In one report with ‘unlikely’ imputability, no hemolysis parameters were determined when an unexplained drop in hemoglobin occurred.

The four reports of delayed hemolytic transfusion reaction subsequent to administration of an incorrect blood component or an other incident will be discussed in the appropriate paragraphs.

Transfusion related acute lung injury (TRALI)

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 hemolysis, 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.

TRALI (transfusion related acute lung injury) is a rare but potentially fatal lung complication that occurs during or within six hours of administration of a plasma-containing blood component. It is accompanied by abnormalities on the chest X-ray. TRIP received twenty-three reports of TRALI in 2006, compared to seventeen in 2005 and nine in 2004. There is an increase from year to year. This occurs at all grades of

severity and all levels of imputability. Note in particular an increase in reports of cases which on analysis fulfil the definition.

TRALI is described as a complication of transfusion of plasma-containing blood components. The reports show that TRALI can follow transfusion of all types of labile blood components. We received two TRALI reports of severity grade 4 in 2006. The first concerned a patient older than 70 with multiple pathologies, for whom the imputability of the breathing problems was judged 'unlikely'; the second concerned a patient with congenitally unstable hemoglobin and a lymphoma; imputability was judged 'possible' in this case.

As in previous years, TRIP assessed whether the reports fulfilled the national definition of TRALI; imputability was judged independently of findings of leukocyte serological investigation. A total of nineteen reports fulfilled the criteria (clinical signs, chest X-ray, interval <6 hours, no more probable explanation) for TRALI. Of the nineteen, the severity was grade 4 once, grade 3 fourteen times and grade 2 four times. Blood components administered were RBC concentrates seven times, plasma once, platelets once and RBCs with plasma and/or platelets ten times.

Table 7 shows a summary of the TRALI reports with the accompanying blood components and findings of the serological testing for HLA-specific antibodies. Of the nineteen TRALIs fulfilling the definition, an immunologic cause was found in seven cases; in five cases, there was a negative leukocyte crossmatch test. In four cases, serological testing for HLA-specific antibodies was incomplete, twice no leukocyte testing was performed and in one case the results of the testing were unknown. It is common knowledge that negative results of leukocyte serological investigation do not exclude TRALI.

Table 7 TRALI reports in 2006

TRALI	2006	Leukocyte serological testing				2005	2004
Fulfils case definition ?	Imputability	positive	negative	Not (completely) performed	Result not known	Imputability	Imputability
yes	5 certain 5 probable 8 possible 1 not assessed	4 2 1	1 1 3	 1 4 1	 1	6 certain 4 probable 3 possible	3 certain 1 probable 1 TRALI + AHTR
cannot judge	2		1	1		1	3
other diagnosis	2			3		3	2

As in the 2005 TRIP report, the level of investigation (information about chest X-ray and the main pathology of the patient) is better than in 2003 and 2004. However, the hospitals still sometimes omit collecting a fresh blood sample from the patient after Sanquin has called up the associated donors. This is the main reason for failing to complete the leukocyte serological investigation since the leukocyte crossmatch test cannot be performed.

The number of research projects are currently being conducted in the Netherlands on the topic of TRALI and this is likely one of the reasons for increased interest in TRALI. It is hoped that the research results will contribute to understanding of the incidence and causes of TRALI.

Since October 2006 Sanquin has exclusively collected plasma from male untransfused donors to prepare plasma for transfusion. This measure will become effective clinically in the course of 2007 because of the six-month minimum quarantine period before components can be released following the donor's next normal test results. This measure, in principle, targets the TRALIs caused by leukocyte incompatibility between donor plasma and recipient leukocytes. In the United Kingdom, where a similar measure was introduced in 2004, the SHOT (Serious Hazards of Transfusion) report for 2005 states that, since that time, plasma transfusions provided by male donors have caused no TRALIs. However, SHOT includes leukocyte serological testing results when judging the likelihood that a lung complication could be a TRALI, whereas TRIP and the international consensus do not (SHOT Report 2005, ISBN 0 9532 789 8 0; Kleinman et al, Transfusion 2004; 44: 1774-1789).

Anaphylactic transfusion reaction

Serious 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 ≥ 20mm Hb systolic and/or diastolic, nausea or vomiting or diarrhoea, possibly with skin rash.
Hemolysis testing and bacteriology negative, carry out testing for anti-IgA.

With 18 reports, of which 13 were grade 2 or higher, numbers are lower than in 2005 (26, of which 21 were grade 2 or higher) but anaphylaxis remains an important category. Five anaphylactic reactions occurred in association with transfusions of platelets, seven with plasma, four with RBC concentrates, two with RBC and platelet concentrate combined (during which one patient also received plasma). Among the diagnoses reported three patients were undergoing plasmapheresis for thrombotic thrombocytopenic purpura.

As recently mentioned, anaphylaxis includes symptoms of hypotension and/or breathing symptoms caused by bronchospasm or glottal oedema (NTVG 2007; 151:574-7). All reports included these symptoms. A majority also showed skin symptoms (urticaria or erythema), while a rise in temperature was reported for approximately a third and nausea/vomiting in two cases. Where reported (n=13), the time interval is short, namely two minutes to 75 minutes. Hypotension or respiratory symptoms are not reported more often where the interval is shortest. Due to the short interval in all these reports the imputability level is relatively often assessed as high: there were six judged as 'certain' and seven as 'probable'.

Recommended testing consists first and foremost of excluding other possible causes, that is to say hemolysis or bacterial contamination and sometimes TRALI. This was not done in all cases or at least not mentioned. Chest X-ray findings were reported more often than in the past.

The national blood transfusion guideline [drafted by a panel of experts with extensive consultation, under the auspices of CBO, the Dutch Institute for Healthcare Improvement] and the TRIP definitions recommend testing for possible IgA deficiency and/or anti-IgA (or IgA subclass antibodies) in patients who have experienced an anaphylactic transfusion reaction. Information on this was included in eight of the 18 reports; this testing did not lead to establishing the cause even once. For one patient, it was recorded that antibodies to HLA and HPA possibly caused the reaction. Once, the reaction occurred upon administering ABO-incompatible platelets to a recipient with blood group O, without being able to demonstrate hemolysis. One patient had previously had an anaphylactic reaction to contrast fluid. It would be useful to do further research into patient factors and possible causes located in the component itself, such as a medicine or another allergen in the donor unit.

Other allergic reactions

Allergic phenomena such as itching, redness or urticaria (but without anaphylactoid signs) arising from a few minutes of starting transfusion till until a few hours after its completion.

The 'other allergic reactions' constitute a numerically important category: 208 or 10.2% of the total. As with the anaphylactic reactions, other allergic reactions occur relatively more often after platelet and plasma transfusions than after RBC transfusions (see Table 5). In this category, the majority was not serious (grade 0-1), but there were ten reports of grade 2. In addition to skin symptoms and in some cases temperature increase, symptoms of bronchospasm and/or blood-pressure drop were recorded; the extent of these was not specified further in all cases. It is possible that a number of these reports should have been classed as anaphylaxis. Under the allergic reactions, it was recorded seven times that there was insufficient yield from a platelet transfusion. As in previous years, a number (13) of patients showed an allergic reaction twice or three times (sometimes with two different types of blood components). In comparison with the categories of non-hemolytic transfusion reactions and hemolytic transfusion reactions, it is worthy of note that the allergic reactions occur in a younger patient population. It is likely that this is the consequence of the younger patient population that receives platelets or plasma. Research on the population of patients receiving blood transfusions can supply valuable information with which to look for risk factors in patients prior to them having a transfusion reaction.

Given the different types of platelet components Sanquin supplies, it would be useful to research possible differences in the incidence of allergic reactions. TRIP does not consistently receive information on the type platelet-concentrate. There are regional differences in the usual types of platelet component which are supplied. However the overall reporting frequency among hospitals (as already indicated) differs significantly countrywide, so there is currently too little to go by to attempt analysis of differences in incidence of this type of reaction.

Transfusion-associated circulatory overload (TACO)

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

After a considerable increase in 2005, the number of reports of transfusion-associated circulatory overload further increased to 34 in 2006, of which 23 were of severity grade 2 or higher. The reports are of importance in connection with the need to distinguish these reactions by physical and supplementary testing (chest X-ray!) from TRALI. It is likely that greater awareness of TRALI has influenced this increase in reports. Presently, the number of reports of transfusion-associated circulatory overload with certain, probable, or possible imputability amounts to 4.5 per 100,000 supplied units (approximately 1 in 22,000), almost two-thirds of the level in France, which also registers this complication. In France the category of transfusion-associated circulatory overload was the most frequent cause of death (29% having certain, probable, or possible imputability) among the transfusion complications in 2000-2005.

One report of transfusion-associated circulatory overload involved a patient with a haematological malignancy, already in poor condition prior to the transfusion. During the transfusion, symptoms of shortness of breath, drop in blood pressure, clinical deterioration, and some temperature increase occurred. The patient died in a state of clinical heart failure and cardiac asthma; no further investigations were done. Imputability was rated as 'possible'.

Bacterial contamination

Bacteraemia following a blood transfusion. Clinical signs may be indistinguishable from a hemolytic transfusion reaction. If the same bacterial species is are found in the patient and in the blood

bag (providing this has been stored under appropriate conditions), contamination is certain. It is preferable to investigate whether the strains are identical.

In 2006 TRIP received seven reports in the category of bacterial contamination (post-transfusion bacteraemia). In three of these, a positive culture was obtained both from the patient's blood and the component, and in one case the culture from the component and the blood culture revealed an identical bacterial strain (*S. epidermis*); the patient showed a febrile reaction and the severity report recorded grade of severity 1. In one of the other reports, a coagulase-negative staphylococcus (CNS) was found in both the blood culture of the patient and in the culture of the blood component (RBCs). The strains, however, were different. The hospital had not received any communication from Sanquin about a positive result upon bacteria screening; however, not all of the blood components are screened but only platelet components and (indirectly) RBC concentrates from the same donations.

Positive cultures in the blood component alone (2x red blood cells, *Acinetobacter* and CNS were seen twice; the patients were already using one or more types of antibiotics and showed symptoms consistent with bacteraemia/sepsis. Here too, no positive results from bacteria screening had been notified.

In conclusion, only in one case are there sufficient grounds for administration of a contaminated blood component to be assumed. Even then the bacterium *S. epidermidis* could possibly have entered the component after the start of transfusion or upon disconnecting the transfusion apparatus.

Information about reports of blood components with positive bacteria screening

Hospitals sent in 27 reports in 2006 about patients who had received blood components which Sanquin subsequently recalled because of positive results of bacteria screening (21 platelet concentrates, 6 RBC concentrates). This is an elective category for the hospitals and it is certain (see below) that the data are not exhaustive. In 17 cases the report gave the identified bacteria: 11x P*ropioni* species, 1x *Propionibacterium acnes*, 3x CNS, 2x *Corynebacterium*.

In one of the patients who already had increased body temperature it rose further; the blood culture identified a different bacterium from the one Sanquin found in confirmatory culture. In the hospital however the culture of the unit remained negative. The condition of another, already septic patient, deteriorated after administration of the platelet component and the patient died. A connection to bacterial contamination (*propioni* species) of the platelet concentrate is unlikely.

In a third report the specialist decided to treat the patient prophylactically with a prolonged course of antibiotics because the patient received the blood component in question during the placement of an aorta prosthesis. The patient’s leukocyte count showed no increase; the cultured bacterium was of the *propioni* species.

Sanquin’s central quality management department also supplied information on distributed blood components that were recalled because of positive results of bacteria screening. It is known that a minimum of 35 platelet concentrates, five RBC concentrates, and 17 blood components (type of blood component not available to central quality department) were administered that were later found to be positive during bacteria screening. The data were not simple to extract due to a transition in the way of registering quality reports. This means that it is unknown at central level how often reports of positive screening findings were confirmed by follow-up testing. However, the regional blood bank divisions consistently asked hospitals whether any relevant patient signs or symptoms had occurred; this had not been the case.

Viral transmission

Any viral infection that can be related to a transfused blood component (hepatitis A, B, C, non-ABC, HIV, HTLV, EBV, CMV etc.)

There were two reports in 2006 of certain infection by transfusion with hepatitis B by products from one 'window' donation; these were discovered because the donor, giving blood several months later, showed seroconversion. In a case of this sort, Sanquin does a 'look-back' by informing customers for all donations up to a period of 12 months prior to the last donation with a negative (good) result, because test results might be unreliable due to the window period. One donation showed a positive result of the individual donation PCR test on the archived sample, and the recipients of the RBC concentrate and of the pooled platelets incorporating the buffy-coat from this donation were infected. (Note: archived samples of all donations are kept for two years). As far as is known, one of the two patients cleared the infection; the other patient already had disturbed liver functions and the specialist in charge of this patient considers the consequences irrelevant for this patient given their general state of health. A different hospital decided not to investigate a recipient of an earlier donation (negative for PCR) from the same donor.

In a second case of hepatitis B seroconversion of a regular donor, testing of the archived sample from two earlier donations did not reveal any hepatitis B DNA. Three recipients were traced but none of them showed serological indications of an infection. A third report submitted by a hospital concerned hepatitis B discovered in a transfusion recipient. A large number of donors was called up and nearly all have now been tested. To of the present day, no evidence found for transmission by transfusion has emerged. Finally, a general practitioner reported to Sanquin that a deceased patient, transfused many times in the past, had been found to be a hepatitis B carrier. The imputability is unlikely though. Reports of this nature underscore the importance of traceability.

One of the other reports deals with CMV in a neonate, but in cases of this nature one cannot exclude a different source of infection than transfusion; no further testing was done. One report deals with a patient in whom hepatitis A was discovered after a transfusion; there already was an increase in liver enzymes before administration of the blood and the imputability is unlikely. Sanquin does not test for hepatitis A, but donors are screened by questionnaire and interview.

The last report deals with the discovery that a recipient of different blood components in the 1980s and 1990s was a hepatitis C carrier. The test for hepatitis C was introduced in the Netherlands in 1991; therefore transmission is conceivable. However, Sanquin carried out a targeted look-back among all recipients from donors who turned out to be hepatitis C positive. In the case in point, donation numbers from the 1980s were no longer traceable and other routes of infection cannot be excluded.

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

In 2006, there were no reports of PTP. Since TRIP began registering events, there has been only one report of PTP and that was in the baseline data on 2002.

Transfusion-associated graft versus host disease (TA-GVHD)

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, with a high mortality. Skin (and liver) biopsies can support diagnosis.

In 2006, as in previous registration years, no reports were received of TA-GVHD. Leukodepletion, as has been practised on all blood components since the end of 2001 in the Netherlands, significantly prevents the occurrence of TA-GVHD. Additionally, irradiated blood components are used for patients at risk.

Hemosiderosis

Hemosiderosis in a multiply transfused patient.

In 2006, two institutions produced five reports in this category. TRIP received reports about hemosiderosis in 2005 for the first time (from one institution). All patients were male and showed ferritin levels far above 2000 µg/L. It is not clear how many transfusions were administered before this complication was discovered. The need for transfusion arose in one case due to a hemoglobinopathy and for the other patients due to a hemato-oncological disease. The manifestations range from no symptoms to chronic complaints (3x grade 2) as a consequence of organ damage. Three patients received treatment: bloodletting, deferoxamine, and intravenous iron-chelation therapy.

These reports are doubtless the proverbial tip of the iceberg. Given the various therapeutic possibilities, it is desirable to map the prevalence of this complication of blood transfusion more thoroughly.

New allo-antibodies

After a transfusion, demonstration of clinically significant antibodies against blood cells (irregular antibodies, HLA antibodies or HPA antibodies) which were previously absent (as far as is known in that hospital).

As in the two previous years, the largest number of reports was in the category of development of new antibodies against blood cell antigens. There were 603 reports (29.7%) from 48 of the 94 hospitals which submitted reports, compared to 523 reports from 42 hospitals in 2005.

In addition to the 603 reports in the category of new allo-antibody production, 13 cases of new antibodies were reported after further testing following a clinical reaction. These were one acute hemolytic transfusion reaction, one febrile non-hemolytic transfusion reaction, two other allergic reactions, and nine delayed hemolytic reactions, for which a grade of severity 2 was reported seven times and grade 1 six times. In two cases there was question of administration of an incorrect blood component in 2005, the cause of antibody production noted in 2006. In 97 reported cases (16.1%), there is question of development of multiple (two or more) antibodies.

Detection is incomplete, because development of a new antibody is only discovered if irregular antibody screening is performed later on after transfusion. If TRIP extrapolates the reporting frequency to all hospitals, then approximately 1274 reports could be expected within one year in the category new antibody production. TRIP intends to continue registering new antibody production for 2007 alongside TRIX, a newly launched national electronic register of antibodies and other crossmatch problems including recipients of allogeneic hematopoietic stem cell transplants.

In 2006 as in previous years the number of reports of anti-E was largest with two hundred and thirty-three reports (38.6%). In second place is the production of anti-K with 143 reports (23.7%). These included eight reports of development of anti-K in women of child-bearing potential (under 45). In two cases, there was question of a mistake in selecting the blood component in 2005, which was followed by detection of anti-K production in 2006. These errors in component selection are referred to in the section on 'incorrect blood component transfused'. Five women received the implicated transfusion before 2004,

when the CBO Consensus Guideline for Blood Transfusion was published. One woman was transfused in 2006, before the cEK-policy was implemented in the hospital in question in August of 2006. [Translator's note: To prevent allo-immunisation against the Kell blood group, the Guideline recommends Kell-negative (or Kell-compatible) RBC transfusion to women of child-bearing potential, taken as up to 45 (as a measure to reduce the risk of hemolytic disease of the newborn). Some hospitals go further and apply a Rhesus phenotype *and* Kell compatible component selection policy in this group. Anti-c and/or anti-E in women under 45 was reported 20 times (15 reports in 2005).

Over the course of 2006, TRIP received 15 reports of development of anti-D. In eight cases (five men and three older women), anti-D developed after a platelet transfusion. In two of the men, O-positive blood was administered massively in an emergency situation because there was insufficient O-negative blood. In the other five reports of anti-D following RBC transfusion (four older women and one man), there was probably question of the G-antigen, but the hospital did not investigate this in all cases.

Other antibodies found in 2006 were: anti-c 52, anti-C 34, anti-e 5, anti-Fy(a) 56, anti-Fy(b) 4, anti-Jk(a) 43, anti-Jk(b) 14, anti-S 24, anti Wr(a) 19, anti-Cw 16, anti-M 19, anti-Lu(a) 12, anti-Le(a) 8.

Other transfusion reactions

Transfusion reactions that do not fit into the categories above.

TRIP uses this category for symptoms that do not fit well into standard categories. A relatively large portion has low imputability: certain or probable 27%, possible 45%, unlikely or excluded 27%. Particularly when a severity of grade 2 or higher (six cases) was recorded it is seen that the patient was seriously ill,. One correctly considers the possibility of a transfusion reaction but after weighing up other possible explanations, arrives at a low degree of imputability.

Among the reported symptoms a blood pressure drop and/or dyspnoea occur most often, but the characteristics do not fit an allergic reaction or other specific TRIP category. A drop in blood pressure without other symptoms was reported three times. Hypotensive reaction is included internationally in some hemovigilance systems as a separate registration category. It is typical that the hypotensive reaction is clearly in the foreground in relationship to other possible symptoms, that it arises quickly and the patient recovers quickly once the transfusion is halted. The pathophysiological mechanism mentioned in the literature is the presence of bradykinin in the blood component. In the three TRIP reports of hypotension unaccompanied by further features, all of which are associated with RBC transfusion, symptoms appeared in two of the three cases within a half-hour of starting the transfusion.

Other often-recorded symptoms in this group were dizziness, nausea, vomiting or diarrhoea, tachycardia or bradycardia. A few reports concern chest or back pain; one records a cardiac arrest that for which no other explanation is found. Malaise is recorded twice, headache three times, tingling in the fingertips twice, reduced consciousness or clinical deterioration twice, blood-pressure increase and arthralgia each once. Two reports record a local reaction in the arm with the IV: petechiae, pain and redness.

Incorrect blood component transfused

All cases where the patient is transfused with a blood component which did not meet all the requirements for a suitable transfusion for that patient, or that was intended for another patient. TRIP requests institutions to report these incidents, even if there are no adverse consequences for the patient.

After a large increase in numbers of reports concerning administration of an incorrect blood component

in 2005, the reporting year 2006 showed a further slight increase. TRIP received 64 reports in this category for 2006, which were associated with a transfusion reaction in 14 cases. These included two reports of new antibody production as a consequence of an incorrect blood component administered in a previous reporting year. *Table 8* shows a summary of the reports of incorrect blood components administered which were associated with transfusion reactions in the patient.

A blood component meant for another patient was administered in eighteen transfusions. Seventeen times this was an RBC concentrate and once plasma; in eleven of the eighteen cases, the blood components were fortuitously ABO-compatible. In only one case was it recorded that there was question of a time constraint. Of the eleven ABO-compatible RBC concentrates, nine were blood-group O. of which three were O-negative; the recipient was AB-positive in one case. In one case it is not recorded whether the administered blood component was ABO-compatible or not. A Rh-positive blood component was administered to an Rh-negative recipient twice among these eleven ABO-compatible RBC concentrates. The administration of the six ABO-incompatible blood components produced an acute hemolytic transfusion reaction twice, a delayed hemolytic transfusion reaction once and an other transfusion reaction once. In two cases, both in patients of 80 or older, in which donor blood with blood group A was administered to a patient with blood group O, no clear evidence of hemolysis was found.

Once O plasma was requested and administered to a patient with blood group A-negative. This was also a patient older than 80 and no symptoms of a transfusion reaction were observed. In an urgent situation, by mistake two units of plasma were requested and administered instead of the necessary RBCs. An ordinary unit of O-negative RBCs was selected and administered to a neonate instead of an exchange transfusion. Errors in determining the blood group led to fourteen units in one case and one unit in another of Rh-positive RBCs being given to Rh-negative patients.

Eight cases report failure to select antibody-compatible components for patients with known irregular antibodies. RBCs were issued and administered without valid antibody screening in two cases. Additionally RBC concentrates for which the crossmatching test was positive were erroneously issued in three instances; the component was partially administered twice and once completely. In two of the cases, the patients in question showed symptoms after transfusion; in the third case, it turned out that the crossmatching test had not been carried out properly so that it showed a false positive.

In 24 reports, there was question of non-conformity with hospital policy for the particular patient group. Non-irradiated blood components (RBCs eight times and platelets three times) were administered in eleven cases where irradiation was indicated. The transfusion advice related to a recent transplantation was not followed in three cases. On five occasions one or more K-positive or non-tested RBC concentrates were administered to women under 45. Once a blood component that was not Parvo-B19-safe was given to a pregnant, antibody-negative woman. RBCs that were O-positive instead of O-negative were given twice (one report) to a neonate and a Rh-positive platelet concentrate was administered to a Rh-negative female patient once. In one report a different screening method was applied supplementally without consulting the senior analyst after the column technique produced a positive DAT and crossmatching result; again without consultation, the component subsequently was issued and transfused. A further report concerns issue (and transfusion) of an ABO-identical blood component without crossmatching while working according to the emergency (computer-down) procedure.

Three reports concern transfusion of a blood component (twice RBCs and once plasma) after the compatibility valid period had lapsed. In another case, non-crossmatched compatible blood was administered without the transfusion laboratory of the hospital where the patient was admitted having released this component.

In a total of seven cases an ABO-incompatible blood component (plasma twice and RBCs five times) was administered. In nine cases, the blood component was incompatible for a demonstrated irregular antibody. In five of these sixteen cases, a hemolytic transfusion reaction occurred. This was acute twice as a consequence of ABO-incompatible RBCs (A-positive to a patient with blood group B) and due to ABO-incompatible plasma (O-positive to a patient with blood group A-positive). A delayed reaction occurred in three cases (blood-group B to a group O patient, C to a patient with anti-C and c to a patient with anti-c). Transfusion of group-A RBC concentrate to a group O patient led to a serious 'other reaction' for which the patient had to be admitted to intensive care. After administration of Kell-positive RBC concentrate to a patient known to have anti-K, a mild febrile reaction was observed. In incidents of failure to observe the Kell policy, an NHTR was observed once; no anti-K was detectable approximately two months after transfusion. An 'other allergic reaction' was observed after administering blood that had been stored in a non-validated refrigerator for 24 hours. A serious 'other reaction' (grade 3) occurred after ordinary O-negative RBC concentrate was used instead of a unit for neonatal exchange transfusion. An 'other reaction' was also observed in the two cases of transfusion of a blood component with positive crossmatching results. Reactions recorded as grade 0 were observed solely in laboratory results; the patients did not show clear clinical symptoms.

Table 8 Clinical symptoms after transfusion of an incorrect blood component

Type of reaction	No.	Severity grade				
		0	1	2	3	4
Acute hemolytic transfusion reaction	2	1	1			
Delayed hemolytic transfusion reaction	3	1	2			
New allo-antibody (N.B. incorrect blood component transfused in 2005)	2	2				
Non-hemolytic transfusion reaction	1		1			
Mild febrile reaction	1		1			
Other allergic reaction	1		1			
Other reaction	4		2	1	1	

Other incidents

Other errors/incidents in the transfusion chain, for instance patient transfused whereas the blood was supposed to be kept in reserve, or transfused unnecessarily on the basis of a wrong Hb result.

There were 87 reports of events in the category 'other incident'. Clinical consequences were observed in a total of eight of these cases. *Table 9* shows a summary of these.

In 39 instances the report had to do with a component incident, of which in 31 cases Sanquin had informed the hospital that subsequent information from the donor meant that the donor had not fulfilled screening criteria. Chiefly this concerned donors who it later turned out had received a blood transfusion themselves in the past. [Translator's note: Deferral of donors transfused in 1980 or later was introduced in November 2004.] Passive transfer of HBV antibodies was the reason for one report; twice a donor subsequently indicated they had been found positive for EBV; once there was question of possible infection with either EBV or Borrelia. Two reports concerned platelets which were received late. In one report the typing of the component did not match the requested typing; a further report was about leakage of more than one bag of plasma.

A problem with pneumatic dispatch, meaning that screening material was lost, led to the administration of four units of un-crossmatched RBCs.

In 13 cases blood was requested and administered on the basis of an incorrect or an out-of-date hemoglobin result (either not determined recently or not redone after transfusion); five of these involved a faulty blood sample (taking the blood from the drip arm) which was the cause of the incorrect information. A mild febrile reaction was observed in one of these cases. In four cases the error was discovered but all the requested blood components were administered nevertheless. Twice a Hb of 10 mmol/l or higher was found after transfusion. Once blood was requested for a patient based on the hemoglobin result of a week ago; despite the laboratory system indicating a Hb above 6.0, the blood was issued and transfused. In another patient, symptoms of transfusion-associated circulatory overload appeared after administering a number of RBC concentrates; the Hb in this case as well was higher than 10 mmol/l.

Limitations of the standard techniques employed for antibody screening resulted in two reports. The first case had to do with a patient known to have irregular antibodies (anti-K), who had two transfusion episodes six days apart. The method used in that hospital gave no decisive answer about possible additional irregular antibodies when new antibody screening was done for the second transfusion episode. Clinical urgency led to a decision to transfuse Kell-negative blood on the basis of negative crossmatching results. The reference laboratory however used an enzyme technique to demonstrate anti-C in the same blood sample; using the same testing method as the hospital the reference laboratory detected a very weak reaction the following day. Two days later (eight days after the first transfusion period) the hospital laboratory was able to detect anti-C itself with the same testing method. There was evidence of a delayed hemolytic transfusion reaction in the patient. In the second case, a patient who already had chronic hemolysis suffered a temperature increase accompanied by chills; on repeating the screening after the onset of the reaction, alternative techniques demonstrated anti-S.

Once plasma was thawed too early and then transfused, meaning that the patient had to have two more units of plasma the following day. Two reports arose from requesting blood components too late or not requesting them at all and from not placing the patient was on the operating theatre list, and in one case this led to avoidable use of uncrossmatched blood.

Twelve reports were about not storing one or more blood components according to directives and protocols in force. The majority of the components in question was rendered unusable unnecessarily due to this omission. In three cases, the component was administered nevertheless and one of these transfusions led to a mild febrile reaction.

Miscellaneous incidents related to transfusion of blood components formed the subject of eight reports. Upon administration of autologous blood using a cell saver, an acute hemolytic transfusion reaction was observed; this case is discussed further under the blood management techniques. The duration of the transfusion was too long in two cases and in one a NHTR occurred (platelets). There were two reports of leakage, once through a connection on the IV line and once from a bag of plasma. Further cases involved incorrect adjustment of a volumetric pump and (twice) transfusion of RBCs through the same giving set as medication or glucose/salt solution. In the latter case an AHTR occurred and no positive effect resulted from the transfusion: a day after the transfusion the hemoglobin was lower than it had been before transfusion and the patient had to be transfused again the following day.

Table 9 Clinical symptoms following other incidents

Nature of reaction	Number	Severity grade				
		0	1	2	3	4
Acute hemolytic transfusion reaction	2		2			
Delayed hemolytic transfusion reaction	1		1			
Transfusion-associated circulatory overload	1			1		
Non-hemolytic transfusion reaction	2		2			
Mild febrile reaction	2		2			

'Near miss' events

Any mistake or error which, if undetected, could have led to a wrong blood group result or to issuance or administration of a wrong blood component, and which was detected before transfusion.

Reports in the category of 'near misses' are about incidents that could have led to transfusion of an incorrect blood component, but that were prevented by routine checks, by human alertness, or by happenstance. In 2006 76 reports recorded a 'near miss'.

As in previous years, errors in identifying both the patient's blood, the blood sample, and the blood component sample amount to more than half of the 'near misses' (47). Of the errors in identification, there were 16 reports where the error was discovered by a discrepancy between the historically established blood group and the new blood group result. In nine cases a discrepancy was noticed between data on the request and on the blood sample. Four additional identification errors were discovered when it was found that blood had been prepared for the wrong patient or because someone asked why the requested blood had not arrived.

Two reports recorded that the antibody typing for the components was found to deviate from that on the label when checked in the hospital. Once blood was issued for which the crossmatching test was positive but the blood component was retrieved on time after discovering the mistake.

Mistakes in requesting a blood component such as failing to record a history of irregular antibodies or failing to request that the component had to be irradiated were the subject of a five reports. There were also two reports of ordering different type of blood component to that intended for the patient.

Administrative mistakes, such as a female patient being entered mistakenly as a man, failing to record data about important medical information such as recent transplantation or an indication for irradiation, or entering an incorrect blood group were the subject of seven reports. A special problem that comes to light here has to do with hand scanning the blood supply, which can result in component data switches. The particular event which was reported arose from entering a blood component into the laboratory information system, during which two of the five bar codes used belonged to a different component and this slip-up led to a change in the blood group which was entered for the blood component in question. Another reported case involving automation concerned the changing of a patient’s blood group after a peripheral blood stem cell transplantation. The laboratory information system retained the previously determined blood group after the change; the system had to be modified to correct this.

Reports relating to autologous blood components

In 2006 TRIP received one report involving a RBC concentrate from autologous pre-donation – the donor, approximately 60 years old and on treatment for serious hypertension, became unwell for a prolonged period after the donation and had to be treated with intravenous fluid in the emergency ward for a

number of hours. The patient had previously undergone therapeutic bloodletting for paraneoplastic polcythemia without problems. In view of the low risks of allogeneic blood transfusion, the indication for autologous pre-donation must be determined with care.

Blood management techniques

TRIP received four reports from four hospitals in 2006 of transfusion reactions connected to blood recovery techniques. It is not known how often such techniques are used in Dutch hospitals. One of these reports records an 'other reaction' (blood-pressure drop and heavy perspiration) to reinfusion of unwashed, filtered drain blood. Three reports record reactions to reinfusion with the aid of a cell saver. There was one non-hemolytic transfusion reaction and one 'other allergic reaction'. The third report concerned an 'other incident': a patient who had had symptoms for several days and was transfused using a cell saver with blood salvaged from the abdominal cavity. This patient developed an acute hemolytic transfusion reaction, which was treated with forced diuresis. All of these cases were reactions of severity grade 1; imputability was 'possible' three times and 'certain' in the case of the acute hemolytic transfusion reaction.

Deceased patients and transfusion reactions (grade 4)

TRIP received four reports in 2006 with severity grade 4. The reported transfusion reactions are summarised below in *Table 10*. The discussion of the categories in question cites all these reactions.

None of the reports in 2006 establishes with certainty the decease of the patient as being a consequence of a serious adverse reaction to the transfusion. In three of the four reports the transfusion complication possibly contributed to the death of the patient while that was unlikely for the fourth patient. *Table 10* shows that in all cases the patients were seriously ill and may well have died much earlier without transfusion therapy.

Table 10 Reports of the decease of a patient following a transfusion reaction

Reaction category	Grade of severity	Imputability	Nature of the underlying pathology
TRALI	4	Possible	Haematological malignancy
TRALI	4	Possible	Septic
Transfusion-associated circulatory overload	4	Possible	Hematological malignancy; no chest X-ray or autopsy
Transfused unit showed positive bacteria screening	4	Unlikely	Septic

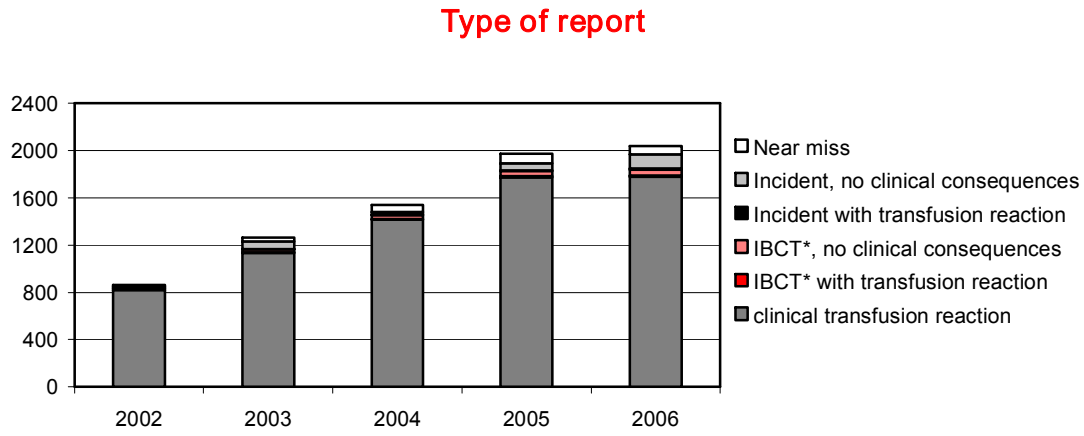
Where are we headed with hemovigilance and transfusion safety in the Netherlands?

There was a slight increase in the number of reports in 2006 compared to 2005 (including the late submissions for that year), but there is no longer of a large increase. A somewhat larger number of hospitals managed to submit reports before the closing date for the 2006 report; the average interval between ascertaining that a reaction or an incident has taken place and reporting it was also somewhat shorter in 2006 than previously. However, TRIP again received late reports during the period of preparing this report, so the final total will be higher than in 2005.

The categories exhibiting an increase worth noting are particularly TRALI and transfusion-associated circulatory overload, new antibody production (in the latter category, mainly because more hospitals

submitted reports), and 'other incidents'.

The number of reports of clinically serious events (grades 2 to 4) was slightly increased in 2006 compared to 2005 and now amounts to 124 (2005: 94); in other words, approximately 1 in 5600 blood components supplied nationally. The main explanation for this is the increase in reports such as non-hemolytic transfusion reactions of grade 2 and with a low imputability. From the explanations accompanying a number of these reports it is seen that they were associated with prolongation of hospitalisation. As explained above, since 2006 one must categorise such a report as grade 2 because the definition was amended within the framework of implementing the European Union Directive. *Figure 5* shows the numbers of the types of reports received by TRIP from year to year.



*IBCT=incorrect blood component transfused

Figure 5 Types of reports 2002 - 2006

Reports received include a number of clusters that do not constitute formal TRIP categories, but that certainly are relevant in the framework of general safety and effectiveness of blood transfusion in the Netherlands. Relevant areas are those of delay in a potentially life-saving blood transfusion, adverse consequences of applying blood management techniques, or insufficient yield of a platelet transfusion. Additionally, a number of conspicuous clusters under 'other incidents' highlight the importance of focusing attention on the entire transfusion chain, as is the intention within the ‘safety management system’ (veiligheids management systeem, VMS) to be implemented in every hospital in 2008.

Preventable reactions

An important question is whether a reaction is preventable. To obtain an impression of the frequency and the type of reactions that occur subsequent to avoidable mistakes in the hospital, TRIP has analysed the reports in the categories of 'incorrect blood component administered' and 'other incident'. It is remarkable that only in a small number of these reports there were clinical symptoms of a transfusion reaction.

It can be concluded that out of the sixty-four reports of 'incorrect blood component administered', sixty-two can be seen as avoidable mistakes. In fourteen cases a transfusion reaction was recorded as a secondary category. Eleven of the fourteen reactions were certainly or probably attributable to the transfusion: five were hemolytic transfusion reactions, four were described as other reactions, and there were two cases of development of a new antibody.

Among the other incidents there are fewer mistakes avoidable by the hospital: 45 out of 87 reports. This is due mainly to the large number of reports where donor information only became known after transfu-

sion of the blood component. Among the 45 reports of avoidable errors in the hospital, six record symptoms characteristic of a transfusion reaction. Of these, three were probably or certainly the consequence of an avoidable error: one was a case of transfusion-associated circulatory overload after transfusion of six RBC concentrates, ultimately producing a Hb higher than 10 mmol/l, and two were acute hemolytic transfusion reactions.

Thus 107 reports of avoidable hospital errors were associated with fourteen transfusion reactions that probably or certainly could have been avoided. Despite the fact that relatively few transfusion reactions occurred because of errors, it remains the aim of a hemovigilance system to reduce these numbers to a minimum, in order to safeguard patients against potentially dangerous transfusion reactions.

2.4 Overview of mandatory reports of serious adverse reactions and events in the transfusion chain

The table below *(Table 11)* is derived from *Table 2*. This is broadly the requisite format for annual reports to the European Commission of serious adverse events and reactions (grade 2 or higher) as provided in Directives 2002/98/EC and 2005/61/EC. Serious adverse events are classed according to their imputability. This table includes clinical reactions after transfusion of an incorrect blood component with the numbers per reaction type.

Table 11 Numbers and imputability in reports of grade 2 and higher in 2006

Category of reaction	No. of serious reports		Not assessed		Excluded, unlikely, possible		Probable		Certain	
	05	06	05	06	05	06	05	06	05	06
Acute hemolytic TR	11	5			1	1	3	2	7	2
Delayed hemolytic TR	2	8				1	1	1	1	6
TRALI	13	20	1	3	4	6	3	6	5	5
Anafylactic reaction	22	13			6	3	11	5	5	5
Other allergic reaction	8	10			2	3	4	3	2	4
Transfusion-associated circulatory overload	11	24	1		7	9	2	10	1	5
Bacterial contamination	5	3				3	2		3	
Viral infection	2	2			2	1				1
Post-transfusion purpura	0	0								
Transfusion-ass. GVHD	0	0								
Other serious reactions	20	39			9	25	4	9	7	5
Total	**94**	**124**	**2**	**3**	**31**	**52**	**30**	**36**	**31**	**33**

The reports in 2006 where the patient deceased are included in the overview. These were two incidences of TRALI and one of transfusion-associated circulatory overload, all three of which had 'possible' imputability, and one 'other reaction' with 'unlikely' imputability.

2.5 Conclusions

1 In 2006 two patients were infected with hepatitis B after receiving blood components from a donor who was in the window phase at the time of the donation. In no other reports where viral transmission was considered was there any evidence of transmission of an illness for which Sanquin tests donations. Once again therefore, analysis of the reports has established that infectious risks attached to blood transfusion in the Netherlands are low.

2 TRIP observed an increase in the number of reports of grade 2 or higher, mainly due to a higher number of reports of 'other serious reactions' with an imputability that is usually low (in EU terms: 'impossible, unlikely, or possible'). Given the amendment of the definition of grade 2 in connection with implementing the EU Directive (inclusion of reports where there is prolongation of hospital admission), the rise does not indicate an actual increase in serious adverse reactions.

3 The increase in the number of reports has slowed down while the level of participation of the hospitals has increased. There is still a slight increase in numbers of non-serious reports. This suggests that the numbers of the serious reports represent reality.

4 Allergic reactions remain an important category, particularly when administering platelet concentrates and plasma.

5 Besides TRALI, circulatory overload is an important category with possible serious consequences for the patient.

6 The number of reports of 'other incidents' increased in 2006. These point out the importance of vigilance in the entire transfusion chain.

7 In the category 'development of new antibodies' there is a relatively large number of reports of anti-c and anti-E in women under 45.

8 Hemosiderosis is underreported in multiply transfused patients.

9 The promptness of submission of reports improved somewhat in 2006 compared to 2005.

2.6 Initiatives and developments in response to recommendations made in the 2005 TRIP report

1 *'Research is needed into the causes of anaphylactic transfusion reactions. Subsequently one needs to search for blood components that cause fewer anaphylactic reactions and to investigate these components in comparative clinical studies.'*
As far as TRIP is aware, no action was taken on this point in 2006.

2 *'Aided by the results of the research into TRALI reports, a search needs to be undertaken for blood components which are less likely to cause TRALI. These then need to be evaluated in comparative clinical research.'*
There are currently a number of current research projects in progress in the Netherlands that should shed light on the causes of TRALI. Sanquin decided in the autumn of 2006 to take the preventive measure of solely preparing fresh frozen plasma from male donors who have never been transfused.

3 *'Attention must be focused on the correct technique for sampling blood components in the hospitals once a transfusion reaction has taken place, in order to obtain reliable bacteriological information. Establishing protocols and furthering education are indispensable in doing this.'*
During TRIP training days for hemovigilance personnel as well as in other settings more and more attention is given to the practical aspects of investigations following a transfusion reaction. To date, protocols often give insufficient instruction for many practical aspects such as taking samples for culturing, but also identifying patients properly.

4 *'Research into possible differences in the incidence of allergic reactions would be useful for the different types of platelet components Sanquin supplies.'*
Research is now being done as part of the HOVON research collaboration [Hemato-Oncologie voor Volwassenen (for Adults) in The Netherlands] as well as in a research project initiated by Sanquin.

5 *'To prevent loss of information, transfusion reactions must be reported as soon as possible to TRIP after their detection (in conformity with the EU Directive for reporting transfusion reactions).'*
'In the second quarter of 2006, a pilot project started to test the use of a web-based reporting system.'
Since the end of 2006, the system has been ready to expand the group of online reporters by adding other volunteer hospitals.

6 *'The transfusion chain needs to be investigated using the methods of 'safety management', making use of the TRIP reports and in collaboration with hospitals that analyse the events.'*
TRIP will be starting a project in 2007 that will analyse the transfusion chain prospectively according to the principles of Healthcare Failure Mode and Effect Analysis (HFMEA).
Hemovigilance staff from a number of hospitals have registered for training in incident analysis using the Prevention and Recovery Information System for Monitoring and Analysis (the PRISMA method). Results will be collectively reported.

7 *'Extra attention and training are necessary to ensure that doctors and nurses fully understand the risks of blood transfusion, perform the necessary transfusion checks with appropriate care, adequately recognise transfusion reactions and respond appropriately. Additionally, training for doctors is needed so that they prescribe blood components correctly when they are indicated.'*

Since the autumn of 2006 TRIP has organised educational sessions a number of times per year for hemovigilance personnel in hospitals. Occasionally TRIP gives lessons and presentations to other groups when invited to do so.

In addition, a national hemovigilance platform has been set up under the auspices of the Dutch Association for Blood Transfusion. The platform promotes communication and mutual support among the regional hemovigilance platforms and, as a result, among hemovigilance officers and assistants. The national hemovigilance platform wishes to contribute to the development of hemovigilance and to the professional development of hemovigilance staff.

2.7 Recommendations

A. Recommendations based on the 2006 TRIP Report

1 Recommendation 1 from the TRIP Report 2005 remains relevant:
Research is needed into the causes of anaphylactic transfusion reactions. Subsequently one needs to search for blood components that cause fewer anaphylactic reactions and to investigate these components in comparative clinical studies.'

2 Besides TRALI, circulatory overload is an important category which requires attention, particularly because relatively simple preventive measures can be taken, like administering diuretics.

3 Vigilance is needed as well in the areas of adverse reactions and events related to blood management techniques.

4 Consideration should be given to recommending selection RBCs for women under 45 that, besides being Kell-negative, also are Rhesus phenotype-compatible, to prevent hemolytic disease of the newborn.

5 More attention must be paid to reporting transfusion-related iron overload in order to gain insight into the occurrence of this adverse consequence of transfusion in the Netherlands.

B. General recommendations

6 Online reporting should be further stimulated to facilitate more rapid reporting and thus promote optimal analysis. Together with this a means should be developed to enable the reporter to electronically send relevant reports of serious adverse reactions or serious adverse events to the competent authority, The Netherlands Health Care Inspectorate (IGZ).

7 Within the framework of introducing safety management systems, directors of hospitals and other involved institutions must ensure that new initiatives are integrated with already existing hemovigilance activities and the general safety system of hospitals.

3. Tissue vigilance

3.1 Introduction

The Dutch Ministry of Health, Welfare, and Sport (VWS) has asked TRIP to develop a system for reporting serious adverse reactions and events related to transplantation of human tissues and cells. As is the case for hemovigilance, all Member States of the European Union are obliged to draw up a summary of these reports annually. This obligation arises from Directive 2004/23/EC, which has been implemented in Dutch law by amendments to the Dutch Quality and Safety of Human Bodily Materials Act [*Wet kwaliteit en veiligheid lichaamsmateriaal*] and the appended Decision on Human Bodily Materials [*Eisenbesluit lichaamsmateriaal*] 2006.

Consistent with the term hemovigilance, TRIP has adopted the term 'tissue vigilance'. This implies: *The systematic monitoring of serious adverse reactions and events in the entire transplantation chain of human bodily materials, with the aim of arriving at a safer and more effective use of tissues and cells.*

3.2 Method

After a preparatory period TRIP informed all tissue establishments and hospitals about the project. In consultations with the VWS a pilot reporting system was launched in August 2006. TRIP has the same role as it does for blood components: collecting, analysing, and reporting serious adverse reactions and events.

All required information was published on the TRIP website and letters were sent to the hospitals and to all tissue establishments known to TRIP (based on published lists called '*Erkenning orgaanbanken*' [Licensing of Organ Banks] from: *Staatscourant* 1 October 2004, issue 189 and '*Tijdelijke erkenningen* orgaanbanken' [Temporary Licensing of Organ Banks] from: *Staatscourant* 19, October 2005, issue 203). At the end of reporting year 2006 tissue establishments were asked to send in reports of serious adverse reactions and/or events from August to December 2006 along with the number of distributed number of components.

Table 12 below summarises the information received about distributed components.

In the spring of 2007 an advisory committee on tissue vigilance was set up with representatives of relevant professional associations. This committee will consider how best to implement tissue vigilance in practice. The 2006 reports were reviewed by the advisory committee.

3.3 Reports and numbers of tissue products distributed

TRIP received a total of eight reports concerning the period from 1 August to 31 December 2006: once about a bone component, once a cornea, once a heart valve, once blood from the umbilical cord, twice allogeneic peripheral blood stem cells (PBSC), and twice autologous PBSC. Although these reports were discussed with the advisory committee they will be presented in detail because consensus must be reached first about the scope of the reporting.

Out of the submitted reports only four belong under the heading 'serious adverse reactions or serious adverse events' from the European Directive. One of these concerns the transmission of a bacterial infection via bone tissue. The imputability is 'certain'. The other three reports record 'other reactions' and the relationship to the transplantation ranges from certain to unlikely.

TRIP will send a first summary of the serious reports to the Ministry of VWS and to the IGZ, with a note that the overview is incomplete. Formally, submission of an annual summary to the European Commis-

sion will become obligatory next year and will cover reports from 2007. However, TRIP thinks it is very useful to go through the steps now. The tissue establishments and hospitals have raised a number of practical questions and these will be passed on to contact persons in the Ministry of VWS, the IGZ, and the European Commission.

Table 12 Numbers of distributed tissues/cells

Type	Units or amounts	Description
Skin	1971375 cm^2	
Bone	3100	Bone, cartilage
Ocular tissue	1200	Cornea
	315	Sclera
	57	Amniotic membranes
Ossicles	37	
Cardiovascular tissue	400	Heart valves, vessels and patches
Hematopoietic stem cells (Unrelated donors)	30	Bone marrow
	24	Peripheral blood stem cells
	16	Umbilical cord blood
Haematopoietic stem cells (related donors and autologous procedures)	Data incomplete	
Reproductive cells	Unknown	
Other types:	Unknown	
• Pancreatic islets		
• Ligament and fascia, tendons, menisci and other 'soft' tissues		
• Adult and embryonic stem cells		
• Foetal tissues		

3.4 Conclusions

1 Professional groups, in consultation with the competent authorities, must work out the practical scope of tissue reporting.

2 TRIP is among the European forerunners in the area of tissue vigilance and consequently can play a leading role and contribute to in decision-making processes.

3 Particular attention should be focused on tissue vigilance within the hospitals. TRIP needs support from the Ministry of VWS and IGZ in doing this.