TRIP REPORT 2015

Hemovigilance

Extended version

TRIP
Hemo-en biovigilantie

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The TRIP annual report 2015, extended version, concerning hemovigilance reports in The Netherlands is published under responsibility of the TRIP Foundation (Transfusion and Transplantation Reactions In Patients).

TRIP
Hemo- en biovigilantie

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Contents

Foreword

This is the thirteenth annual TRIP hemovigilance report, giving a picture of transfusion safety in The Netherlands in 2015. The number of reports of the various types of transfusion reactions and incidents is similar to previous years. The transfusion chain is generally very safe, with less than one serious reaction per 5000 units transfused and fewer than 1 case of transfusion-transmitted bacterial or viral infection per 125,000 units transfused. However the reports show that there is still room for improvement of the safety of blood transfusion.

In accordance with the vision of the Hemovigilance Advisory Board and the TRIP Board, this report chiefly focuses on areas which are important for improving safety. In the chapters we have only included discussion where this was needed for clarification or for drawing attention to a relevant trend.

The TRIP board and the Hemovigilance Advisory Board are keen to ensure that reporting is as efficient and effective as possible. In 2015 the new online reporting form for hemovigilance was constructed with particular attention to detail and user-friendliness. The new system provides more support to people reporting, e.g. through clarity about the details which are needed for each type of transfusion reaction or incident. Several features which had been requested by users have been incorporated in the system; a short user guide explaining the changes is available (in Dutch) on www.tripnet.nl.

At various stages of the development of the new reporting tool, hospital hemovigilance officers and transfusion safety officers assisted in testing the reporting form and its functions. TRIP wishes to publicly acknowledge their important contribution and thank them for the time and effort which they were willing to invest in this work. The collaboration underlines the essential role played by the Dutch transfusion professionals in the hemovigilance system and in the ongoing endeavour to improve the safety and effectiveness of the transfusion chain.

Martin R. Schipperus
President of TRIP Foundation

CHAPTER 1

Main 2015 findings

1.1 Hemovigilance trends in 2015

The numbers of blood components transfused and of transfusion reactions and incidents reported to TRIP in 2015 were broadly similar to 2014. The number of serious reactions judged to have definitely, probably or possibly been caused by the transfusion is 103, comparable to previous years. Among the serious reactions the largest categories are transfusion-associated circulatory overload (TACO), other reaction and anaphylactic reaction (Figure 1). Transfusion reactions which had a fatal outcome were reported in the categories of transfusion-associated circulatory overload (TACO), acute hemolytic transfusion reaction (AHTR), other transfusion reaction and transfusion-related acute lung injury (TRALI).

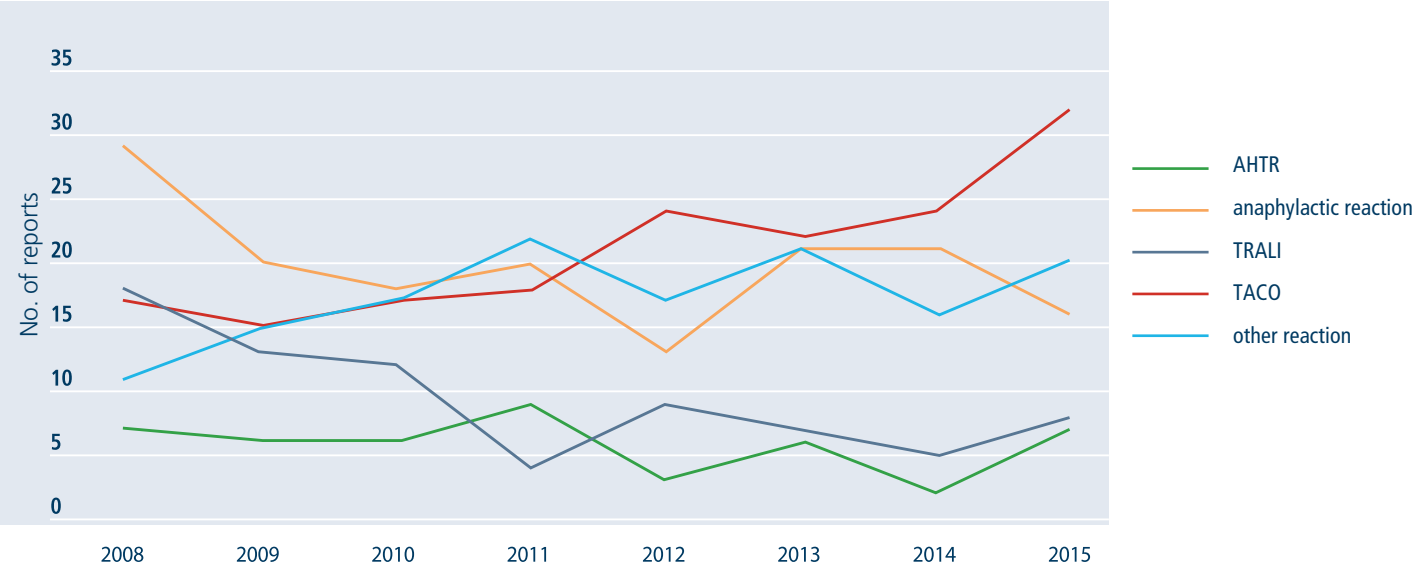
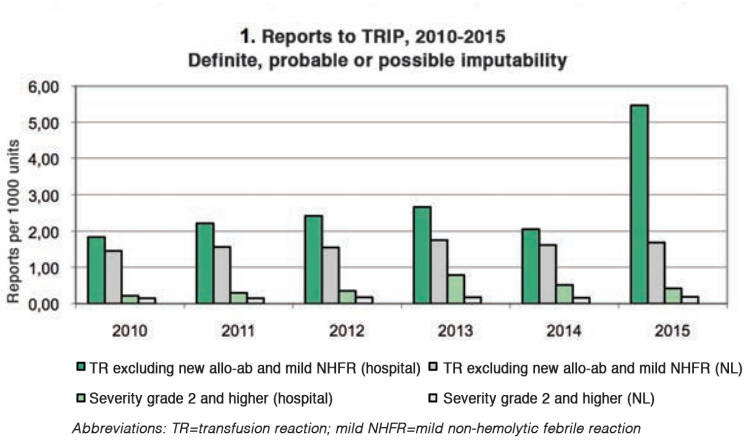


Figure 1. Reports of serious types of transfusion reaction (grade 2 or higher and definite, probable or possible imputability) in 2008-2015

Abbreviations: AHTR=acute hemolytic transfusion reaction; TRALI=transfusion-associated acute lung injury; TACO=transfusion-associated circulatory overload

The number of reported transfusion reactions per 1000 blood components transfused shows considerable variation between hospitals, as was the case in 2014 and earlier years. It can be surmised that various factors influence this, including the case mix and the safety culture in a hospital. TRIP recommends hospital blood transfusion committees to discuss the reports and provides them with benchmarking graphs showing their own reporting rate in comparison tot he national average (see illustration below).



Abbreviations: TR=transfusion reaction; mild NHFR=mild non-hemolytic febrile reaction

Transfusion-associated circulatory overload (TACO)

The overall number of reports of transfusion-associated circulatory overload is stable in comparison to last year, but there is a trend of more serious reports of definite, probable or possible imputability (2015: n=32, 2014: n=24). Measures to prevent this complication can be taken when prescribing and administering blood transfusions. TRIP and the Hemovigilance Advisory Board are developing a tool to support the assessment of TACO risk factors before transfusion; the draft tool is available on request from the TRIP office pending its validation which is in progress.

Acute hemolytic transfusion reacton (AHTR)

Among the 18 reported acute hemolytic transfusion reactions there were two with a fatal outcome (see the case history in the AHTR paragraph of chapter 3.3). In 12 out of the reported AHTR the patient had auto-immune hemolytic anemia and the hemolysis worsened in temporal association with the transfusion. The Dutch "CBO" transfusion guidelines recommend only administering red cells to patients with AIHA when clinically necessary, not aiming for a normal hemoglobin level but assessing the patient clinically after every ½-1 red blood cell unit.

Errors in the transfusion chain

Since 2013 there has been a declining trend in the reports of incorrect blood component transfused (IBCT) where the patient was, or could have been, transfused with an ABO incompatible unit (ABO risk cases, Figure 8 on page 20). Near miss incidents with a potential ABO risk, which were discovered at the time of checking the identifiers of the patient and blood unit at the bedside before transfusion, are occasionally reported to TRIP. If these near miss cases are reported, the impact of preventive measures such as the use of electronic identification of patient and unit will be shown.

In 2015, as in 2013 and 2014, the largest number of IBCT reports (n=16) concerned cases of failure to observe recommendations for preventive matching of red blood cell units for Rhesus phenotype and Kell antigens for certain patient groups in order to avoid allo-immunisation. The 2011 revision of the CBO guidelines extended the recommendations so that more groups now require Rhesus phenotyping before component selection; implementation of these changes by hospitals has contributed to these IBCT reports.

Infectious transfusion complications

The risk of infections transmitted by transfusion in The Netherlands is very low. In 2015 one non-serious reaction was reported in which transmission of bacteria, Streptococcus anginosus and Staphylococcus epidermidis, through administration of a red blood cell concentrate was judged to be likely. In addition a case of post-transfusion hepatitis E in an immunocompromised patient was judged to be of probable imputability. Blood donations are not currently tested for this type of viral hepatitis, which usually has a mild or completely asymptomatic course in patients with normal immunity.

1.2 Recommendations

Recommendation	Who?
1 Prevention of circulatory overload Promote knowledge and awareness of risk factors for circulatory overload and use of preventive interventions in at-risk patients	Hospital blood transfusion committees, professional societies of medical specialists and clinical chemists, TRIP
2 Patients with auto-immune hemolytic anemia Transfusion according to clinical need, not aiming for normal hemoglobin levels but re-assessing clinical status after ½-1 RBC unit.	Hematologists, Sanquin transfusion physicians, clinical chemists, hemovigilance officers and transfusion safety officers
3 Preventive selection of (rhesus) phenotype compatible units for specific patient groups Check whether the CBO recommendations for preventive matching of blood components for named patient groups have been implemented in the hospital protocols and are known to the professionals of the transfusion chain.	Hemovigilance officers and transfusion safety officers with the hospital blood transfusion committees
4 Near miss A. Always report to TRIP if preventive measures have been implemented or if analysis reveals an unexpected cause, so that occurrence of this type of problem can be highlighted. B. Thematic collection of information about particular types of near miss in order to support implementation of specific measures, e.g. electronic identification when collecting blood samples ("bulk" reports of blood group discrepancies).	Hemovigilance officers and transfusion safety officers in consultation with the hospital safety committee and in collaboration with TRIP

CHAPTER 2

Overview of hemovigilance results in 2015

2.1 Reports in 2015 in comparison to previous years

Summary information about the reported cases is given in the following tables and figures:

Table 1. Incidents reported to TRIP, 2008-2015

Incident	2008	2009	2010	2011	2012	2013	2014	2015	No. of hospitals with reports in 2015
Incorrect blood component transfused*	59	61	59	47	55	45	76	56	34
Near miss	55	72	70	45	50	39	33	40	14
Other incident	83	111	118	138	139	107	120	91	33
Hemolysed product	-	-	-	2	-	-	1	-	-
Total (incidents)	**197**	**244**	**247**	**232**	**244**	**191**	**230**	**187**	**50**

* *Including reports of calculated risk situations*

Table 2. Transfusion reactions reported to TRIP, 2008-2015

Reaction	2008	2009	2010	2011	2012	2013	2014	2015	Reports of grade 2 or higher#	No. of hospitals with reports in 2015
AHTR	18	18	21	17	7	11	17	18	7	13
DHTR	18	8	7	9	8	4	5	6	1	6
New allo-antibody	610	757	814	831	851	848	762	692	-	68
TACO	39	42	47	39	56	69	76	76	32	36
TA-GVHD	1	0	0	0	0	0	0	0	-	-
Hemosiderosis	5	2	4	2	0	4	16	2	-	2
NHTR	453	488	506	504	456	442	419	437	9	73
Mild febrile reaction	275	360	363	366	383	340	311	328	3	61
TRALI	21	13	17	12	9	9	6	8	8	7
Anaphylactic reaction	65	71	73	67	59	70	53	42	16	24
Other allergic reaction	171	181	184	191	180	193	153	143	1	38
Post-transfusion purpura	1	0	0	2	1	0	1	0	-	-
Other reaction	101	136	164	217	225	221	191	201	20	62
Post-tf bacteremia/sepsis	37	55	41	61	50	47	55	78	5	39
Post-tf viral infection	7	3	1	5	2	5	0	2	1	2
Post-tf malaria	0	0	0	1	0	0	0	0	-	-
Total	**1822**	**2134**	**2242**	**2324**	**2287**	**2263**	**2065**	**2033**	**103**	**92**
Total, grade 2 or higher#*	131	102	96	102	101	98	96	105		
Total reports	**2055**	**2412**	**2591**	**2629**	**2580**	**2503**	**2316**	**2247**		

 # Imputability certain, probable or possible

** Total including transfusion reactions following an incident*

Abbreviations: NHTR=non-hemolytic transfusion reaction; AHTR=acute hemolytic transfusion reaction; DHTR=delayed hemolytic transfusion reaction; TRALI=transfusion-related acute lung injury; TA-GVHD=transfusion-associated graft versus host disease; Tf=transfusion; TR=transfusion reaction

Table 3. Reports per type of blood component in 2015 compared to 2014

Type of blood component (bc)	2015						2014				
	Units distributed	Transfused units	No. of reports		Reports per 1000 bc distributed		Units distributed	No. of reports		Reports per 1000 bc distributed	
			All	Serious#	All	Serious#		All	Serious#	All	Serious#
Red blood cell concentrate	427242	410324	1830	79	4.28	0.18	428245	1819	51	4.31	0.12
Platelet concentrate	55556	53413	290	21	5.22	0.38	56883	272	24	4.82	0.42
Fresh frozen plasma	7221	11715	7	0	0.97[1]	0.00	55726	54	6	0.97	0.11
Blood management techniques[2]			3	0				25	2		
SD-plasma[3]	60885	45536	20	2	0.33[1]	0.04[1]		7	4		
Other products[4]			3					1	0		
Combinations			50[$]	3				54[$]	9		
Not stated			44	0				63	0		
Total	**550904**		**2247**	**105**	**4.08**	**0.19**		**2316**	**96**	**4.18**	**0.17**

 # Imputability certain, probable or possible

$ Including combinations with SD-plasma

1 Calculated using number of units transfused, see chapter 3.5

2 See chapter 3.4

3 SD=solvent-detergent treated plasma, Omniplasma®; number of units distributed in 2014 not known to TRIP

4 granulocyte concentrates

Table 4. Distribution of types of blood component per reporting category* in 2015

A. Incidents	RBC	Platelets	Plasma	SD-plasma$	Combination	Other#	Not stated
Incorrect blood component transfused	48	0	0	3	0	0	5
	86%	0%	0%	5%	0%	0%	9%
Other incident	79	5	0	1	2	0	3
	87%	5%	0%	1%	2%	0%	3%
Near miss	11	1	0	0	0	0	28
	28%	3%	0%	0%	0%	0%	70%
Bacterial contamination of blood	5	17	0	0	0	0	0
component	23%	77%	0%	0%	0%	0%	0%
Look-back	2	3	0	0	0	0	0
	40%	60%	0%	0%	0%	0%	0%
B. Reactions	**RBC**	**Platelets**	**Plasma**	**SD-plasma$**	**Combination**	**Other# and BMT**	**Not stated**
Acute hemolytic transfusion reaction	18	0	0	0	0	0	0
	100%	0%	0%	0%	0%	0%	0%
Delayed hemolytic transfusion reaction	6	0	0	0	0	0	0
	100%	0%	0%	0%	0%	0%	0%
New allo-antibody	654	21	0	0	12	0	5
	95%	3%	0%	0%	2%	0%	1%
Transfusion-associated circulatory	66	3	0	2	5	0	0
overload	87%	4%	0%	3%	7%	0%	0%
Non-hemolytic transfusion reaction	357	59	1	0	14	2	3
	82%	13%	0%	0%	3%	0%	1%
Mild non-hemolytic febrile reaction	305	15	1	1	4	2	0
	93%	5%	0%	0%	1%	1%	0%
TRALI	5	3	0	0	0	0	0
	63%	38%	0%	0%	0%	0%	0%
Anaphylactic reaction	9	29	0	3	1	0	0
	21%	67%	0%	7%	2%	0%	0%
Other allergic reaction	30	99	2	6	6	0	0
	21%	69%	1%	4%	4%	0%	0%
Other reaction	162	28	3	3	3	2	0
	81%	14%	1%	1%	1%	1%	0%
Post-transfusion bacteremia/sepsis	70	6	0	1	1	0	0
	90%	8%	0%	1%	1%	0%	0%

* *Smallest categories not shown*
$ *Solvent-detergent plasma, Omniplasma*
# *3 granulocyte concentrates and 3 autologous units from blood management techniques, see chapter 3.4*
% *Percentage of all reported incidents/reactions in that category*

Table 5. Transfusion reactions reported in 2008-2015 per type of blood component

Reporting category	RBC	Platelets	Plasma (incl. SD-plasma)	Combination including platelets	Combination not including platelets	Total
Acute hemolytic transfusion reaction	119	4		3	1	127
Anaphylactic reaction	104	246	116	20	10	496
Other allergic reaction	301	723	298	45	21	1388
Mild non-hemolytic febrile reaction	2552	116	18	19	10	2715
Non-hemolytic transfusion reaction	2940	505	28	81	23	3577
New allo-antibody	5780	148		136	43	6107
Other reaction	1093	204	47	32	16	1392
Post-transfusion bacteremia/sepsis	376 (4)*	37 (10)*	1	8	1	423 (14)*
Post-transfusion purpura	2	1		2		5
Post-transfusion viral infection#	15	2		5	2	24
TRALI	55	15	4	14	7	95
Transfusion-associated circulatory overload	368	31	10	20	14	443
Totaal	**13705**	**2032**	**522**	**383**	**148**	**16792**

* *(n)=number of probable or confirmed cases of TTBI as assessed by the TRIP Expert Committee*

\# *all imputability levels, including cases where transmission by the transfusion was judged to be unlikely or excluded*

Severity and imputability

Figures 2 and 3 show the severity and imputability of the reported transfusion reactions in 2008-2015. In 2015 there were more grade 4 reactions (i.e. reactions with fatal outcome; n=12) than grade 3 (7). However the numbers are too small to draw any conclusions about this. In practice it is difficult to draw a line between grade 2 and grade 3. Recognised criteria for 'life-threatening' are transfer to intensive care, requirement for ventilatory support, administration of adrenalin. It is helpful if hospitals report grade 4 reactions, even if after analysis the imputability is judged to be unlikely, because these reports give insight in the complexity of transfusion practice in seriously ill patients.

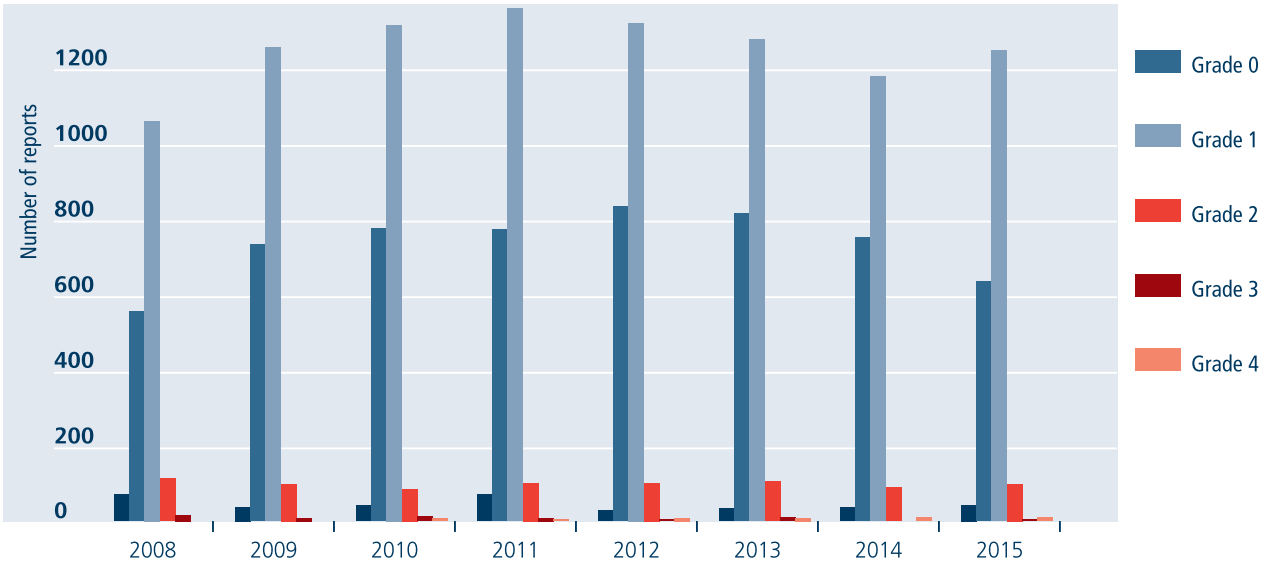


Figure 2. Severity of the transfusion reactions*, 2008-2015

**this includes reports in the transfusion reaction categories and reactions which occurred following an incident. Severity is not assessed in cases where there is no reaction.*

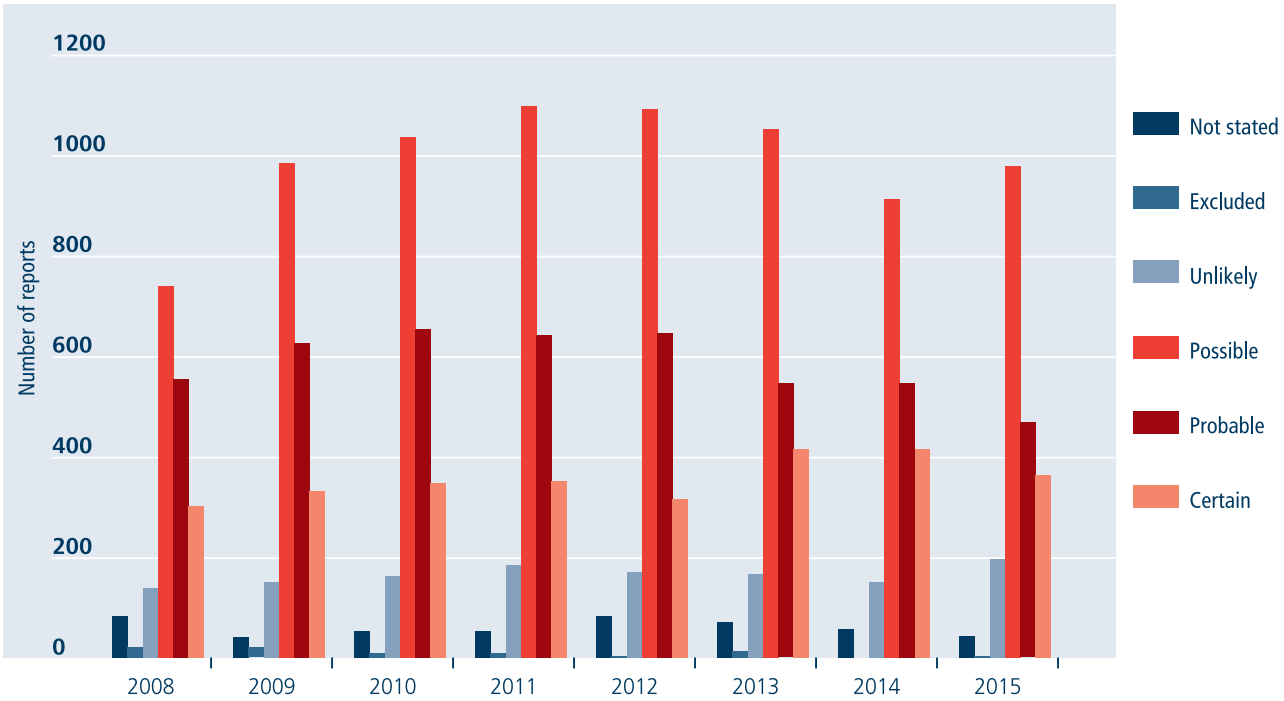


Figure 3. Imputability of the transfusion reactions*, 2008-2015
**this includes reports in the transfusion reaction categories and reactions which occurred following an incident. Imputability is not assessed in cases where there is no reaction.*

2.2 Transfusion reactions associated with platelet transfusions in 2008-2015

The number of reported transfusion reactions associated with platelet transfusions is fairly stable from year to year; the rate per 1000 units is higher than with red blood cell concentrates or plasma (Figures 4 and 5). All types of transfusion reactions can occur with platelets; the rate of allergic reactions is over twice as high as with plasma.

Furthermore non-hemolytic transfusion reactions and TRALI are reported relatively often with platelets, whereas mild non-hemolytic febrile reactions and TACO are less often reported in association with platelet transfusions (Table 5). For TACO, it is accepted that the volume of the blood component and the infusion rate are important factors. If they were the only determinants one would expect similar rates of TACO with platelets and RBC transfusions, since the volume is similar and the infusion rate for platelets is usually higher. It is likely that differences in component characteristics, such as the viscosity, play a role. Patient characteristics must also be considered, for instance older patients less often receive platelets and older patients are at greater risk of TACO.

The number of reports of post-transfusion bacteremia/sepsis in relation to the number of distributed units is similar for red blood cells and platelets. However the number of cases of Transfusion Transmitted Bacterial Infection (TTBI) was higher for platelets than for RBC, though the numbers remain small.

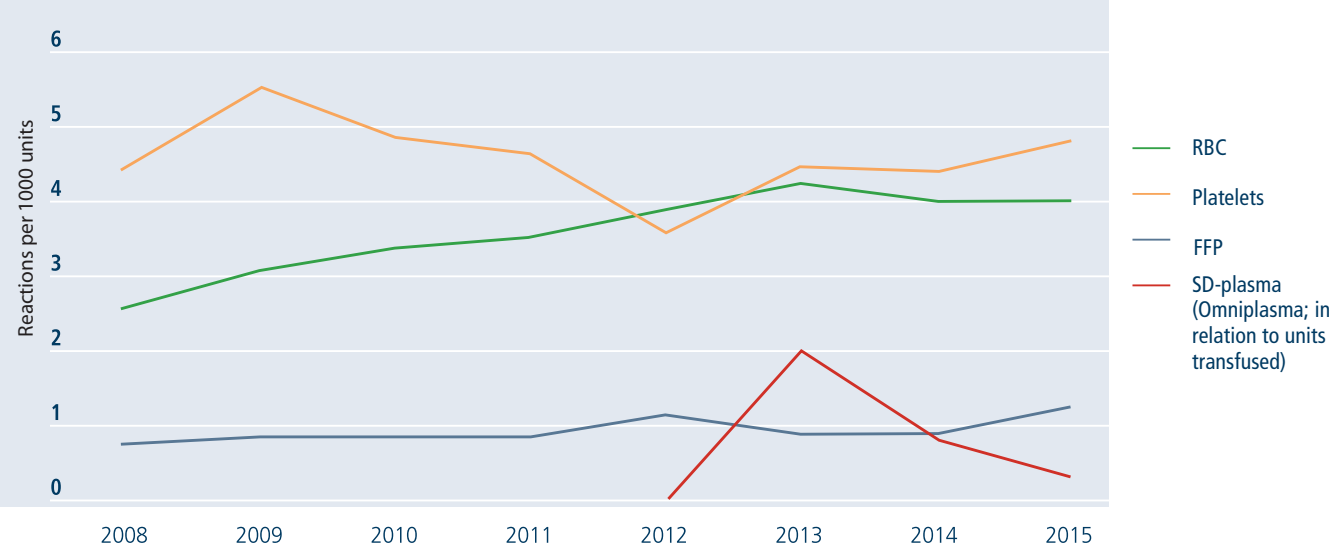


Figure 4. Number of reports per 1000 units per type of blood component

** reactions with combinations of blood component types not included*

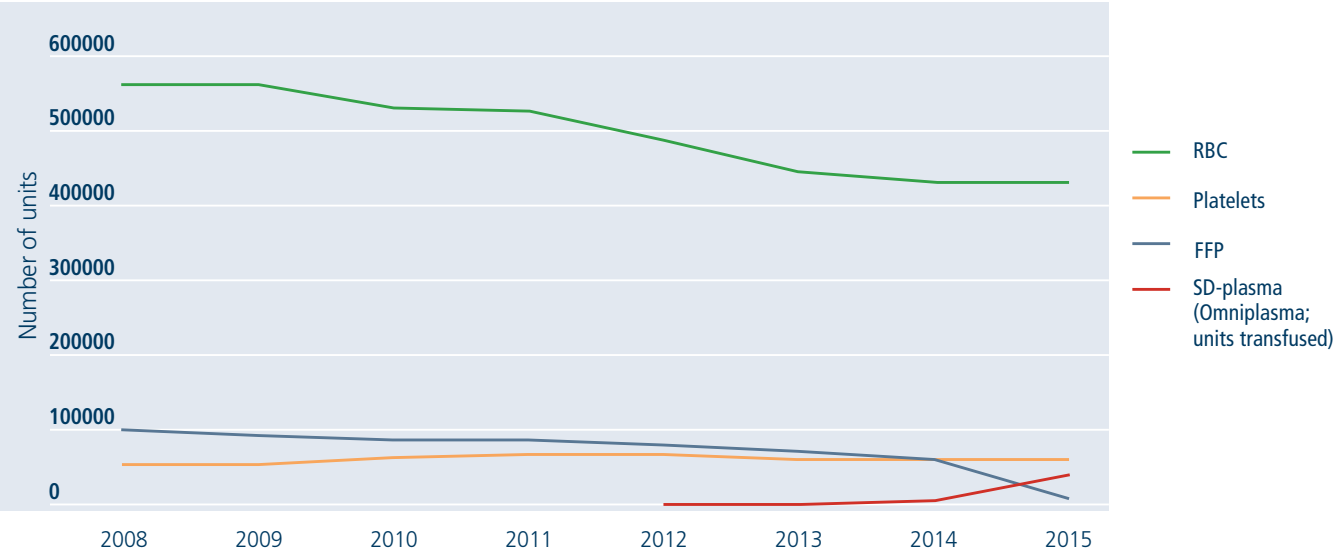


Figure 5. Distributed units per year

2.3 Overview of mandatory reports of serious transfusion reactions

Each year TRIP compiles an overview of the mandatory reports of serious adverse reactions and events (SARE) in the transfusion chain. As recommended by the "Common Approach" document provided by the European Commission, only reactions of definite, probable or possible imputability are included in the overview. Reactions which occurred after transfusion of an incorrect blood component or after an other incident are included in the appropriate reaction category in the overview. Serious adverse reactions or events associated with (only) SD-plasma are not reported to the European Commission because of the different legal status of the product (SD-plasma is classed as a medicine) and different reporting route; they have not been included in Table 6.

Tabel 6. Number and imputability of reactions of grade 2 and higher in 2015

Severity	Grade 2			Grade 3			Grade 4	
Imputability	Certain	Probable	Possible	Certain	Probable	Possible	Probable	Possible
Acute hemolytic transfusion reaction	3	3	-	1	-	-	1	1
Delayed hemolytic transfusion reaction	-	-	1	-	-	-	-	-
Anaphylactic reaction	3	8	4	-	-	-	-	-
Other allergic reaction	-	1	-	-	-	-	-	-
Mild non-hemolytic febrile reaction	-	1	2	-	-	-	-	-
Non-hemolytic transfusion reaction	1	1	7	-	-	-	-	-
Other reaction	1	2	15	1	-	-	-	1
Post-transfusion bacteremia/sepsis	-	-	5	-	-	-	-	-
Post-transfusion viral infection	-	1	-	-	-	-	-	-
TRALI	1	1	3	-	-	1	-	2
Transfusion-associated circulatory overload	2	13	9	-	3	1	1	2
Total	**11**	**31**	**46**	**2**	**3**	**2**	**2**	**2**

Figure 6 shows the numbers of serious reactions (grade 2 or higher) in 2008-2015. The graph includes reactions which occurred after transfusion of an incorrect blood component or another type of incident. In order to give a complete picture the graph also includes the two serious reactions (an anaphylactic reaction and a case of TACO) which were associated with transfusion of SD-plasma.

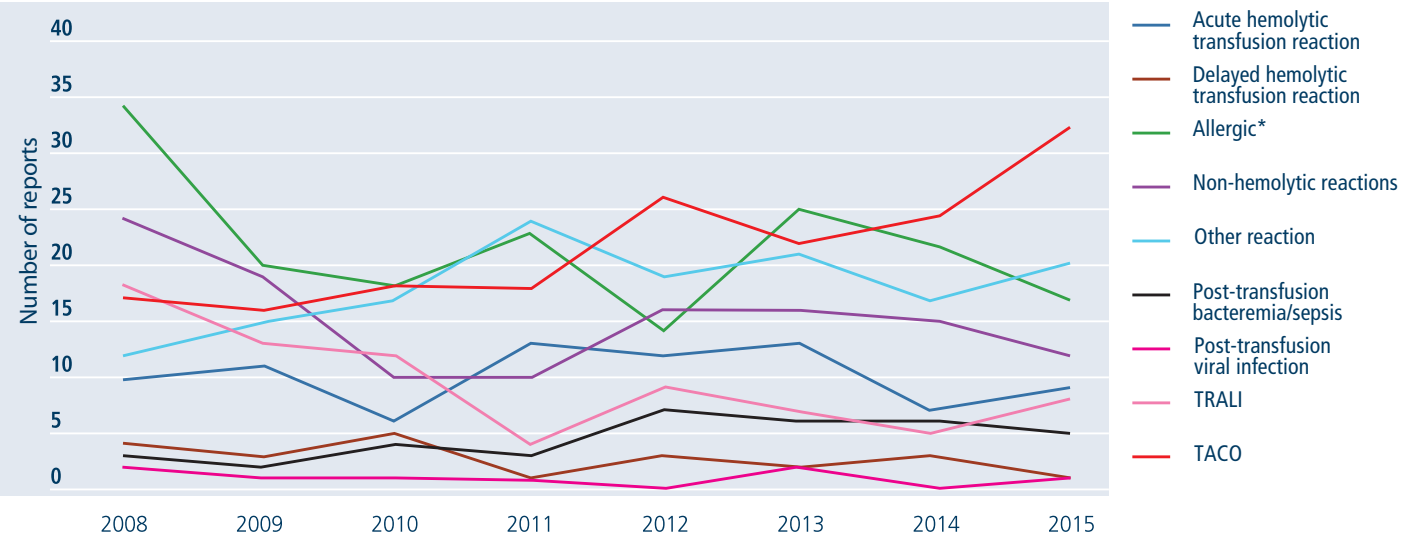


Figure 6. Serious reactions# (certain, probable or possible imputability), 2008-2015

** Anaphylactic reactions + other allergic reactions*

 # Post-transfusion purpura, allo-antibody formation, hemosiderosis and post-transfusion other infection (accounting for 19 serious reports in total) not shown. Reactions following incidents have been counted in the appropriate reaction category.

2.4 Deceased patients and transfusion reactions (grade 4)

In 2015 there was a total of 13 transfusion reaction reports of grade 4 severity.
They are summarised in Table 7.

Table 7. Reports where a patient died after a transfusion reaction (n=13 in 2015)

Reporting category	Gender, age	Blood component	Imputability	Clinical situation
Acute hemolytische TR	M, 74	RBC	Probable	See case description in AHTR paragraph
Acute hemolytische TR	V, 96	RBC	Possible	See case description in AHTR paragraph
TRALI	V, 65	RBC	Possible	Pt. with pancreatitis on CT-scan; respiratory deterioration after Tf, expired within 15 mins
TRALI	V, 77	Platelets	Possible	Multiple myeloma and pancytopenia. <1h after Tf: desaturation to 70%, CXR consistent with TRALI. Not ventilated because of palliative setting.
TACO	V, 78	RBC	Probable	Admitted with sepsis; desaturation and clinical deterioration <4h after Tf, enlarged heart on CXR. History of heart failure; patient declined ICU care
TACO	M, 68	RBC	Possible	Cardiac history and impaired renal function; worsening of respiratory status and increase of vascular markings on CXR after Tf; ventilated but no diuresis in response to treatment
TACO	V, 77	RBC	Possible	Myelodysplastic syndrome. Became dyspneic after Tf, chest X-ray consistent with circulatory overload; deterioration despite diuresis in response to medication
TACO	V, 71	RBC and platelets	Unlikely	Trombocytopenia and hemorrhage after SCT: respiratory deterioration after Tf, CXR shows (nonspecific) infiltrative changes and pleural fluid
Other reaction	M, 73	Platelets	Possible	Ventilated septic patient with PCP, became hemodynamically unstable
Other reaction	V, 39	SD-plasma and RBC	Unlikely	Liver transplantation; hypotension/asystole
Other reaction	M, 83	RBC	Unlikely	Previous CVA, recent diagnosis of leukemia; died during RBC transfusion
Non-hemolytic TR	M, 57	RBC	Unlikely	Extensive medical history incl. oesophageal varices and treatment complications; became febrile during Tf and then died
Post-transfusion bacteremia/sepsis	M, 44	RBC	Unlikely	Bacteremia (Pseudomonas aeruginosa) in immunodeficient patient

Abbreviations: TR=transfusion reaction; RBC=red blood cells; TRALI=transfusion-related acute lung injury; pt.= patient; Tf=transfusion; CXR=chest X-ray; TACO=transfusion-associated circulatory overload; SCT=hematopoietic stem cell transplantation; PCP=pneumocystis pneumonia

Table 8 summarises the grade 4 reactions with certain, probable and possible imputability reported to TRIP since 2008. The most important categories are transfusion-associated circulatory overload (10), other reaction (9) and TRALI (6), followed by acute hemolytic transfusion reaction (5) and post-transfusion bacteremia/sepsis (4).

Table 8. Grade 4 reports (certain, probable or possible imputability) 2008-2015

Reaction	2008	2009	2010	2011	2012	2013	2014	2015	Total
AHTR	-	1	-	1	1	-	-	2	5
Other reaction	1	-	3	1	1	2	-	1	9
Post-transfusion bacteremia/sepsis*	-	1	-	-	1	-	2	-	4
Post-transfusion purpura	-	-	-	-	-	-	1	-	1
TRALI	-	1	2	-	1	-	-	2	6
Incorrect blood component transfused	1	-	-	-	-	-	-	-	1
Transfusion-associated circulatory overload	-	-	2	1	1	-	3	2	9
Total	**2**	**3**	**7**	**3**	**5**	**2**	**6**	**7**	**35**

** The report in 2009 and one in 2014 were confirmed cases of transfusion-transmitted bacterial infection.*

2.5 Variation between hospitals in number of reports in relation to transfused blood components

Last year the annual hemovigilance report included an analysis of the number of reports from each hospital in relation to the number of blood components transfused. This should be comparable for the transfusion reactions. Statistically the variation in rate should be smallest when looking at hospitals with highest blood use. The number of reactions per 1000 blood components in 2015 showed considerable variation as in 2014, even between the large hospitals (Figure 7A). The variation in rate is less for the serious reactions (Figure 7B).

Each year TRIP provides benchmarking graphs to the hospitals, showing how their own rate of reports in each reporting category per 1000 units - providing they were submitted before the annual closing date - compares to that of other hospitals. It can be presumed that part of the variation is related to staff attention and reporting practices. On the advice of the TRIP Advisory Council TRIP actively circulated the benchmarking graphs to the hospital blood transfusion committees after publication of the 2014 annual report.

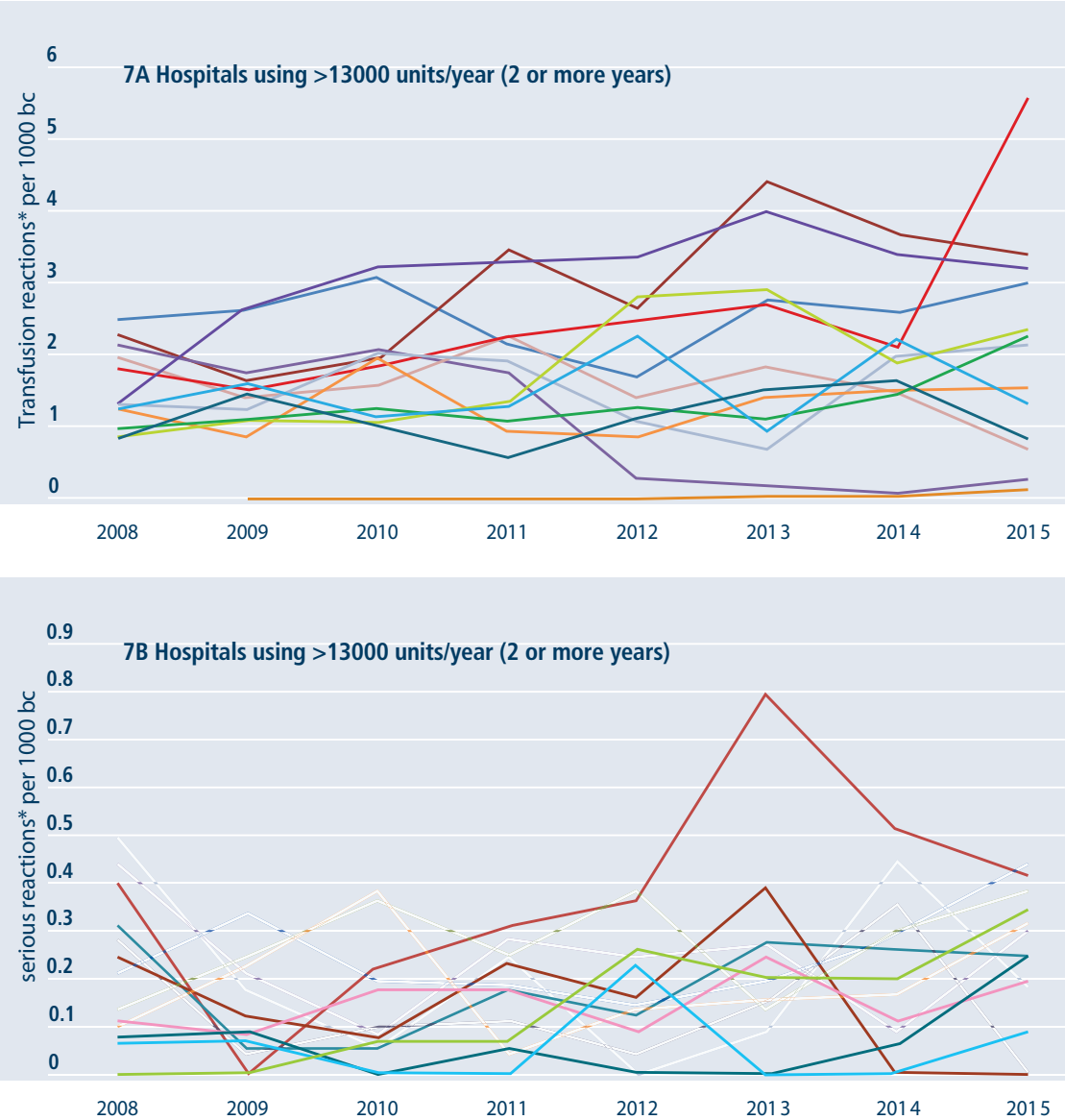


Figure 7 a-b. Reported transfusion reactions per year in relation to blood use in hospitals with high blood use; A all severity levels; B serious reports, grade 2 or higher

** Reports of certain, probable and possible imputability, excluding new allo-antibody formation and mild non-hemolytic febrile reaction, as these are not systematically reported by all hospitals.*

2.6 Late reports from previous years

Besides variation in reporting level, late receipt of reports from one or several hospitals also has a negative effect on the potential for drawing valid conclusions and recommendations from the hemovigilance information.

There were 56 late 2014 reports, submitted by nine hospitals after the closing date for the 2014 annual TRIP report (there were 48 late reports from 2013 in the 2014 report); seven were of severity grade 2 (Table 9). The late reports have now been reviewed according the standard procedures and included in all relevant tables and figures of this report. One hospital submitted 13 reports of hemosiderosis. In chapter 3.1 the late reports of incorrect blood component transfused are discussed.

Tabel 9. Late 2014 reports

Reporting category	Severity					No reaction, severity not applicable
	Not stated	1	2	3	4	
Incorrect blood component transfused						14
Near miss						5
Other incident						9
Anaphylactic reaction			2			
Other allergic reaction		2				
Hemosiderosis	13					
Mild non-hemolytic febrile reaction			2			
Non-hemolytic transfusion reaction		3	2			
New allo-antibody formation	1					
Other reaction		1				
TRALI			1			
Transfusion-associated circulatory overload		1	1			

CHAPTER 3

Discussion of reports per category

3.1 Incidents in the transfusion chain

Incorrect Blood Component Transfused (IBCT)

All cases in which a patient was transfused with a component that did not fulfil all the requirements of a suitable component for that patient, or that was intended for a different patient.

- 52 IBCT reports from 36 hospitals, 1-4 reports per hospital
- 12x reaction reported (registered as additional category): 3x AHTR; 2x mild NHFR; 7x new allo-antibody formation (Table 10)
- 6 reports with additional category IBCT/IBCT in the past from 6 hospitals (Table 11)
- 4 reports from 2 hospitals classified as calculated risk
- 13 IBCT reports from 2014 were submitted after the closing date for the 2014 annual report.

As in previous years, TRIP assessed all the reports of incorrect blood component transfused to establish which was the worst potential risk to which a patient was exposed through transfusion of an incorrect blood component. For instance in the case of a mix-up of units intended for two patients, if patient X receives the blood which was intended for patient Y the worst risk is that the unit could be ABO incompatible – though it may happen to be ABO compatible. The descriptions of the risk groups which TRIP includes in this analysis can be found on www.tripnet.nl. In addition the reports are classified according to the first error (in time) which led to the transfusion of an incorrect unit: this first error is classified according to the type of error, for instance identification error, communication error, selection error. The step in the transfusion chain when the first error occurred is also noted; see the TRIP diagram representing the transfusion chain on www.tripnet.nl.

Since 2013 there has been a declining trend in the IBCT cases in which the patient could have been, and in some cases actually was transfused with an ABO incompatible unit. As in 2013 and 2014, the largest group of IBCT reports was that of cases where there was failure to follow guidlines for preventive matching for specific patient groups in order to avoid allo-immunisation (prevention of Irregular antibody formation, prevention irrab; n=16), see Figure 8. The 2011 revision of the national "CBO" blood transfusion guidelines stipulated more groups of patients who should receive preventively matched blood, and who therefore need to be typed for Kell and Rhesus phenotype before transfusion; this has probably contributed to the occurrence of these IBCT reports.

In 2015, 17% of the IBCT reports (n=13) from 2014 were submitted after the closing date for the annual report for that year. Late submissions make it difficult to draw conclusions as to trends and specific problems, and reduce the value of the annual report. The late reports have been included in the relevant graphs and tables of the 2015 report. It is noteworthy that 5 of the reported incidents concern cases of failure to take a recent ABO incompatible organ transplantation into account.

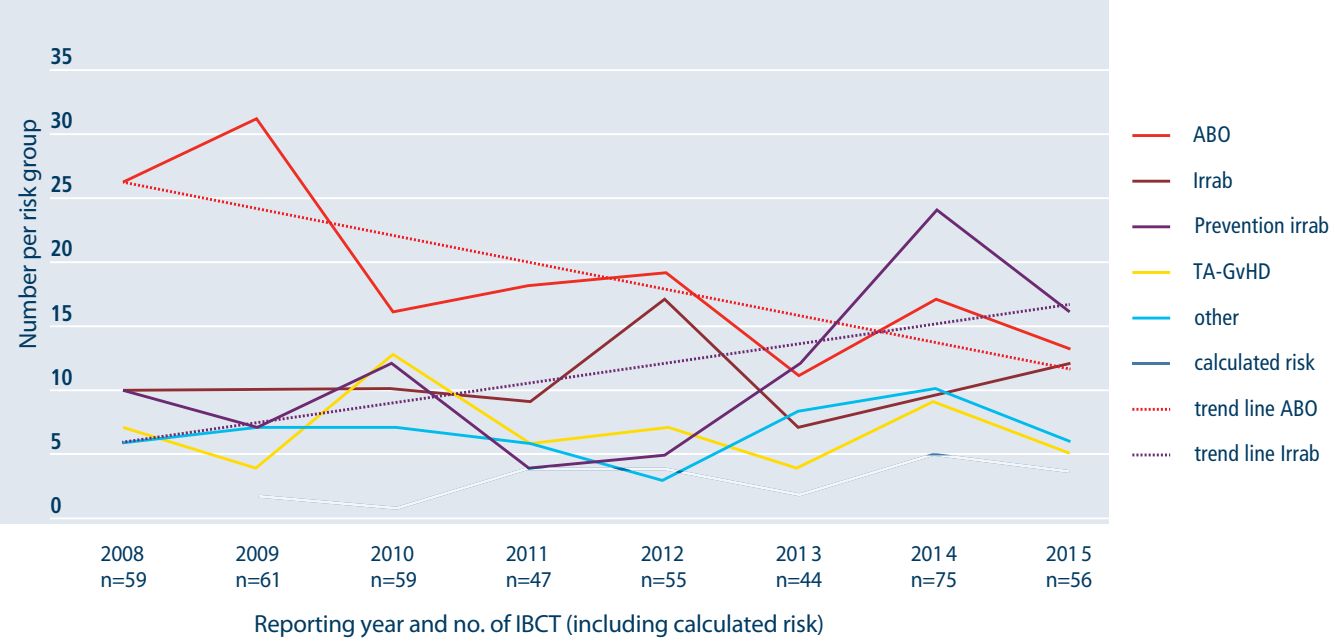


Figure 8. Incorrect blood component transfused broken down according to risk group, 2008-2015

Abbreviations:
ABO=risk of an ABO incompatible transfusion
Irrab=risk of an irregular antibody incompatible transfusion
Prevention irrab=guidelines not followed with regard to prevention of irregular antibody formation
TA-GVHD=risk of transfusion-associated graft versus host disease (after transfusion of a non-irradiated blood component)

- Among the 13 ABO risk cases, in 6 cases (46%) by chance an ABO compatible blood component was transfused; 5x the unit also happened to be rhesus D compatible and 1x O pos red cells were administered to an A neg recipient who did not need a blood transfusion; 1x the ABO rhesus blood group was not stated in a report concerning a stem cell transplant recipient
- In 3 reports, incompatible SD-plasma (blood group O plasma and group A recipient) was transfused in an emergency situation with massive blood loss
- 3x ABO incompatible RBCs were transfused, in 1 case they were also rhesus D incompatible
- In 12 cases with irregular antibody risk, 2x the blood happened to be compatible with the known antibody, 2x the antigen type of the red cell unit component with respect to the known antibody is not known and in the other 8 cases the unit was not compatible.

Table 10. Clinical symptoms after transfusion of an incorrect blood component in 2015

IBCT Risk group	Blood component	Reaction (additional category)	Imputability*	Severity*
ABO	RBC	AHTR	certain	2
	RBC	AHTR	certain	1
Irrab	RBC	AHTR	probable	2
	RBC	Milde NHKR[$]	unlikely	1
	RBC	Milde NHKR[$]	unlikely	1
Prevention irrab		New allo-antibody:		
	RBC	Anti-C	certain	
	RBC	Anti-c	certain	
	RBC	Anti-E	certain	
	RBC	Anti-E, anti-Jkb, anti-Leb	certain	
	RBC	Anti-E	not stated	
	RBC	Anti-c[&]	probable	
	RBC	Anti-E	not stated	

* *Imputability and severity grade apply to clinical symptoms of a transfusion reaction; new allo-antibody formation is severity grade 0 by definition*

[$] *mild increase in temperature in patient with recurrent febrile episodes, unit happened to be negative for the cognate antigen*

[&] *female patient < 45y*

Table 11. 2015 Reports with additional category IBCT/IBCT in the past *

Reaction category	IBCT risk group (additional category)	Description: Analysis following the reaction reveals	Number of IBCT (additional category)
Reaction category	TA-GVHD	Selection error → failure to select irradiated RBCs	1
		Selection error → failure to select irradiated RBCs	1
Non-hemolytic transfusion reaction	Prevention irrab	Communication error → in the past, patient not flagged as multiply transfused and this was not noted on lab requests, consequently patient not phenotyped	several
New allo-antibody formation	Prevention irrab	Selection error → in the past, need for rhesus sub-phenotype matching not taken into account in multiply transfused patient	2
		Communication error → in the past, patient not flagged as poly-transfused and this was not noted on lab requests, consequently patient not phenotyped	several
		Selection error → in the past, need for rhesus phenotype matching not taken into account in patient with known irregular antibody	1

Abbreviations: Irrab=irregular allo-antibody; RBC=red blood cellEC=erytrocytenconcentraat

* *IBCT or IBCT in the past is recorded as additional category if the error was discovered following a reaction*

Near miss

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

- 40 near miss reports from 15 hospitals, range 1-9 reports per hospital
- In 25 incidents (62.5%) there was a mix-up of patients, labels, blood samples, blood components or testing materials
- 18x the mix-up was detected because there was a blood group discrepancy
- In one case there was a calculated risk situation where in the end the patient did not need transfusion
- None of the near miss cases mentions CyberTrack or a similar verification system as an important factor which led to timely discovery of the mistake.

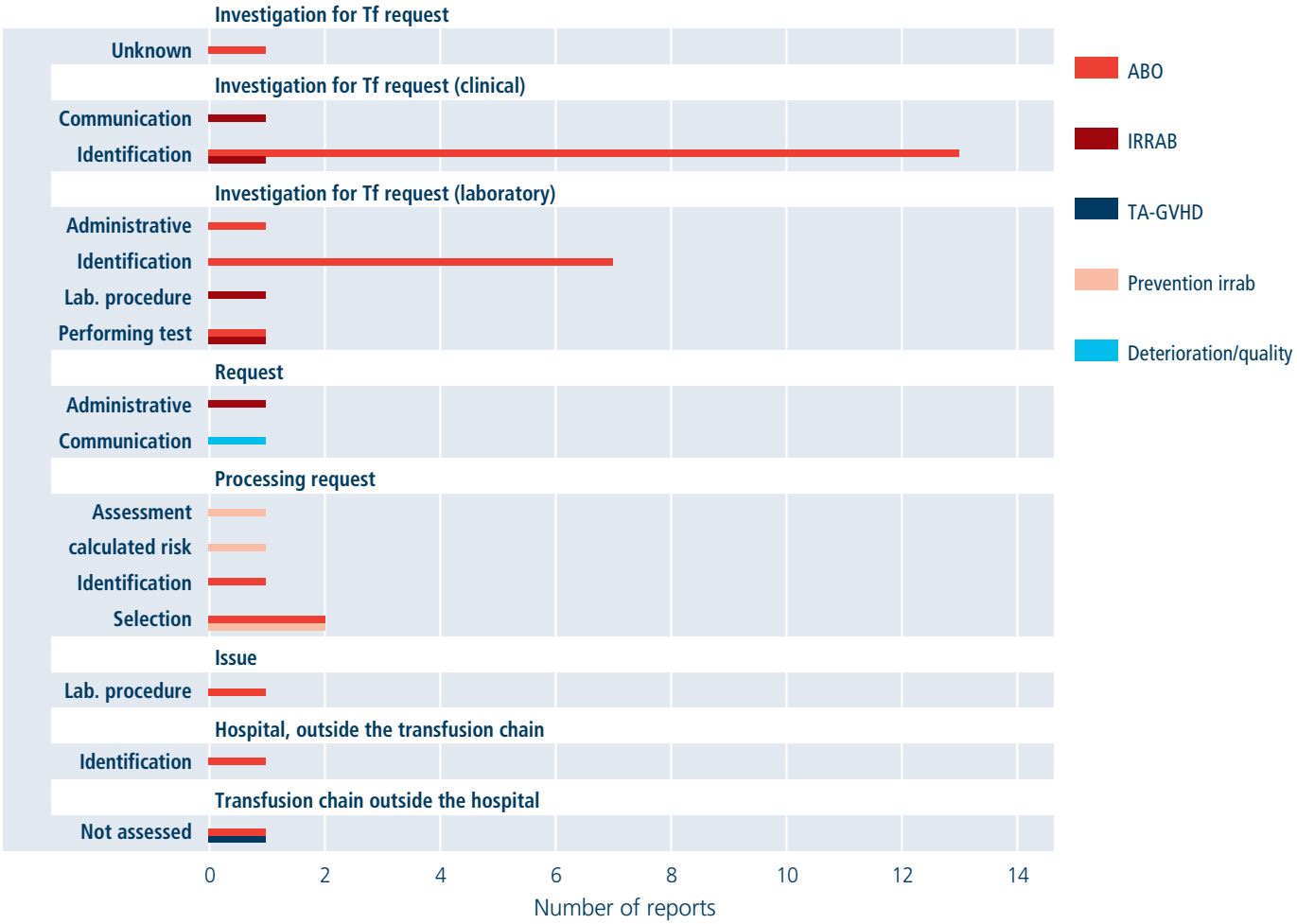


Figure 9. Near miss reports in 2015: type of error and step in the transfusion chain, broken down by risk group

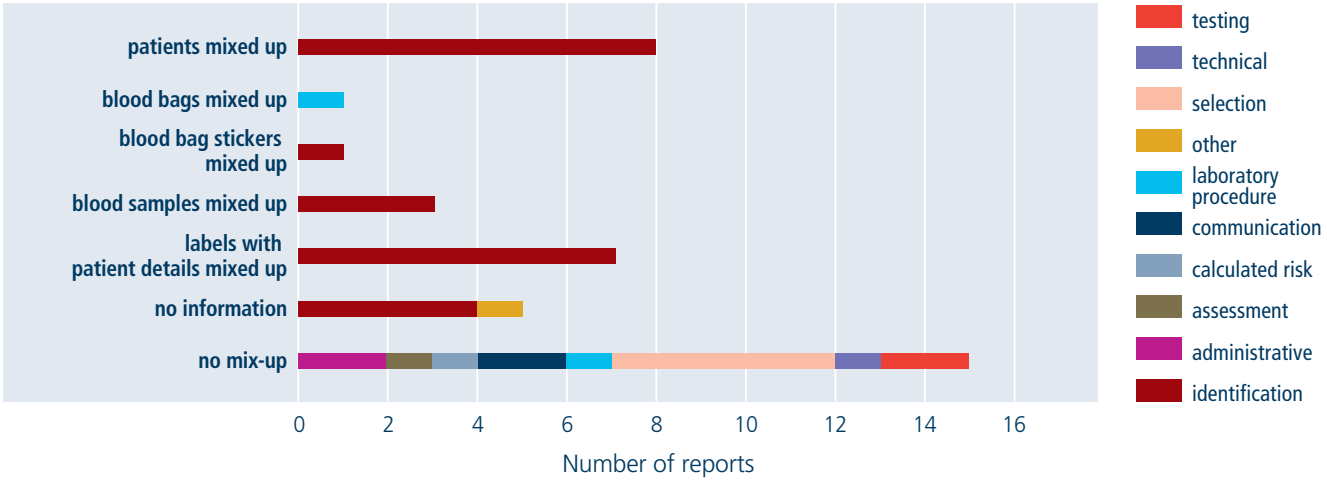


Figure 10. Near miss reports in 2015, type of mix-up broken down according to type of first error

Other incident (OI)

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

- 91 OI reports from 32 hospitals, 1-10 reports per hospital
- 9x OI associated with a reaction (additional category): other reaction (7x); other allergic reaction (1x) and mild non-hemolytic febrile reaction (1x)
- Mix-ups occurred in 8 reports: mix-ups of blood samples,type of blood component or labels/forms with blood component details
- 19 reports in other categories recorded OI as an additional category

One of the larger subgroups of OI in 2015 is that of (nearly) an unnecessary transfusion (n=23), among which in 4 cases the error was discovered before transfusion but 3x the unit still had to be destroyed although this could have been avoided by timely appropriate action.The largest subgroup is formed by reports of loss of a blood component, excluding cases of unnecessary transfusion (n=36). In 16 of these cases the loss of the blood component is regarded as avoidable. For instance, there could be problems in the pre-transfusion observations (e.g. febrile patient or refusal of transfusion), followed by failure to return the unit to the transfusion laboratory in timely fashion. In the other 20 reports, where loss of the component is regarded as unavoidable, 9x the unit was lost through accidental puncturing at the time of administration and 9x infusion failed through IV line problems. Among the remaining OI reports there were small clusters involving delay in starting transfusion (n=7), with loss of a blood component in two cases, wrong transfusion speed (n=8), use of incorrect IV fluid to flush the line (n=3) and incorrect, wrongly completed or lost forms (n=5).

The additional category of other incident was most often recorded (n=12) because a transfusion reaction was not reported, or not reported in timely fashion to the transfusion laboratory. One OI noted as an additional category related to the discovery, on analysing a non-hemolytic transfusion reaction, that the blood component was being administered through the same IV line as an anaesthetic drug; one, with a case of transfusion-associated circulatory overload flagged the administration of a non-indicated third unit (Hb 6.2 mmol/L after 2 RBC units).

3.2 Infectious transfusion complications

Bacterial problems associated with blood transfusion

Post-transfusion bacteremia/sepsis

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

Bacterial contamination of a blood component

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

Table 12 gives an overview of the reports concerning bacterial problems associated with blood transfusion in 2010-2015. Explanations of the reporting categories and additional categories can be found in diagrams on www.tripnet.nl. The diagrams also show how reports are subdivided and how TRIP, together with the Expert Committee, assesses the possibility of a transfusion-transmitted bacterial infection (TTBI) based on the findings of microbiological investigations. Further on in this chapter, the numbers of reports in 2015 are given for each stage of the arrow representing this assessment (Figure 11).

Table 12. Overview of reports of bacterial problems, 2010-2015

	2010	2011	2012	2013	2014	2015
Bacterial contamination of blood component (including positive bacterial screening)	44	43	42	25	12	15
Bacterial contamination of blood component (including reports of positive bacterial screening) as additional category	17	19	16	10	14	7
Post-transfusion bacteremia/sepsis	41	61	50	47	55	78
(cases of TTBI as assessed by experts)	(3)	(2)	(1)	(2)	(2)	(1)
Post-transfusion bacteremia/sepsis as additional category (not TTBI)	17	13	14	6	10	4

Post-transfusion bacteremia/sepsis

- 78 reports of post-transfusion bacteremia/sepsis from 41 hospitals, 1-6 reports per hospital
- 2x reported with additional category of bacterial contamination of blood component, see Cases 1 and 2, Figure 11 and Tables 12 and 14
- 1 report classified as TTBI by the expert committee: TTBI associated with RBC transfusion, probable imputability (Case 1)
- For 1 report of a different transfusion reaction (transfusion-associated circulatory overload confirmed by chest X-ray), post-transfusion bacteremia/sepsis was recorded as an additional category because a clinically relevant positive blood culture result was returned
- In 23 cases the patient had a pre-existent infection
- Subdivision into patient groups:
  - 23 hemato/hemato-oncology patients (7 with pre-existing infection, 2 recently transplanted)
  - 21 gastro-enterology/hepatology patients (6 with pre-existing infection, 8 recently operated)
  - 25 patients in other specialties (10 with pre-existing infection, 10 with recent operation, intervention or hemodialysis
  - 9x no details about medical problem or clinical situation given.

Case 1 (TTBI)

A patient with hemato-oncological condition is to receive two units of RBC on the day ward. The first RBC unit has been given without any problems and the second is started at 4 pm. Roughly 45 minutes later, nearly all the bag has been infused and the patient complains of palpitations and feeling unwell. The temperature has risen by more than 2°C and the blood pressure has gone up slightly.

The transfusion is halted and blood samples, including blood cultures, are taken to investigate the transfusion reaction; 2 mg Tavegil is administered. An ECG shows no abnormalities. In the evening the patient feels better and the temperature has gone down. The patient is allowed to go home but will contact the hospital if there is a recurrence of temperature or other symptoms.

The next day a positive result is obtained from the patient's blood culture and soon afterwards the culture taken from the remnant of the unit proves positive. All cultures yield the same bacterial species: Streptococcus anginosus species and Staphylococcus epidermidis (coagulase negative staphylococcus, CNS). In all likelihood the bacteria were transmitted from the blood unit to the patient.

As far as is known the patient had no further symptoms and did not receive any antibiotics. At the next check-up a week later a blood culture was taken, which gave negative results. Presumably the patient's immune system cleared the bacteremia.

TRIP report:

Post-transfusion bacteremia/sepsis, additional category bacterial contamination of blood product; imputability probable, severity grade 1.

This case was presented to the TRIP experts and judged to be a probable case of Transfusion Transmitted Bacterial Infection (TTBI).

Case 2 (post-transfusion bacteremia/sepsis)

A child with acute lymphatic leukemia receives a unit of red blood cells. After the unit has been infused the patient develops rigors and a slight rise in temperature. On laboratory investigation of the transfusion reaction only the patient's blood culture and culture of a sample from the bag reveal abnormalities. However the positive cultures from the patient's blood and the unit do not yield the same bacterial species: the blood culture is positive for Pseudomonas aeruginosa and the culture from the unit shows growth of Staphylococcus capitis.

TRIP report:

Post-transfusion bacteremia/sepsis with additional category bacterial contamination of blood component, imputability possible and severity grade 1.

On review of the case with the TRIP experts it was concluded that in view of the non-identical bacterial species the criteria for Transfusion Transmitted Bacterial Infection (TTBI) are not met.

Bacterial contamination of blood component

In the past (2008-2013) separate TRIP reporting categories were in use for positive bacteriological screening and bacterial contamination of a blood component. In cases where initial positive results (colour change in bottle) of the bacteriological screening of a platelet unit were not confirmed by a positive culture and identification of a species – these cases were classed as positive bacterial screening – there could have been bacteria in the sample. For safety's sake Sanquin follows the same procedure for all screening-positive units, whether or not bacteria are confirmed. In 2013 the TRIP advisory board decided there was no value in maintaining separate reporting categories based on that distinction. Thus all cases detected by Sanquin are reported as bacterial contamination of blood component; hospitals are requested to report cases to TRIP if the patient had symptoms during or after transfusion (sometimes this was only noted in retrospect) or where the information that a unit had (presumably) been contaminated had consequences for a patient who had received such a unit. For instance, in some cases prophylactic antibiotics may be prescribed or extra investigations ordered. Each year Sanquin provides an overview of the total numbers (Table 13).

Table 13. Overview of bacterial screening of platelet concentrates by Sanquin, 2010-2015

Total numbers (Sanquin)	2010	2011	2012	2013	2014	2015
Platelet concentrates with initial positive result	332	321	238	165	214	190
Units already transfused (Platelet concentrates and associated red blood cell units)	106	125	90	83	80*	82#

* *1x Sanquin was informed that the patient had had a reaction*

\# *3x mild reaction reported to Sanquin, no serious reactions; for 6 units no response was received from the hopsital.*

Reports to TRIP from hospitals

- 15 reports of bacterial contamination of a blood component (13x Propioni bact. sp.; 1x Bacteroides sp.; 1x species not stated) following notification by Sanquin, 9 reporting hospitals, 1-5 reports per hospital (Figure 11).
- 6 reports of bacterial contamination of a blood component as an additional category: unit cultured by the hospital when investigating a transfusion reaction (see Figure 11 and Table 14).
- For 1 patient with post-transfusion bacteremia/sepsis and additional category of bacterial contamination of a blood component the same species of bacteria was found in patient's blood culture and a sample from the unit - this case was judged to be a case of TTBI and is discussed under post-transfusion bacteremia/sepsis (see Tables 12 and 14, Figure 11 and Case 1).

Table 14. Overview of reactions with additional category of bacterial contamination of a blood component

Clinical features	Blood component culture (performed by hosp.)	Reaction	Total	Patient blood culture				Patient blood culture not performed or no info
				CNS	Pseudomonas sp.	Strept. sp.	No growth	
TR with features suggestive of bacteremia* in patient without pre-existing infection	Strept. sp. and CNS	Post-transfusion bacteremia/sepsis	2	x		x		
	Staphylococcus sp.				x			
	Strept. sp. and Granulicatella adiacens	Other reaction	1				x	
	Acinetobacter sp.	Mild NHFR	1					x
(Only) itching, facial swelling and rash	Serratia marcescens	Other allergic reaction	1				x	
(Only) dyspnea, hypertension and tachycardia	Gram negative rods	TACO	1				x	
Total			**6**					

Abbreviations: TR=transfusion reaction; pt=patient; bc=blood component; hosp.=hospital; sp=species; CNS=coagulase negative staphylococci; Strept=streptococci

** Symptoms: increase in temperature and/or rigors, with or without other symptoms*

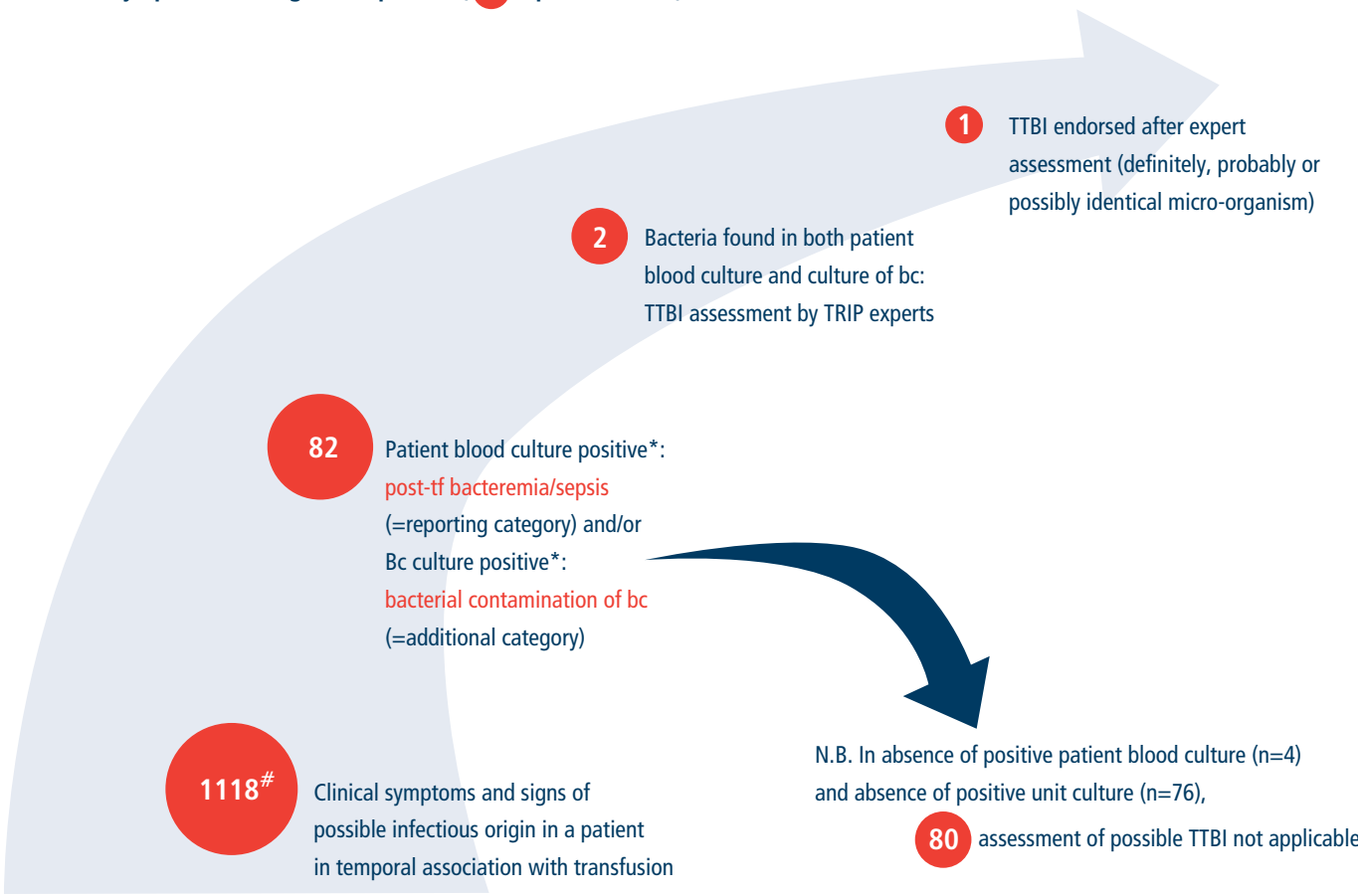


Figure 11. TTBI assessment, route A*

Abbreviations: pt=patient; bc=blood component; tf=transfusion; TTBI=transfusion-transmitted bacterial infection

 # Number of reports in 2015 (in relevant categories: non-hemolytic TR, mild non-hemolytic febrile reaction, post-tf bacteremia/sepsis, transfusion-associated circulatory overload, transfusion-associated acute lung injury, anaphylactic reaction, acute hemolytic TR, other reaction

** Culture result should be deemed relevant*

Post-transfusion viral infection and viral infection of a blood component

Post-transfusion viral infection

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

Viral contamination of blood component

Retrospective analysis by Sanquin demonstrates viral contamination of a blood component which has already been administered to a patient.

Information from hospitals

In 2015 there were two reports of post-transfusion viral infection. One report was of hepatitis E which was diagnosed in a patient 2.5 months after transfusion of a platelet concentrate; Sanquin's testing of the archived samples demonstrated a low concentration of HEV in the unit (insufficient material for investigating genetic identity, imputability probable). The second report was of an HIV infection, however the investigations of the donors by Sanquin exclude transmission by the transfusion.

Look-back by the supplier

Retrospective notification of a possibly infectious donation, leading to investigation of the recipient for that infection, but where no infection is demonstrated in the recipient.

Information from hospitals

In 2015 TRIP received five reports from hospitals about look-back notifications from Sanquin. In one of these cases, testing of the recipient of a unit donated in 2014 by a donor who subsequently seroconverted for HIV, yielded a coincidental serological finding that the recipient had had hepatitis B in the past. The donor in question also had laboratory results consistent with previous hepatitis B but had never had test results indicating HBV viremia, so transmission by the transfusion is unlikely.

TRIP requests hospitals to continue to send reports to TRIP if look-back investigations give any findings suggestive of an infection in the patient. In other look-back cases it is not necessary to submit a TRIP report because Sanquin provides summary figures to TRIP about seroconversions, recalls and look-back investigations. These revised reporting instructions were circulated when the new TRIP reporting system was introduced at the beginning of 2016.

Information from Sanquin

In 2015 there were 5 seroconversions (3x HBV, 2x syphilis). Sanquin conducted look-back investigations according to protocol and no transmitted infections were found.

3.3 Non-infectious transfusion reactions

Transfusion-associated circulatory overload (TACO)

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

- 76 reports from 39 hospitals, 1-7 reports per hospital
- 3x additional category of other incident (2x unnecessary transfusion, 1x excessive transfusion speed)
- 6 reports (2x TRALI, 1x NHTR, 1x mild NHFR, 1x post-Tf bacteremia/sepsis and 1x other reaction) record TACO as an additional category

The number of TACO reports of severity grade 2 or higher (n=33) still shows a rising trend. Just as last year, TACO is the reaction category with the highest number of serious reactions; Table 15 shows the breakdown of cases by severity and imputability.

The reports of TRALI and post-transfusion bacteremia/sepsis with an additional category of TACO are cases where there was also circulatory overload. In a further three of these cases it is uncertain whether the dyspnea was caused, or worsened by (new or increased pre-existing) circulatory overload.

The majority of the TACO reports are associated with transfusion of one or more red blood cell concentrates (n=65) or of more than one type of blood component in the setting of acute major blood loss (n=6). Only a minority of the reports were ascribed to exclusive transfusion of plasma (FFP, n=2) or platelet concentrate (n=3). Circulatory overload following administration of SD-plasma was reported once in a patient with factor XI deficiency who received 7 (200 ml) units because of hemorrhage during a laparoscopic intervention. A second report associated with SD-plasma was of increased circulatory overload during plasmapheresis of a patient who had circulatory overload before the treatment.

The patients who developed TACO after transfusion of platelets also had a degree of circulatory overload beforehand.

Factors which contribute to the development of TACO relate to patient characteristics such as build, pathology and (adverse effects of) medical treatment on the one hand and transfusion parameters on the other. It seems plausible that not only the volume and speed of administration of the transfused product, but also its characteristics such as viscosity and hematocrit play a role in the development of TACO.

Table 15. Severity and imputability of TACO cases in 2015

Imputability	Total no. of reports	Severity grade			
		1	2	3	4
Certain	4	2	2	-	-
Probable	30	13	13	3	1
Possible	41	28	10	1	2
Unlikely	1	-	-	-	1
Total	**76**	**43**	**25**	**4**	**4**

Acute hemolytic transfusion reaction (AHTR)

Symptoms of hemolysis occurring within a few minutes of commencement or until 24 hours subsequent to a transfusion: one or more of the following: fever/chills, nausea/vomiting, back pain, dark or red urine, decreasing blood pressure or laboratory results indicating hemolysis within the same period. Biochemical hemolysis testing positive; blood group serological testing possibly positive; bacteriology negative.

Table 16. Acute hemolytic transfusion reactions (AHTR), 2006-2015

	AHTR	F	M	AHTR with certain, probable or possible imputability	Severity				
					0	1	2	3	4
2006	19	10	9	18	1	11	5	1	
2007	11	7	4	10		8	2		
2008	18	14	4	17		10	7		
2009	18	13 *	4 *	17		11	4	1	1
2010	21	8	13	20		14	5	1	
2011	17	10	7	15		6	8		1
2012	7	5	2	7		4	2		1
2013	11	8	3	11		4	7		
2014	17	8	9	12		10	2		
2015	18	12	6	16		9	4	1	2
Total	**157**	**95 ***	**61 ***	**143**	**1**	**87**	**46**	**4**	**5**

* *1x gender not stated*

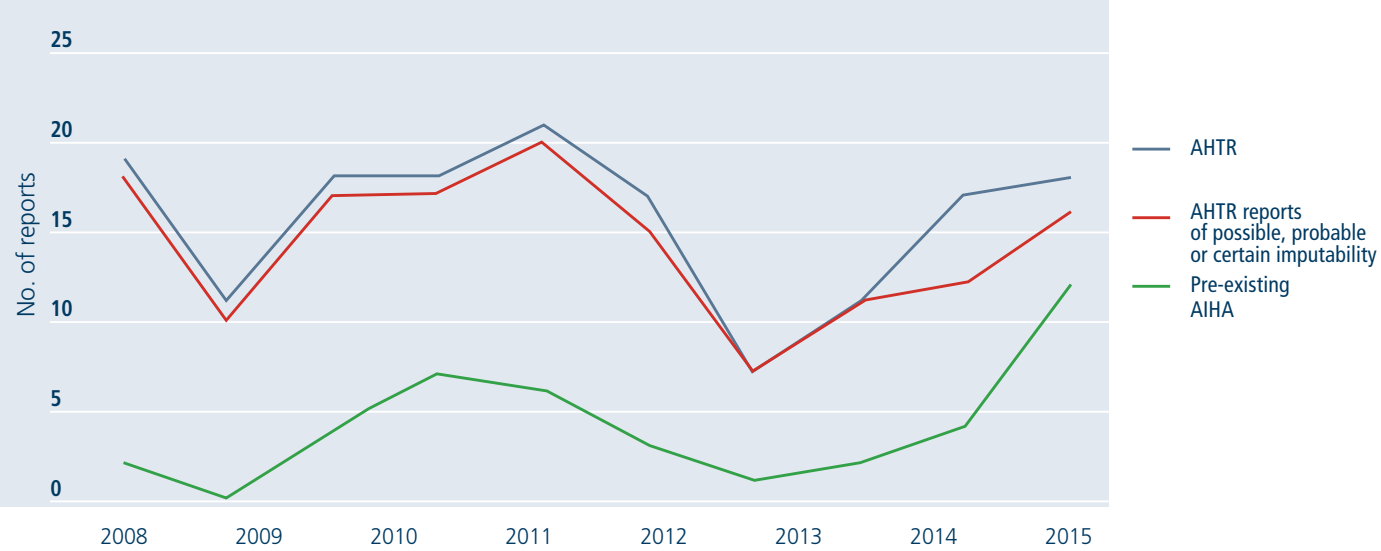


Figure 12. Acute hemolytic transfusion reactions, 2006-2015
Abbreviations: AHTR=acute hemolytic transfusion reaction; AIHA=auto-immune hemolytic anemia

- In 2015 a total of 18 acute hemolytic transfusion reactions were reported, among which seven were serious (grade 2 or higher; Table 16).
- Two cases were of severity grade 4 and were judged to be of probable and possible imputability respectively (see AHTR case descriptions 1 and 2 below).
- In twelve of the 16 AHTR reports of certain, probable or possible imputability the patient already had an auto-immune hemolytic anemia and there was a transfusion reaction accompanied by worsening of the hemolysis parameters and/or insufficient Hb increment (Figure 12). Two patients with AIHA developed a second AHTR following blood transfusion.
- In two cases of AHTR it was possible to identify the causative antibody: anti-A1 (see case description) and anti-K.
- In three reports of incorrect blood component transfused an acute hemolytic transfusion reaction occurred (registered as an additional category), discussed in chapter 3.1.

Conclusions

An acute hemolytic transfusion reaction is a rare but potentially lethal transfusion reaction. In patients with ongoing hemolysis as in sickle cell anemia, thalassemia and auto-immune hemolytic anemia, transfusion can trigger serious (hyper)hemolysis. In hyperhemolysis the patient's own red blood cells are also lysed. The recommendation is to treat a patient with auto-immune hemolytic anemie with medication as described in the 2011 CBO blood transfusion guidelines, only administering blood if clinically indicated and evaluating the need for further transfusion after each ½ to 1 unit of red blood cells. Close communication between the hematologist, clinical chemist and the Sanquin tranfusion medicine unit can support transfusion decisions for individual patients.

Case 1 AHTR

A 96 year old woman (A pos) with atrial fibrillation is prescribed 2 (A pos) RBCs for chronic symptomatic iron deficiency anemia. The blood group has been previously determined twice and registered in the computer system. A short blood group determination is performed, the irregular antibody screening is negative. Ten minutes after starting administration of the first RBC unit the patient becomes short of breath and the transfusion is stopped after 50 ml. A chest X-ray is performed and shows considerable increase of the pleural fluid on the right side. This leads to the conclusion that it is unlikely to be a transfusion reaction. The unit, which has been taken down, is returned to the transfusion lab for investigations according to the protocol.

Meanwhile, administration of the second unit of RBC is not delayed because the transfusion is still deemed to be medically urgent. Once again the patient becomes dyspneic and the second RBC is halted after 150 ml. A blood sample for INR testing (prior to pleurocentesis) arrives at the lab and is seen to be hemolytic. On serological investigation the patient is found to have blood group A2 with a strong anti-A1 antibody; antiglobulin crossmatch tests with the two transfused units are found to be positive.

The patient is placed under extra observation and receives a further two O pos RBCs. During the night renal function deteriorates because of intravascular hemolysis. The patient becomes increasingly dyspneic and dies.

Investigation by the reference laboratory demonstrates a weakly positive direct antiglobulin test in the pre-transfusion sample and the eluate yields an anti-A1, active at 30 °C.

Conclusion: it is unclear whether anti-A1 is the cause of this transfusion reaction since it was on the cells before transfusion. Nevertheless the anti-A1 in this case led to hemolysis, which must be regarded as unusual.

TRIP report:

acute hemolytic transfusion reaction, severity grade 4, imputability possible

Case 2 AHTR

A 75 year-old patient with chronic lymphatic leukemia also has an auto-immune hemolytic anemia caused by strong nonspecific cold antibodies (reactive at 30 °C). He is treated with high doses of corticosteroids and intravenous immunoglobulins. Despite treatment his hemoglobin level decreases to 2.8 mmol/L so a transfusion is ordered. Four RBC units are crossmatched by the reference laboratory and transfused using a blood warmer. The patient becomes increasingly dyspneic and deteriorates with increasing hemolysis (LDH 2168->6485). He is transferred to the ICU with respiratory insufficiency and suffers asystolic cardiac arrest which is ascribed to hyperkalemia.

TRIP report:

acute hemolytic transfusion reaction, severity grade 4, imputability probable

Delayed hemolytic transfusion reaction (DHTR)

Symptoms of hemolysis occurring longer than 24 hours after transfusion to a maximum of 28 days: 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.

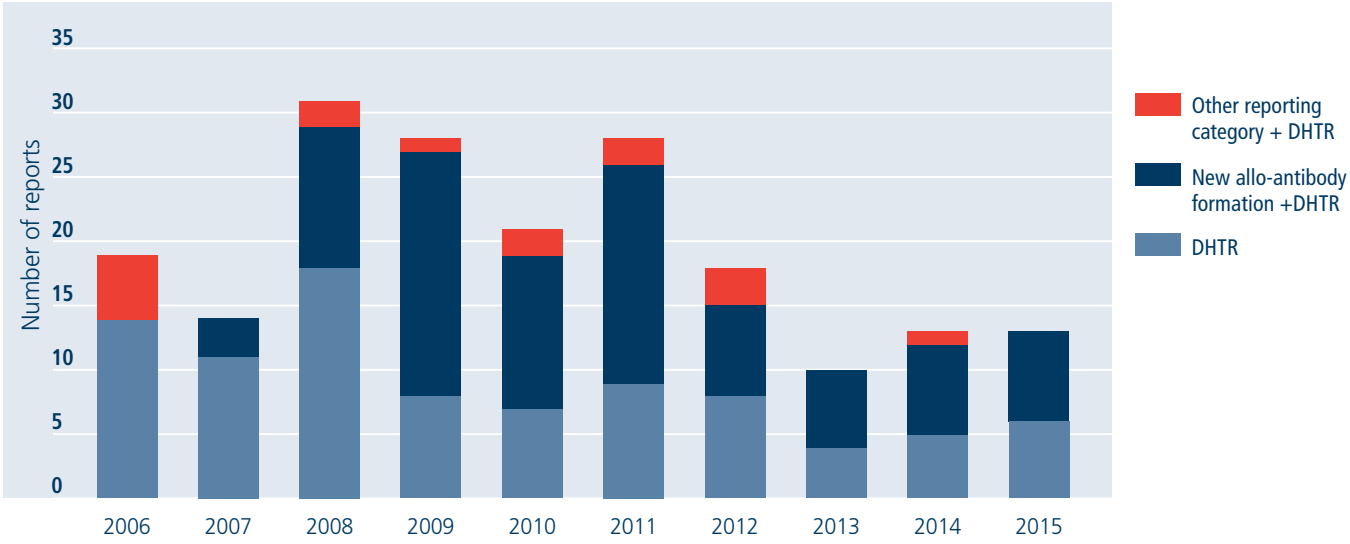
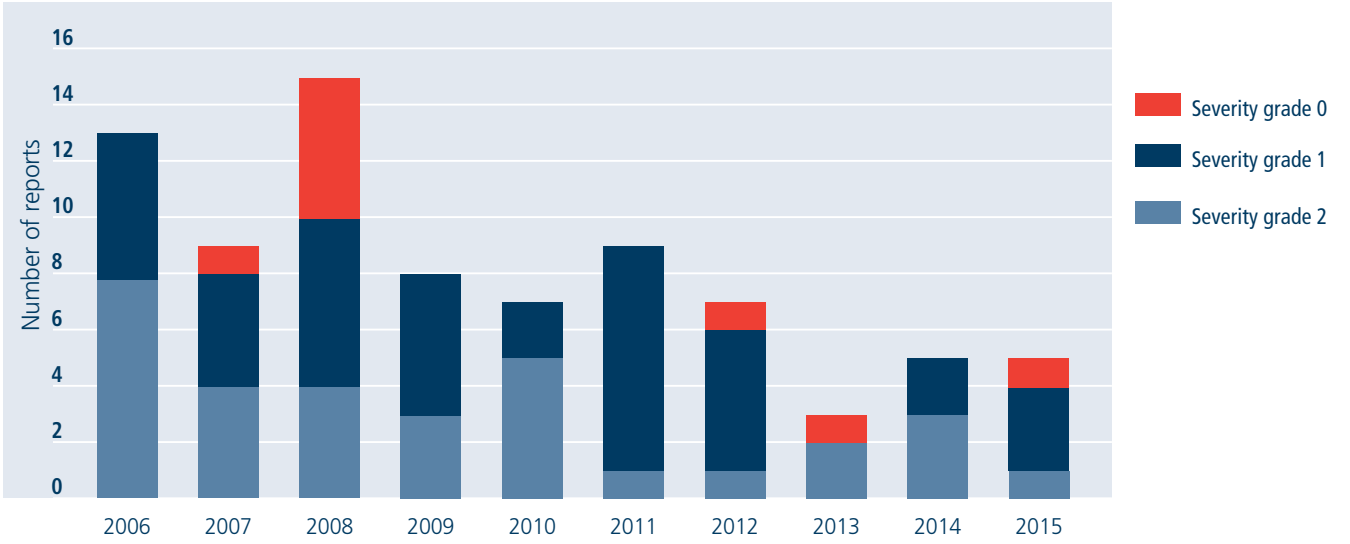


Figure 13. Delayed hemolytic transfusion reaction (reporting category or additional category), 2006-2015



Severity of delayed hemolytic transfusion reactions, 2006-2015

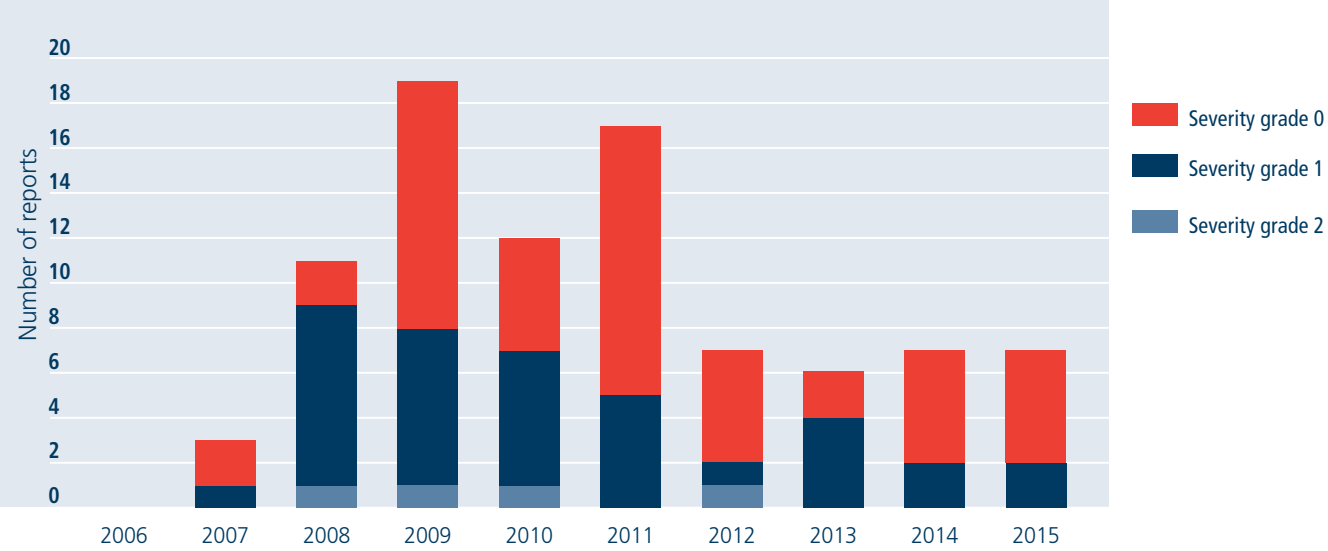


Figure 15. Reports of new allo-antibody formation associated with delayed hemolytic transfusion reaction, subdivided by severity grade, 2006-2015

In 2015, a total of 13 reports of delayed hemolytic transfusion reaction were registered: six reports were submitted in that category, with new allo-antobody formation recorded as additional category in three. In seven reports a delayed hemolytic transfusion reaction is reported as an additional category in association with new allo-antibody formation (Figure 15). The reported causative allo-antibodies are: anti-Jka (5x), anti-Fya (3x), anti-c, combinations: anti-E and anti-K, anti-Jkb and anti-Wra. In one patient with auto-immune hemolytic anemia, three successive transfusion episodes gave rise to two AHTR and one DHTR.

For the third year in succession, no DHTR arose following transfusion of an incorrect blood component. It should be noted that sometimes following an error, insufficient follow-up investigations are performed to confirm or exclude a DHTR (recommended laboratory tests: see below). In all, 12 reported IBCT carried a risk of a potential reaction from irregular antibodies (see chapter 3.1).

Laboratory investigations for possible DHTR:

- LDH, bilirubin, haptoglobin, Hb results over time (poor increment or unexplained drop?)
- Eluate (even if DAT is negative)
- Autocontrol
- Are transfused RBCs positive for the relevant antigen (mixed field?)

If there are no changes in hemolysis parameters, **repeat after 24-48 hours**.

The overal number of DHTR has remained stable. This year there were no reports of DHTR from hospitals which have yet to implement their connection with the national "TRIX" database (Transfusion Register of Irregular antibodies and crossmatch(X)problems) of irregular antibodies. DHTR cannot always be prevented, even when use is made of TRIX. Patients are not systematically monitored for the development of new allo-antibodies and it is always possible to miss an allo-antibody if it has gone below the detection threshold.

Transfusion-related acute lung injury (TRALI)

Dyspnea 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

In 2015 there were eight reports of TRALI: two of severity grade 4, one grade 3 and five grade 2.
After the closing date for the 2014 report one case of TRALI was submitted; it was assessed by the TRIP experts together with the 2015 reports.

- All these TRALI cases were judged to be of certain, probable or possible imputability
- The 2015 cases occurred after transfusion of red blood cells or platelets.
- Figure 16 shows the types of blood component which were administered in the TRALI cases from 2008.
- Since the introduction of male-only plasma a total of four TRALI reports have been reported in association with transfusion of only plasma (quarantine fresh frozen plasma).

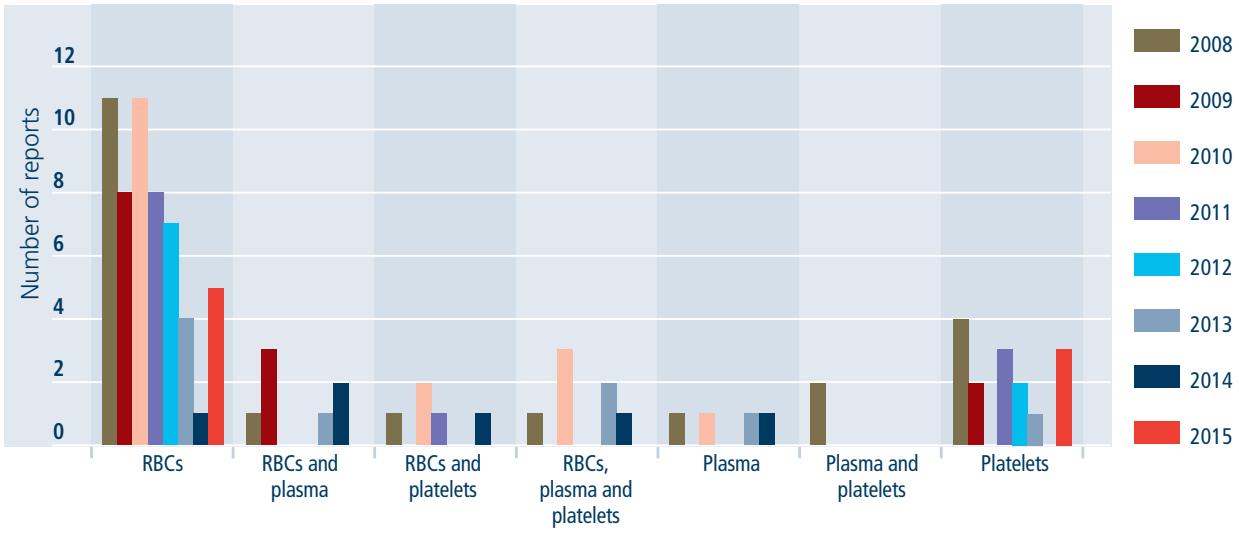


Figure 16. Type of blood component in TRALI reports of imputability certain, probable or possible, 2006-2015

Other reaction

Transfusion reactions that do not fit into the categories above.

- 4th position among the reporting categories
- Since 2010, one of the three largest categories of serious reactions of certain, probable or possible imputability.

The reporting category of other reaction was instituted in order to be able to collect and discern previously unknown transfusion reactions. This includes reports of necrotising enterocolitis (1 report to TRIP in 2011, small numbers of cases also reported to SHOT (Serious Hazards of Transfusion, United Kingdom) and other hemovigilance systems. Necrotising enterocolitis occurs in premature babies and an association with blood transfusion has been reported in the literature.

Table 17 shows the different subgroups (reasons) for cases registered as other reaction. The cases in 2015 and the breakdown are similar to 2012-2014 and in relation to the number of distributed blood components

Table 17. Types of reactions registered as other reaction in 2015 compared to 2012-2014

Type of reaction	2012	2013	2014	2015	2015 certain, probable	2015 possible	2015 ≥ gr 2*
Reactions with hypotension	42	47	30	42	6	31	2
Reactions with dyspnea	30	34	20	38	7	26	4
Subgroup: met criteria for TAD	*Not assessed*	*Not assessed*	*3*	*5*	*3*	*1*	-
Rise in blood pressure	14	6	3	17	1	14	1
(Possible) cardiac symptoms	10	9	5	13	1	7	2
Did not completely fit TRIP definition for standard category	63	73	77	39	11	17	5
Unproven sepsis	Not assessed	2	3	2	-	-	-
Other signs	57	45	53	48	5	32	7
Total	**216**	**216**	**191**	**199**	**31**	**127**	**21**

Comment on Table 17

There are various reasons for a report being registered as an other reaction.

- Reactions where dyspnea is mentioned as well as a rise in temperature, and where the respiratory symptoms were more pronounced than expected with a non-hemolytic transfusion reaction, or the degree of dyspnea could not be ascertained.
- Dyspnea as the sole or most prominent feature. If TRALI, transfusion-associated circulatory overload and hemolysis or other specific transfusion-related causes have been excluded (as far as reasonably possible), and the dyspnea cannot be explained by the medical condition of the patient, from 2016 the new reporting category of transfusion-associated dyspnea, TAD, may be used. Reports which have not been sufficiently investigated will not be accepted as TAD. In this way TRIP hopes to collect cases which will make it clearer whether TAD is an entity with a pathophysiology distinct from that in TRALI or TACO, or perhaps a reaction with pathophysiology corresponding to TRALI or TACO but which for diverse reasons does not meet criteria for registration in those categories. Out of the reports in 2015, four could have been classified as TAD (3 of probable imputability, 1 possible, all of severity grade 1; see the case description below).
- Reactions with hypotension as the sole or most prominent feature. Internationally, some hemovigilance systems specifically capture cases of hypotensive transfusion reactions. These tend to arise soon after a transfusion is started. The patient usually recovers after stopping the transfusion, without treatment or with supportive treatment only. The patient's medical condition must be eliminated as a possible cause of hypotension. The international definition of hypotensive transfusion reaction (ISBT working party for hemovigilance, 2011) requires a drop in blood pressure during or within 1 hour after transfusion, with a drop in the systolic blood pressure of ≥ 30 mm Hg and systolic blood pressure ≤ 80 mm Hg. This amount of drop in blood pressure was reported to TRIP four times in 2015 in cases where the patient's illness could not explain the change in blood pressure. For the present, the TRIP Hemovigilance Advisory Committee does not support the introduction of a separate reporting category for hypotensive transfusion reactions.
- Reactions with increased blood pressure. Do these represent cases of (incipient) circulatory overload? Some reports have been well investigated, and that does not appear to be the case. Stress is a possible explanation.

- (Possible) cardiac symptoms, with either chest pain or an apparent arrhythmia during or after transfusion.
- Reactions which do not fit the TRIP definitions for the standard reporting categories, for instance reactions with an increase in temperature which could have been caused by a pre-existing infection so that formally, a microbiological cause could not be excluded. The term reaction is used in the sense of a change in symptoms or clinical parameters during or after a blood transfusion, which could have been caused by the transfusion and a role of the transfusion cannot be excluded.
- One other reaction in 2015 (three in 2014) in a patient receiving plasmapheresis treatment was clinically diagnosed as hypocalcemia.
- Diverse symptoms or signs with a temporal relation to the transfusion, but which possibly or presumably were caused by the patient's disease or clinical condition, and where the clinical and laboratory features do not support diagnosis of one of the standard types of transfusion reaction.

Case description: hypotensive reaction

A woman aged 71, receiving treatment for breast cancer, was anemic (Hb 3.6 mMol/l) and a unit of RBCs was started. Before the transfusion her blood pressure was 119/97 mm Hg, roughly 10 minutes after the start it dropped to 75/50. The transfusion was halted, she was given 1.5 L/24 hours saline intravenously and recovered without further treatment. Blood group serology showed no abnormalities.

Case description: reaction with hypertension

A 59 year-old patient was transfused with RBC for melaena with a low Hb. After 2 hours a rise of temperature from 36.7 to 38.1 °C and chills occurred accompanied by hypertension (without symptoms): the pre-transfusion blood pressure was 146/90 mm Hg and it rose to 204/110 mm Hg. The patient had no respiratory symptoms and saturation did not change. Laboratory investigations showed no abnormalities suggestive of hemolysis.

Case description: reaction with dyspnea

A 72 year-old patient was investigated by jejunoscopy for gastro-intestinal hemorrhage. 1 hour and 15 minutes after starting transfusion of a RBC unit an increase of temperature of >1 <2 °C, dyspnea, cyanosis, tachycardia and a slight drop in blood pressure were observed. The oxygen saturation dropped from 99 to 88%; chest X-ray showed no abnormalities suggestive of either circulatory overload or TRALI. Blood cultures and a culture of the unit yielded no growth of micro-organisms and blood group serology and biochemistry gave no indication of hemolysis.

3.4 Blood management techniques (BMT)

The annual number of reports to TRIP associated with the use of blood management techniques increased from 2007 to 2011 and has declined since then (Figure 17). In 2015 only three reactions were reported associated with the use of drain blood: two other reactions and one NHTR, all grade 1 in severity and with possible imputability. In all, 13 serious reactions have been reported since 2008 (12x grade 2 and 1x grade 3).

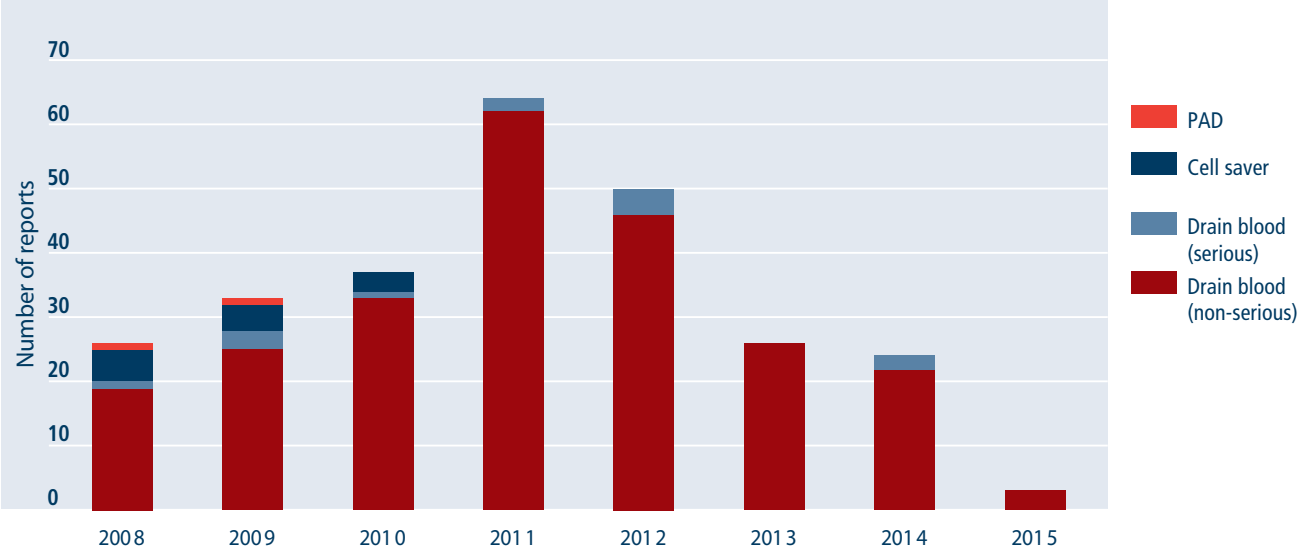


Figure 17. Reports regarding blood management techniques, 2008-2015

Figure 18 shows the figures collected by TRIP on the annual use of blood management techniques; note that not all hospitals were able to provide information. The use of reinfused drain blood has declined from its peak in 2011. In 2015 only 6 patients were reported to have been referred for preoperative autologous donation; 8 units were collected and 2 were used. Figure 19 shows the number of hospitals each year in which the hemovigilance contact persons indicated that drain blood reinfusion was performed, not performed, or that they did not know whether drain blood procedures took place in their hospital. The figure shows that the percentage of hospitals using drain blood procedures has gone down. The percentage of hospitals where the hemovigilance officer cannot indicate whether drain blood reinfusion is practised is still high and shows little decline.

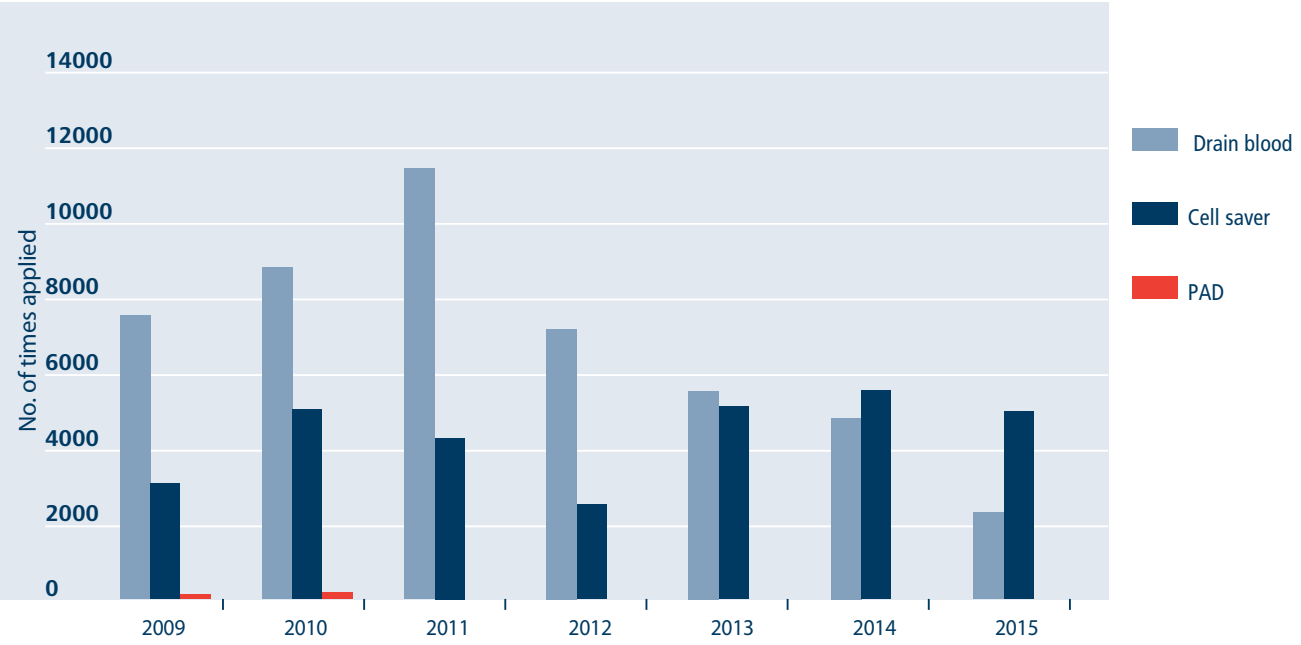


Figure 18. Application data for drain blood procedures, cell saver procedures and patients referred for preoperative autologous donation (data from 11, 26 and 6 hospitals respectively)

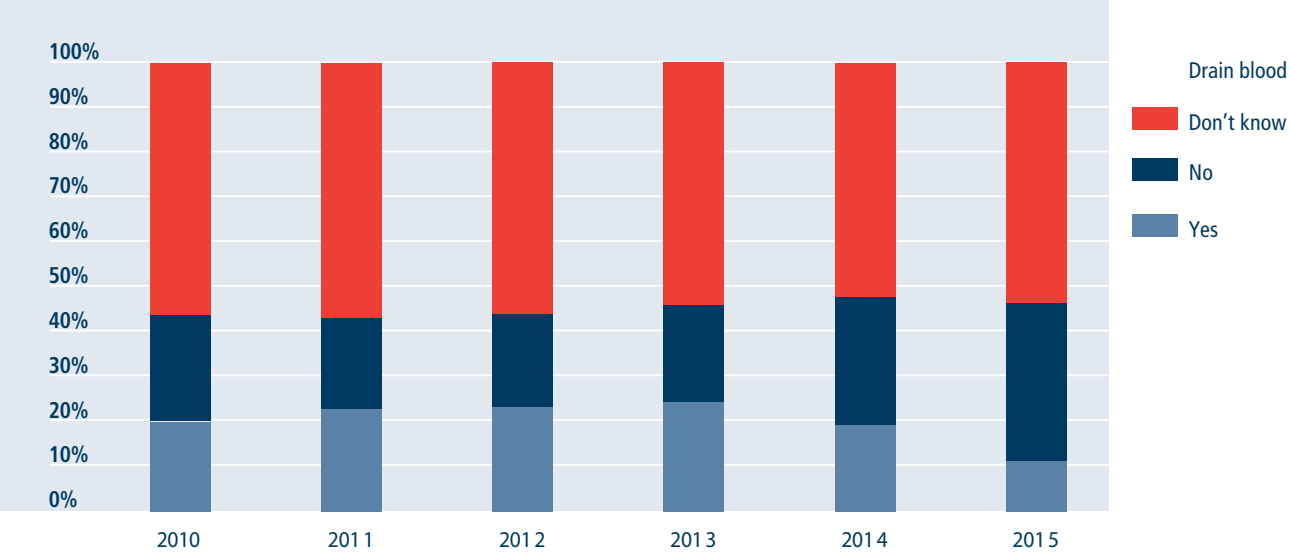


Figure 19. Hospitals' replies regarding application of drain blood (n=98 hospitals)

3.5 Reports associated with SD-plasma in 2015

Under co-authorship of Lareb (Netherlands Pharmacovigilance Centre)

Use of SD-plasma in The Netherlands

SD stands for solvent-detergent, a pharmaceutical pathogen reduction treatment for large pools of donor plasma. Since the beginning of 2014 Omniplasma®, SD-plasma produced from Dutch plasma donations collected by Sanquin, has been progressively rolled out by Sanquin as the standard plasma product for transfusion.

SD-plasma was used by 68 hospitals in 2015 (2014: 20). During the transition period the number of distributed units was larger than the number of units administered because the stocks of FFP were being used up and appropriate stock levels of the new product had to be achieved. For this reason, Table 3 (page 9) uses the number of units transfused as the denominator for calculating the number of reports per 1000 units of SD-plasma.

Reports associated with SD-plasma

In 2015 a total of 21 reactions and six incidents were reported in association with SD-plasma, including reports where RBCs and/or platelets were also transfused. There were 17 reactions and five incidents involving only SD-plasma. The overall number of reports in 2015 per 1000 units of SD-plasma (point incidence) is lower than that in 2014 and is also lower than for Q-FFP (quarantaine fresh frozen plasma), however these are not statistically significant differences. Table 4 on page 10 shows the distribution of reports with SD-plasma in 2015.

The proportions of different types of reactions are similar to what is known for fresh frozen plasma. Two serious reactions were reported with SD-plasma: an anaphylactic reaction (imputability possible, see case description below) and a report of transfusion-associated circulatory overload (imputability possible). In addition an other reaction was reported in a patient who also received RBCs – the patient subsequently died; the imputability was judged to be unlikely (Table 7 on page 15).

A patient receiving plasmapheresis treatment with administration of SD-plasma suffered from an anaphylactic and an other allergic reaction. Both times the patient recovered after treatment with an antihistamine.

The incidents reported in 2015 were firstly an other incident, the bag being accidentally punctured "because more force was needed to get the spike in". This comment was only received once. There were three reports of incorrect blood component transfused: in an emergency situation blood group O SD-plasma was selected and administered. Similar cases with FFP were reported in the past.

Case description: anaphylactic reaction

A man with chronic hepatitis and liver cirrhosis, age group 60-80 years, needed emergency surgery. Induction at 00.57 hrs was followed by a dip in arterial blood pressure (64/50 mm Hg, recovery after administration of noradrenalin). Omniplasma administered 1.08 to 1.36 hrs, Voluven started at 1.36 hrs. At 1.30 generalised urticaria and redness were noted, with erythema, angio-oedema, drop in blood pressure to 50/34 (1.41) and shortness of breath/dyspnea. At 1.50 blood pressure was 60/48 (non-invasive measurement), adrenalin given; Tavegil and dexamethason at 1.57 (88/50).

Other medication:

In the operating theater the antibiotics Kefzol and Flagyl were given. Anesthetic drugs: propofol, lignocaine, sufentanil, rocuronium; sevoflurane. The patient is on maintenance treatment with daily norfloxacin 400 mg. The reporting hospital judges causation of the reaction by the other medication to be unlikely.

Laboratory results

Before theatre: PT (INR) 1.5 INR; APTT 38 sec; PT 16.2 sec; Hb 7.1 mMol/L; Ht 0.34.
Tryptase in pre-transfusion sample 3.42ug/L, post-transfusion 7.88 ug/L. Haptoglobin after the reaction 1.2 g/L. The patient has no known allergies. IgA deficiency excluded.

TRIP report:

anaphylactic reaction, severity grade 2, imputability possible

Conclusion

The reports to TRIP about SD-plasma Omniplasma® since it was introduced in 2013 are similar to those seen with Q-FFP.

CHAPTER 4

General information

4.1 TRIP working methods and participation in TRIP reporting

A central registration system for blood transfusion reactions and incidents makes it possible to monitor the transfusion chain and detect any weak links in it. The incidence of known side effects of blood transfusions is tracked and previously unknown reactions to transfusion of current or new blood products can be detected in timely fashion.

TRIP foundation (originally: Transfusion Reactions In Patients) was created in 2001 by representatives of the various professional societies involved in blood transfusion. The national TRIP Hemovigilance and Biovigilance Office has operated a registry for transfusion reactions and incidents since 2003 in collaboration with the contact persons in the hospitals and the national blood service, Sanquin. Since August 2006 TRIP has also run a national reporting system for serious adverse reactions and events in the chain of clinical application of human tissues and cells. When the biovigilance activities were structurally assigned to TRIP the foundation's statutes were changed (2012) and its name became Transfusion and Transplantation Reactions in Patients. The tissue and cell vigilance findings are reported in a separate annual biovigilance report which is also available on www.tripnet.nl under publications/reports.

Reporting to TRIP is anonymous. Though voluntary in principle, it is regarded as the professional standard by the Healthcare Inspectorate and the national "CBO" transfusion guidelines. Reporting to TRIP is separate from the hospitals' responsibility to provide care.

Nearly all reports to TRIP are submitted through the online reporting system (>95% since 2012). Reporters of transfusion reactions and incidents are asked to provide results of relevant investigations and grade the clinical severity of the reaction. The imputability, i.e. the likelihood that the reaction can be ascribed to the administered transfusion, is also assessed. If necessary TRIP requests further explanation or details from the reporter. All reports are reviewed by the TRIP physicians, who assess their coherence and verify the reporting category of (potentially) serious reports. Each year TRIP checks for duplicate reports and merges them in consultation with the reporting hospitals.

An Expert Committee (EC), consisting of experts appointed by the TRIP Board, additionally reviews all serious reports and some non-serious reports. Only after this are the reports included in the annual report. The EC is composed of representatives of professional societies and people who are appointed for their expertise in a particular domain; the members are also members of TRIP's Hemovigilance Advisory Board.

Under the requirements of European Directive 2002/98/EC it is mandatory to report serious adverse reactions and incidents which could have a relation to quality and/or safety of blood components. TRIP provides the analysis of these serious reports (severity grade 2 or higher) and prepares the annual overview for the competent authority, the Ministry of Health, Welfare and Sports, and the Healthcare Inspectorate. The hospitals can send the serious reports to the Healthcare Inspectorate and Sanquin using the TRIP online reporting system.

The benefit from collecting and reporting at the national level about transfusion reactions and incidents depends on the participation of all the reporting establishments. In 2015 the number of contact addresses was the same as in 2014: 98 hospitals and four clinics licensed by the Ministry to administer blood transfusions. All 98 hospitals participated by providing information to TRIP: up till the closing date for the annual report 91 had submitted reports and four indicated that there had been no reportable reactions

or events. Three hospitals which previously had been included in the list of transfusing hospitals, as well as the four licensed clinics, informed TRIP that they had not performed any transfusions in 2015. For the first time since national hemovigilance reporting, all transfusing establishments provided figures of units transfused. At the time of writing this report, a few 2015 reports are still being concluded.

TRIP is renewing the hemovigilance reporting system; the new system will be used for reports from 2016. The considerations which led to the renewal project are:

- Efficiency and effectiveness of reporting
- Clarity about what details are needed and why.

The guiding principles are unchanged:

- Learning from incidents and preventing repetition
- Safety of blood transfusion
- Ongoing collection of relevant data so that trends can be shown.

List of terms and abbreviations

AHTR	acute hemolytic transfusion reaction
BMT	blood management techniques
Bc	blood component
CBO	CBO quality organisation in healthcare
DHTR	delayed hemolytic transfusion reaction
EU	European Union
FFP	fresh frozen plasma
Hosp.	hospital
IC	intensive care
Irrab	irregular antibodies
Mild NHFR	mild non-hemolytic febrile reaction
New allo-ab	new allo-antibody formation
NHTR	non-hemolytic transfusion reaction
OI	other incident
PAD	preoperative autologous donation
PAS	platelet additive solution
Pt	patient
PCR	polymerase chain reaction
Plts	platelets, platelet concentrate
Post-Tf bact/sepsis	post-transfusion bacteremia/sepsis
PTP	post-transfusion purpura
RBC	red blood cell concentrate
Sanquin	Sanquin Blood Supply
SD	solvent detergent (a viral reduction method)
TA-GvHD	transfusion-associated graft versus host disease
TACO	transfusion-associated circulatory overload
TAD	transfusion-associated dyspnea
Tf	transfusion
TR	transfusion reaction
TRALI	transfusion-related acute lung injury
TRIP	TRIP Foundation (Transfusion and Transplantation Reactions In Patients)
TTBI	transfusion-transmitted bacterial infection
Tx	transplantation

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