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Haemovigilance Annual report 2014

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Additional information is available on the Haemovigilance section of the Swissmedic website:
www.swissmedic.ch/market surveillance ->
Blood components

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Abbreviations

°C	degrees Celsius
AB	antibodies
AML	acute myeloid leukaemia
ARDS	acute respiratory distress syndrome
ASAT	aspartate aminotransferase
BG	blood group
Bili	Bilirubin (total)
BP	blood pressure
BPr	blood product
C3d	fragment of the complement system
CMV	cytomegalus virus
cPC	conventional platelet concentrate
CT	computed tomography
DAT	direct antiglobulin test, also known as direct Coombs test
DD	differential diagnosis
e.g.	for example
ECG	electrocardiogram
FGP	fresh frozen plasma
FNHTR	febrile non-haemolytic transfusion reaction
G/l	giga (109) per litre
g/l	grams per litre
GI	gastrointestinal
h	hour(s)
Hapto	haptoglobin
Hb	haemoglobin
HIV	human immunodeficiency virus
HTR	haemolytic transfusion reaction
HV	Haemovigilance
IBCT	incorrect blood component transfused
ID	identification
IgM	class M immunoglobulins
IH	immunohaematology
iv	intravenous
K	antigen/antibody of the Kell blood group
kg BW	kilogram of body weight
LDH	lactate dehydrogenase
M.	morbus = disease
ml	millilitre
mm Hg	millimetre mercury column, unit of measurement for (blood) pressure
NM	near miss
NT-pro-BNP	N-terminal brain natriuretic peptide
O_2	oxygen
Op	operating theatre
PC	platelet concentrate (PCa: apheresis-derived;PCb: whole blood-derived)
PE	pulmonary embolism
PI-PC	pathogen-inactivated platelet concentrate
pos	positive (e.g. BG O_{pos} = blood group O, rhesus factor positive)
pRBC	Packed red blood cells
PubMed	database of the US National Institute of Health
Rh	rhesus (factor)
Rx	x-ray
SRC	Swiss Red Cross
T&S	type and screen (to define blood group and detect irregular antibodies)
TACO	transfusion-associated circulatory overload
TAD	transfusion-associated dyspnoea
TR	transfusion reaction
TRALI	transfusion-related acute lung injury
U/l	unit(s) per litre
µmol	Micromol

1. General information on haemovigilance

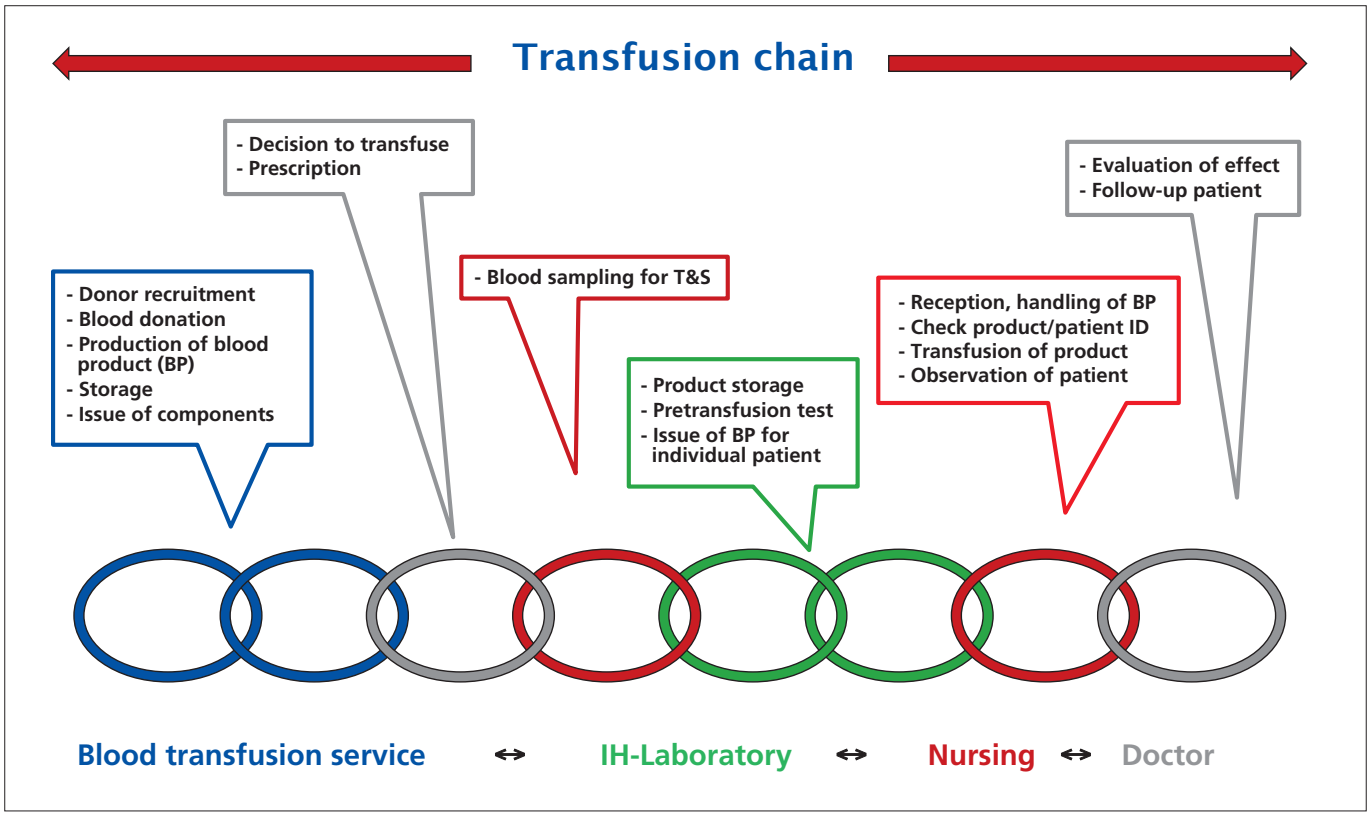
1.1 Introduction

In this Annual Haemovigilance Report we present the evaluation of the reports received in 2014 on transfusion reactions (TR), cases of incorrect blood components being transfused (IBCT) and near misses (NM).

1.2 Origin, effects and clarification of haemovigilance events

The diagram of the transfusion chain shows which occupational groups play a role in carrying out a transfusion and are required to report events (Figure 1). Notifiable events include not only transfusion reactions but also transfusion errors and near misses. Events that have been investigated and analysed are the cornerstone of a transparent, intelligent and therefore functioning haemovigilance and quality assurance system in hospitals. The investigation of events should establish the diagnosis of the affected patient, contribute to harm reduction and, within the framework of the national haemovigilance system, enable information to be gained about current risks and potential for optimisation. This is why a consistently high level of willingness to report events remains so important.

Figure 1: Transfusion chain



1.3 Reporting of events and national haemovigilance data

A national haemovigilance system was introduced in Switzerland as early as 1996 [1] and expanded in subsequent years. Reporting of suspected transfusion reactions, transfusion errors and quality defects became mandatory with the enactment of the Therapeutic Products Act in 2002.

Apart from the early detection of new risks and quality defects, the main tasks of a national haemovigilance system are to initiate and evaluate preventive measures. Table 1 shows the measures adopted in Switzerland in recent years on the basis of national haemovigilance data.

Table 1: Measures adopted in Switzerland with their major effects and the issues involved

Measures	Issues	Introduction/evaluation
Prevention of infectious diseases	- Classic blood-borne infections (HIV, hepatitis B, hepatitis C) - Chagas screening in at-risk donors - Hepatitis E screening - Other emerging infections or blood-borne infections not previously observed in Switzerland	Measures are adapted and evaluated on an ongoing basis Since 2013 Currently under discussion Ongoing evaluation
Strategy of predominantly male donors of plasma	- Reduction of TRALI* risk, emergence of other risks?	Evaluation completed in 2014
Changes to the manufacturing process	- Pathogen inactivation of blood platelets - Efficacy in preventing infection - Impact of reduced plasma content - Effects on platelets, increased consumption, reduced efficacy? - Emergence of other risks, TRALI? - Storage time of 7 days, impact - Pathogen inactivation of plasma for transfusion	Introduced in 2011, evaluation updated continuously on the basis of new data Introduced in 2013 in 1 centre**
Quality assurance in the transfusion processes	- Blood bank and laboratory - Trends in alloimmunisation and near misses - Learning from the mistakes of others - Users of blood products - Trends in transfusion errors and near misses - Learning from the mistakes of others	Continuous qualitative and quantitative increase in quality assurance measures introduced in laboratories and hospitals
Recommendations	- Transfusion medicine lab testing of patient samples [2]	First edition 2008, updated regularly

* Transfusion-related acute lung injury

** The case numbers are still too low for an evaluation using national haemovigilance data

1.4 Methodology: Reporting pathways and mode of operation of the national haemovigilance system

The national haemovigilance system (HV system) covers the whole of Switzerland. Under the Therapeutic Products Act, all institutions that transfuse blood products (‚users') and the manufacturers of blood products are obliged to report transfusion reactions, transfusion errors and quality defects. It is also mandatory for both users and manufacturers to set up a quality assurance system and to appoint a responsible person for haemovigilance (haemovigilance officer). This person ensures that events are investigated correctly and that the user and the blood bank or manufacturer work together effectively. This increases the quality of the individual reports. In addition, prevention aspects are taken into account, particularly if a problem potentially effects several products.

The reports are either sent directly to Swissmedic by the users or first go to the manufacturer, who adds information about the product history, the history of the donor and – where applicable – additional results of investigations of the incident before passing the report on to Swissmedic. At Swissmedic the reports are entered into the haemovigilance database and evaluated by a clinical reviewer. The Swissmedic reviewers obtain additional information from the reporters where necessary and carry out the final assessment. If this assessment deviates significantly from the report sent by the professional, the local haemovigilance officer is consulted, as is the initial reporter if the local haemovigilance officer thinks this is necessary, to ensure that all the available information is taken into account adequately when the report undergoes its final evaluation. (Individual cases of particular interest are discussed with external experts in anonymised form.)

The Swiss haemovigilance system is based on spontaneous reporting; in other words it is what is known as a passive monitoring system. Active monitoring by the national system, such as in cohort studies for example, does not take place. The individual professional or haemovigilance officer determines whether a transfusion reaction is investigated and reported. It can therefore be assumed that, in spite of the statutory reporting requirement, under-reporting occurs to a degree that cannot be precisely quantified.

The number of blood components supplied for transfusion is used to quantitatively evaluate transfusion risks (with exposure data as the denominator). Transfusion risks may be underestimated as a result of under-reporting, and for this reason the risks described in this report should be understood as minimum figures. Under-reporting depends on a number of factors, some of which are not known and cannot be controlled. Under certain conditions, however, it can be assumed that the volume of under-reporting of a reaction is constant, and this permits reliable comparisons to be made through the national HV system such as before-and-after comparisons following implementation of measures. In particular, declining reporting rates for individual categories of events (such as allergic transfusion reactions due to platelet transfusions since the Intercept pathogen inactivation system was introduced) against a background of increasing reporting rates overall can be interpreted as a real reduction in the number of these transfusion reactions.

2. Reports received

2.1 Summary

Swissmedic received a total of 1,937 haemovigilance reports in 2014. Correction for duplicate reports etc. leaves 1,935 reports, comprising 1,077 suspected transfusion reactions, 49 transfusion errors, 784 near misses, 13 donor reactions and 12 quality defects (Table 2).

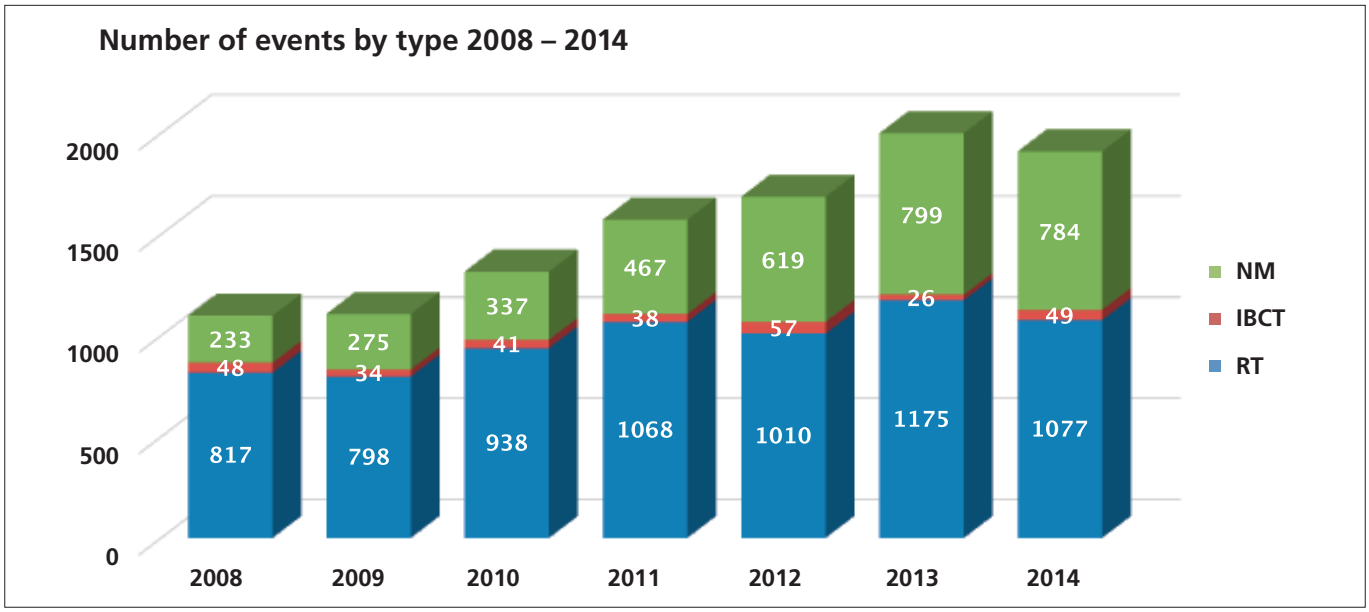
2.2 Distribution of the reports

Figure 2 shows all the reported events in recipients of blood components. The decrease in the total number of reports in 2014 parallels a decrease in the number of products transfused. The reporting rate, expressed as the number of reports per transfused product, rose again in 2014 (Figure 5, chapter 2.4.2).

Table 2: Number of haemovigilance reports in 2014

Type	Number
Transfusion reactions	1077
Transfusion errors / incorrect blood component transfused (IBCT)	49
Near misses (NMs)	784
Donor reactions	13
Quality defects	12
Total number of reports evaluated	**1935**

Figure 2: Events reported in 2014 compared with previous years



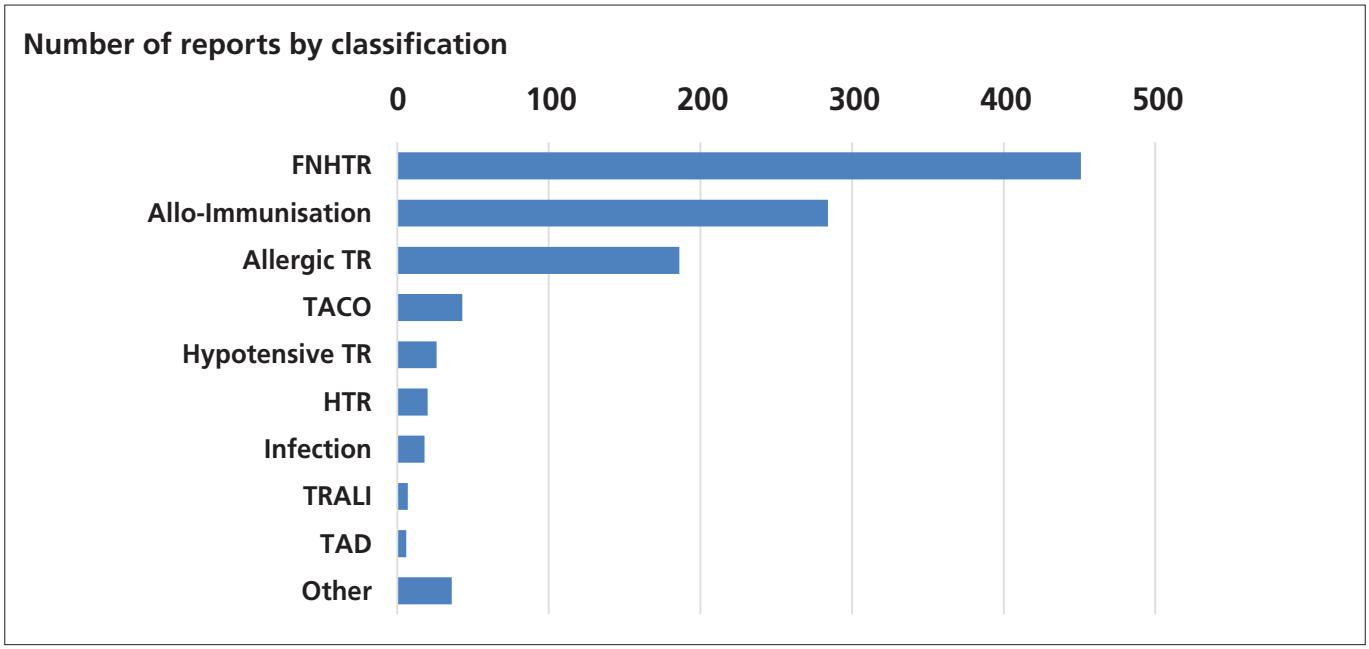
TR = Transfusion reaction, IBCT = Incorrect blood component transfused, NM = Near miss

2.3 Transfusion reactions (TR)

2.3.1 Transfusion reactions by category

In 2014 there were 1,077 reports of suspected transfusion reactions. The distribution of these reports among the different categories is shown in Figure 3.

Figure 3: TR reported in 2014 by category, N=1,077



FNHTR = Febrile non-haemolytic TR
TACO = Transfusion-associated circulatory overload
TRALI = Transfusion-associated acute lung injury
TAD = Transfusion-associated dyspnoea

Alloimmunisations, febrile non-haemolytic TR (FNHTR) and allergic TR together continue to account for almost 90% of the transfusion reactions reported. Compared with previous years, there is a trend towards more haemolytic reactions; this is described in more detail and discussed in chapter 2.5. There is also a trend towards more infections, which is interpreted as an artefact. Cases in which transfusion-related infection was a possible diagnosis – often with a differential diagnosis of ‚FNHTR' or ‚infection due to the underlying disease' – were systematically categorised as ‚Infection' from 2014 onwards and the category was retained even if investigations showed that it was probably not a transfusion-related infection. The absence of a causal relationship with the transfusion is taken into account by assigning a correspondingly low imputability. This procedure has the advantage that cases in the important ‚Infection' category are recorded as such in the database. A total of 18 cases were categorised as ‚Infection' in 2014, but 14 of them have a low imputability (Table 3).

2.3.2 Imputability (relationship to the transfusion)

Table 3: Number of events in 2014 by category and imputability

Imputability	all	low	‚possible'	high
Allergic TR	186	8	38	**140 (75%)**
FNHTR	451	74	284	**93 (21%)**
Alloantibodies	284			**284 (100%)**
H TR: acute	10	2	2	**6**
delayed	10	2	2	**6**
Hypotensive TR	26	5	14	**7**
Infection: bacterial	13	10	1	**2**
other	5	4	1	
TACO	43	3	15	**25 (58%)**
TAD	6	2	3	**1**
TRALI	7	4	3	
Other	36	21	14	**1**
Number of events	**1077**	**135 (13%)**	**377 (35%)**	**565 (52%)**

Low imputability: causal relationship with the transfusion ‚excluded' or ‚unlikely'
High imputability: causal relationship with the transfusion ‚probable' or ‚certain'

In 2014 high imputability was attributed to 565 reactions (52% of reported TR), i.e. the likelihood of there being a causal relationship with the transfusion was considered to be probable or certain. In the following, only cases with high imputability are presented in order to provide the most specific illustration possible of transfusion risks in Switzerland.

2.3.3 Severity

The degrees of severity are defined as follows:

Grade 1: non-severe
Grade 2:
severe, i.e. one of the following criteria is fulfilled:
- Time in hospital prolonged as a result of the reaction
- Permanent damage (or permanent risk in the case of alloantibodies)
- The reaction must be considered as medically important for other reasons (e.g. if permanent damage or a fatal outcome was avoided by timely intervention)

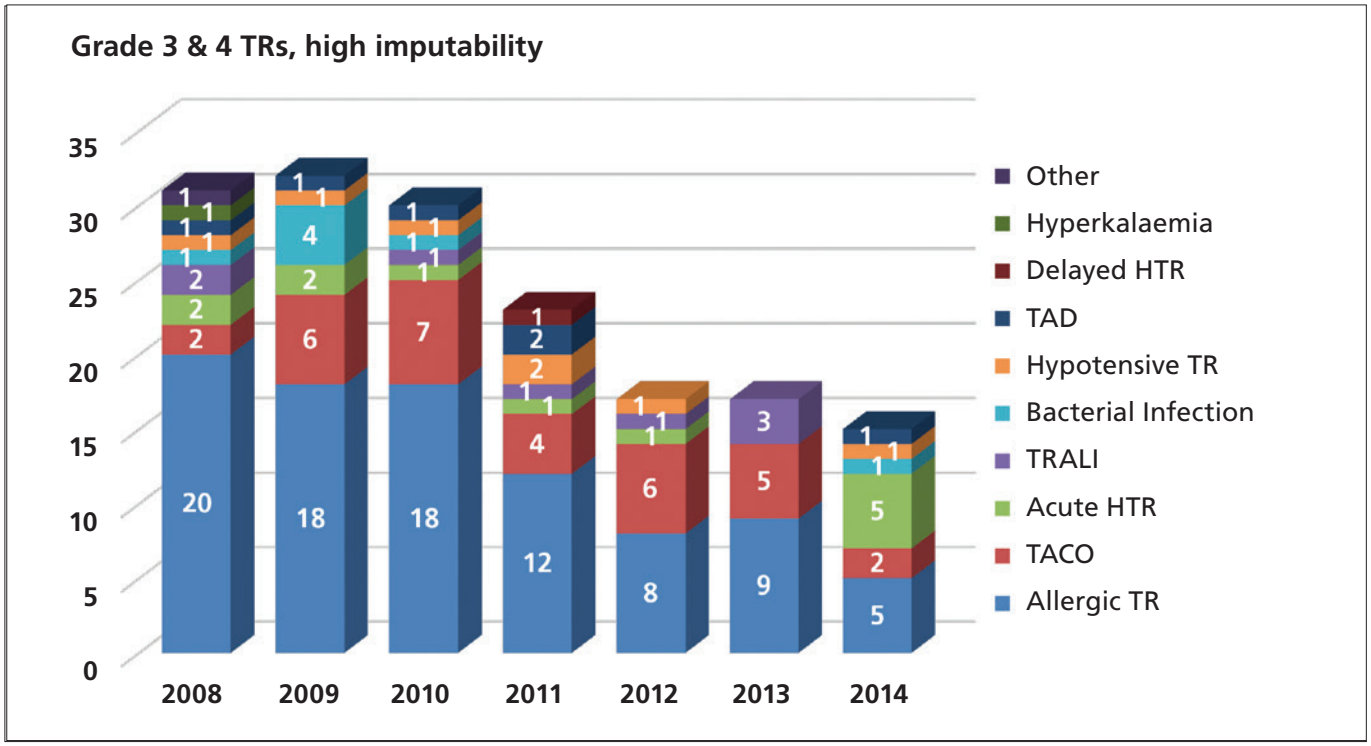
Grade 3: life-threatening
Grade 4: death

Table 4: High-imputability reactions by category and severity

Severity	all	Grade 1	Grade 2	Grade 3	Grade 4
Allergic TR	140	126	9	5	
FNHTR	93	92	1		
Allo-AB	284		284		
HTR	12	5	2	4	1
acute	6	1		4	1
delayed	6	4	2		
Hypotensive TR	7	6		1	
Infection	2		1	1	
TACO	25	17	6	2	
TAD	1			1	
Other	1	1			
Total	**565** 100%	**247** 44%	**303** 54%	**14** 2.5%	**1** 0.2%

The proportion of life-threatening (Grade 3) or fatal (Grade 4) transfusion reactions was about the same as in previous years at 2.7%. The development of the absolute figures from 2008 to 2014 is shown in Figure 4.
Of the 15 cases of life-threatening or fatal transfusion reactions in 2014, 11 occurred in connection with packed red blood cells (pRBC), 2 with platelet concentrates (PC) and 2 with fresh frozen plasma (FFP).

Figure 4: Life-threatening or fatal events with high imputability



Between 2008 and 2014,
6 transfusion-associated deaths occurred

in 2008 one TACO after FFP and one TRALI after PC
in 2009 one acute HTR after pRBC and one bacterial infection after PC
in 2012 one TACO after pRBC
in 2014 one acute HTR after pRBC.

One fatality with high imputability was reported in 2014. The haemolytic reaction with a fatal outcome is described in more detail in chapters 2.5 and 4.1. A further 10 deaths in temporal association with transfusions were shown to be unlikely related to the transfusion once they had been investigated and a final evaluation had been effectuated. The imputability was rated as ‚possible' in one case. This case is described in chapter 4.1.

2.3.4 Transfusion reactions by blood components

The percentage distribution of the 565 high-imputability TR by blood components is shown in Table 5.

Table 5: Proportion of reported TR accounted for by blood components

Packed red blood cells (pRBC)	**425 (75%)**
Platelet concentrates (PC)	**98 (17%)**
- Apheresis-derived (PCa)	72
- Whole blood-derived (PCb)	18
- Unknown	8
Fresh frozen plasma (FFP)	**25 (4%)**
- Quarantine	23
- Solvent/detergent	2
Multiple blood components	**17 (3%)**

Three-quarters of the reports involving PC and practically all of those involving plasma describe allergic reactions, while the reactions due to pRBC fall into many categories. The next chapter describes the general and component-specific risks.

2.4 Number of transfused blood components and risks in Switzerland 2014

2.4.1 Number of transfusions

The annual statistics of the Blood Transfusion Service of the Swiss Red Cross (SRC) show the number of blood components issued in Switzerland over the past 7 years (Table 6).

The total number of blood components issued was again lower than in the previous year. Approximately 6% fewer pRBC and approximately 13% fewer FFP products were issued than in 2013. The use of PC increased by 1.5% in comparison with the previous year, while the proportion of whole blood-derived PC declined from 35% in 2013 to the current level of 28%.

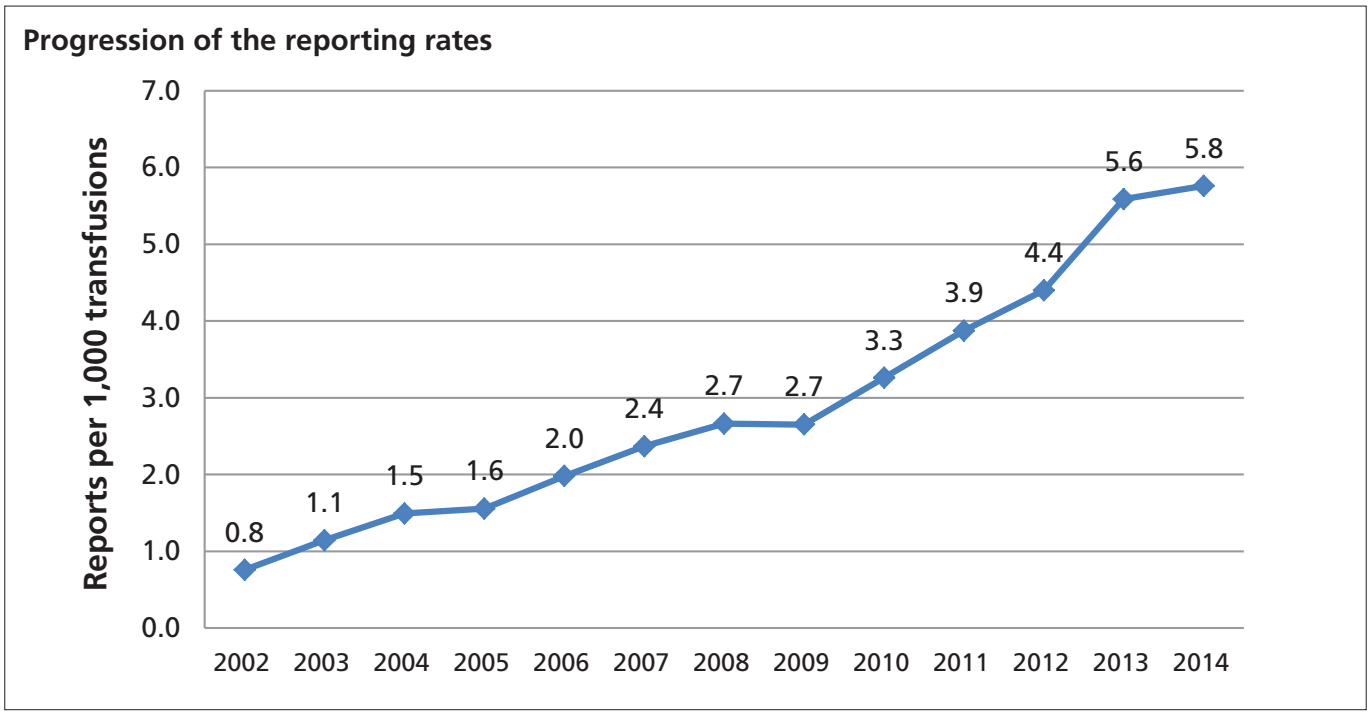
Table 6: Number of transfusions

Blood components	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
pRBC	313‘587	311‘521	308‘670	308‘627	297‘582	279‘510	262‘953
FFP (therapy units)	65‘800	70‘300	61‘500	50‘063	49‘832	44‘083	38‘183
PC (products)	27‘600	29‘600	29‘900	33‘068	34‘265	34‘750	35‘328
Total blood components	**407‘079**	**411‘528**	**400‘070**	**391‘758**	**381‘679**	**358‘343**	**336‘464**

2.4.2 Reporting rates

The overall reporting rate is calculated from the total number of reports per 1,000 transfusions. The calculation includes all types of reports and all imputability classifications, i.e. all 1,935 reports in 2014. The reporting rate rose slightly again in 2014 and currently stands at 5.8 reports per 1,000 transfusions (Figure 5).

Figure 5: Progression of the reporting rate (reports per 1,000 transfusions), all reports

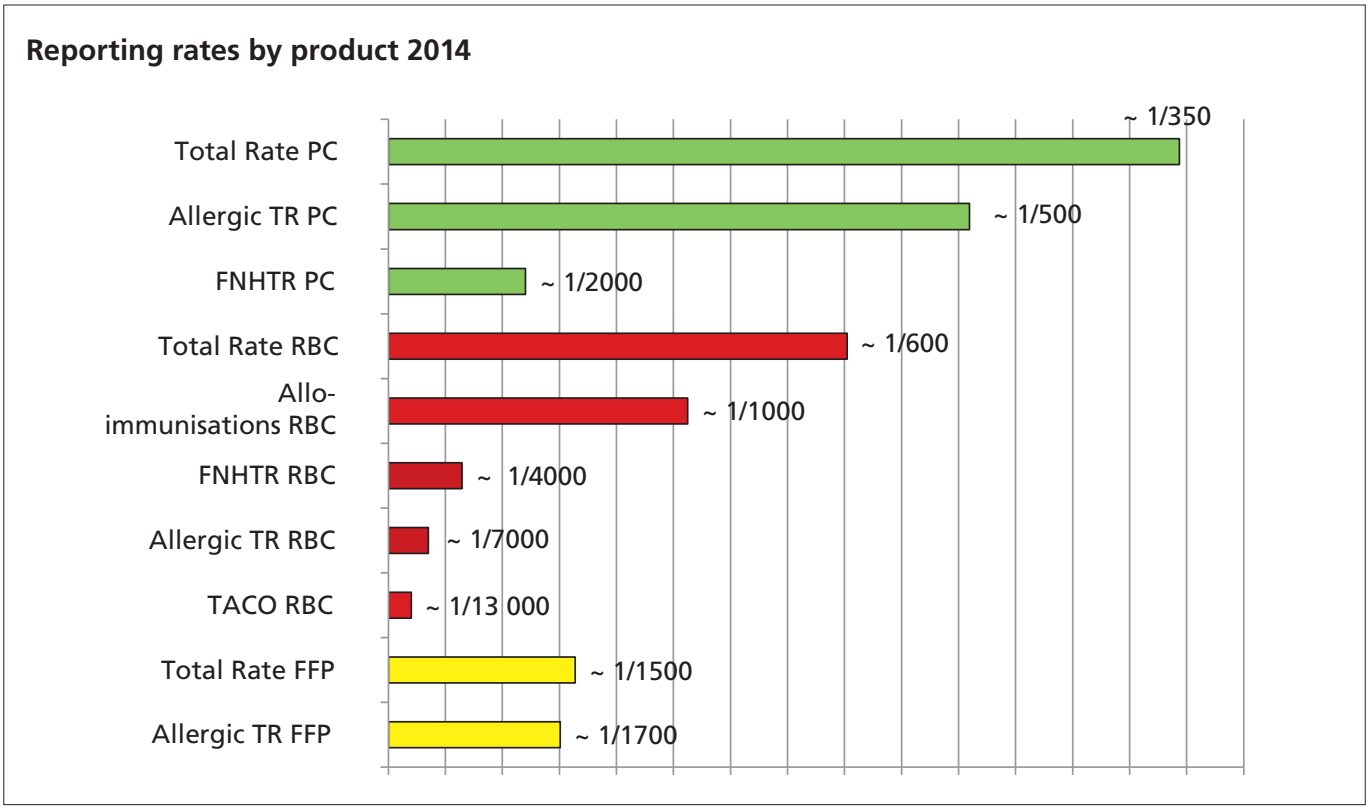


2.4.3 Transfusion risks

The presentation of transfusion risks provides the treating doctor with a basis for the risk-benefit analysis when considering a transfusion and for duly informing the patient about possible adverse effects. For potentially avoidable transfusion reactions, the frequency of the events shows where risk minimisation measures are indicated and documents the effect of measures that have already been taken.
The reporting rates for transfusion reactions in 2014 are shown for **pRBC**, **PC** and **plasma** based on the number of transfusion reactions with high imputability and on the number of blood components issued (Figure 6). Only TR for which there were more than 10 reports are taken into account. Events occurring more rarely cannot be reliably expressed as risks on an annual basis because of the small absolute number of cases.
The reporting rates shown provide information on the type and extent of transfusion risks in Switzerland at the present time. These risks must be viewed as minimum risks because of the possibility of under-reporting.
While allergic reactions account for the lion's share of reports involving PC and plasma by far, they account for only a small proportion of reports involving pRBC. This means that an acute transfusion reaction is more

likely to be of the allergic type with plasma (and PC), while it is more likely to be of the FNHTR type with pRBC.

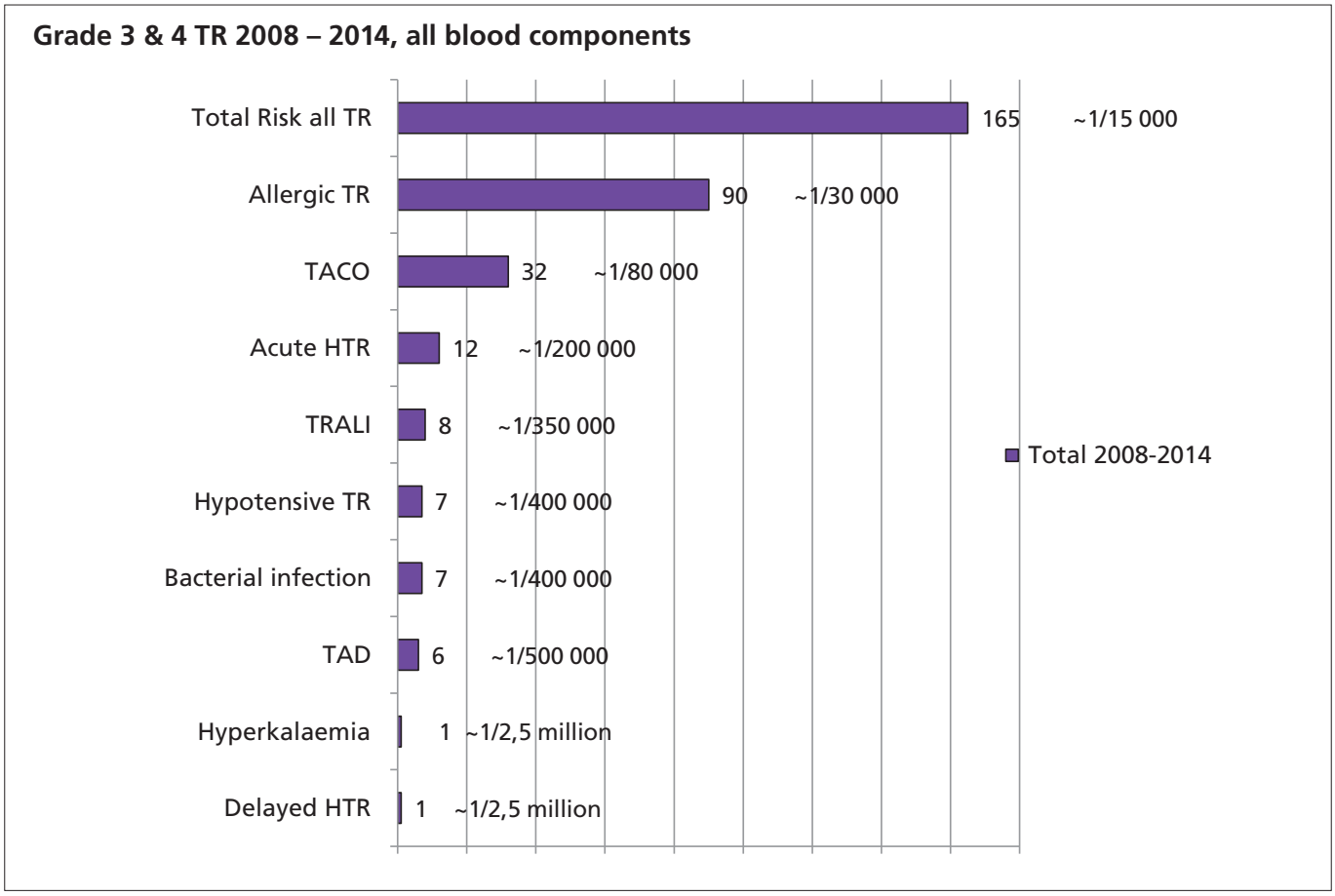
Figure 6: Reporting rates by product and category, only high imputability



2.4.4 Risk of life-threatening and fatal transfusion reactions

Figure 7 shows the Grade 3 and 4 TR for all blood components by category and number for the past 7 years. Once again, only cases with high imputability are shown.

Figure 7: Risk of life-threatening and fatal transfusion reactions

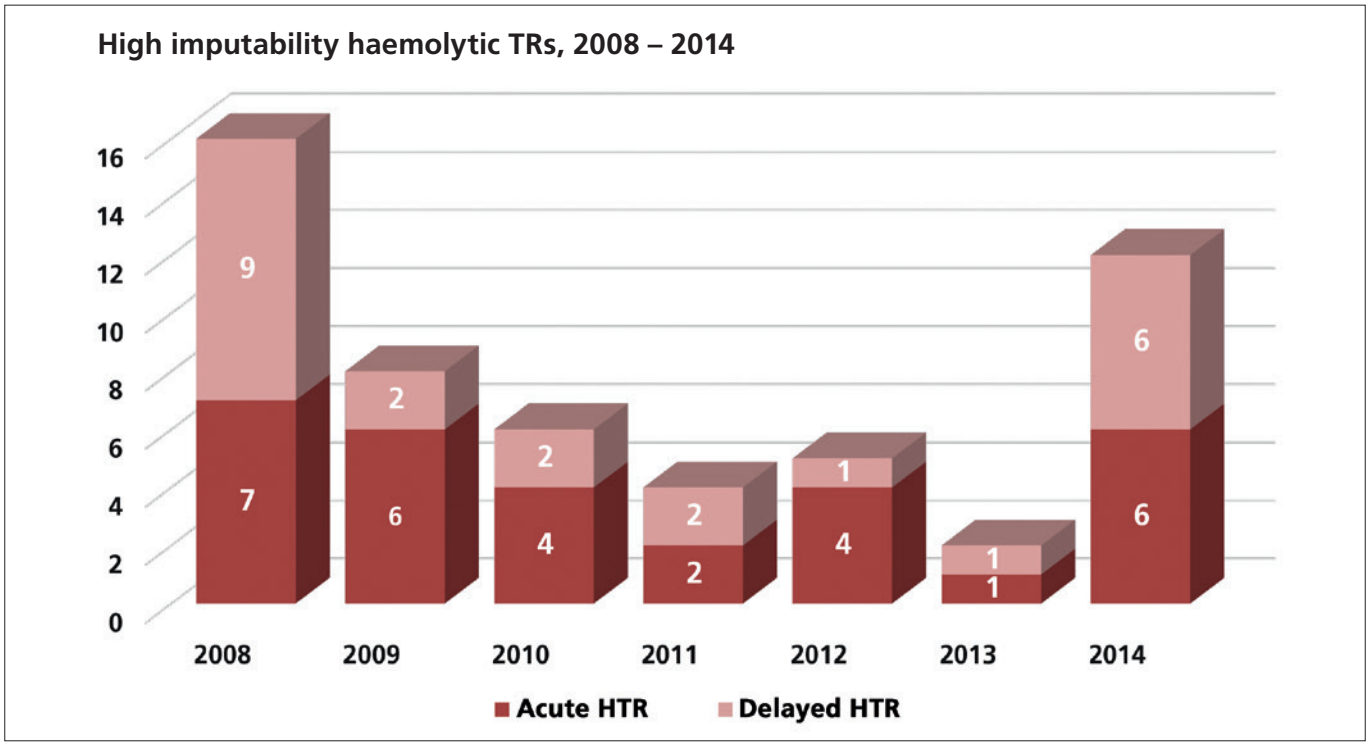


As shown in Figure 7, allergic reactions account for most of the Grade 3 and 4 TR, making up more than half of all life-threatening or fatal events. They are followed by volume overload and, in third place for the first time, acute haemolytic reactions with a total of 12 cases between 2008 and 2014, 5 of them in 2014. These will be described in more detail in the following chapter.

2.5 Haemolytic transfusion reactions

Figure 8 shows the number of haemolytic transfusion reactions (HTR) of all degrees of severity reported between 2008 and 2014. Once again, only high-imputability cases are shown.

Figure 8: Haemolytic transfusion reactions 2008–2014



Following a continuous decline in previous years, the number of reports increased in 2014, with 3 of the 6 acute HTR occurring as separate repeated reactions in one and the same patient.
In spite of the low number, it is important to examine the cases in 2014 for potential common causes in order to identify any possible trends promptly. Table 7 shows all cases with a severe, life-threatening or fatal course (severity grades 2–4).

Table 7: Haemolytic transfusion reactions, Grade 2–4

Case	Symptoms	Hb (g/dl)	Lab	Grade	Cause	Comments
1, acute	Lower back pain, Hypertension	8.0→ 9.4→ 8.4	LDH↑↑↑, Bilirubin↑	4	Cold auto-aglutinins	Insufficient warming of blood components
2a, acute	Fever 40°C, BP 96/60, Pulse 125, shivering, dark urine	6.7→ 8.2→ 6.1		3	?	Immunohaematological tests neg., also in the reference laboratories in Berne and Paris (CNRGS)
2b, acute	Fever 38.5°C, dark urine	6.1→ 7.7→ 5.0	Free Hb↑↑, Haptoglobin↓	3	?	
2c, acute	Dark urine	5.0→ 6.9→ 5.4	LDH↑	3	?	
3, acute	Shivering, BD 77/51 O_2-Sat. 80%	9.3→ 10.5	LDH↑↑, Bilirubin↑, AST↑	3	RBC A_{pos} ↓ Patient O_{pos}	IBCT
4, delayed	Performance↓	5.7→ 11.2→ 9.2	LDH↑, Haptoglobin↓, DAT (C3d)	2	Anti-S	DD Auto-Antibodies
5, delayed	Nausea	6.9→ 7.5→ ~7	LDH↑, Haptoglobin↓	2	Anti-E, -Fy(a), -P1, -H	

The cause of the fatal haemolytic reaction in case 1 was insufficiently prewarmed pRBC, which in this female patient with Waldenström's macroglobulinaemia led the pre-existing cold antibodies to trigger haemolysis. This case is described in chapter 4.1 Case reports. It was not possible to identify unequivocally the pathophysiological mechanism behind the three haemolytic reactions 2a–2c experienced by a female patient. Possible explanations include anti-Jk(b) antibodies compatible with the results of blood group genotyping and/or hyperhaemolysis representing a bystander effect. In case 3, the cause is clear: a classic incorrect transfusion of a pRBC with BG A_{pos} to a male patient with BG O_{pos} after two pRBCs had been inadvertently interchanged. In cases 4 and 5, alloantibodies were detected as the cause of the haemolysis.

To summarise, there is no indication of a common cause of the cases of haemolysis in 2014, and the most likely reason for the increase in the number of reports is therefore a statistical fluctuation due to the low numbers. Other factors such as greater vigilance may also have played a role. It should also be noted that one patient accounting for 3 of the reactions made a substantial contribution to the higher number of cases.

2.6 IBCT (incorrect transfusions / transfusion errors) and near miss events

In 2014, 49 IBCT and transfusion errors were reported, representing a reporting rate of 0.15 per thousand transfusions. There were also 784 reports of so-called near misses, events in which an error or deviation occurred, but was discovered in sufficient time to prevent an IBCT. The reporting rate for 2014 was 2.3 near miss reports per thousand transfusions.

The number of IBCT reports is comparable to previous years. For the first time since the Swiss Haemovigilance System came into being, there was no increase in the absolute number of near miss reports. However, if the declining number of transfusions is taken into account, this produces a slight increase in the reporting rate for near miss events in the year under review.

2.6.1 IBCT

The deviation leading to the transfusion of a blood component that was intended for another patient or was not optimally suited to the patient to whom it was administered occurred during preparation (prescription/ordering) in 1 case, in the laboratory in 15 cases and during administration in 33 cases. In some of the events, sub-optimal products were intentionally administered, for example during massive transfusions when Rhesus-incompatible pRBC had to be given because O_{neg} products were not available.
For further analysis we are only considering the 18 reported cases of transfusion errors in the stricter sense. We define this as the transfusion of a product for which compatibility in terms of ABO, Rh or other blood group antigens is not ensured or is either partial or fortuitous (this category excludes transfusions which are Rh or allo-Antibody-incompatible or which are not known to be compatible but which are performed in emergency situations). Table 8 shows the 18 transfusion errors in the strict sense. In most cases, the deviation occurs at the administration stage, the last stage in the transfusion chain. This contrasts with the near misses (see below), in which errors in the early stages of the transfusion chain (during preparation or in the laboratory, for example) are discovered and corrected at a later stage.

Table 8: Transfusion errors in the strict sense and localisation of deviation

Transfusion error	Number	Description	Localisation of deviations in the transfusion chain
ABO system incompatible	3	A_{pos} pRBC⟶ O_{pos} patient (stopped after 10–30 ml, no symptoms)	Administration
		A_{pos} pRBC⟶ O_{pos} patient Acute HTR (see case 3 in chapter 2.5)	Administration
		Plasma intended for another patient with BG O given to patient with BG B_{neg} during plasmapheresis	Administration
ABO system compatible by chance	5	Wrong product taken from refrigerator, fortuitously ABO identical but not irradiated	Administration
		The blood group had previously been determined incorrectly, and plasma from the wrong blood group was given (fortuitously compatible, A plasma to O patient). Transfusion was started before BG was redetermined. (Emergency situation)	Preparation/ laboratory/ administration
		O_{pos} pRBC⟶ A_{pos} patient	Administration
		PC, fortuitously ABO identical, given to wrong patient	Administration
		Plasma BG A⟶ to patient with BG O	Administration
Allo-Antibody compatibility not ensured	7	Transfusion to wrong patient after valid bedside test, Rh phenotype and K fortuitously compatible?	Administration
		Anti-C^w alloantibodies known elsewhere not taken into account	Laboratory
		Administration of O_{neg} ccddee $Kell_{neg}$ pRBC to patient (born 1982) with CCD.ee phenotype. (Communication problems about urgency)	Administration or failure to communicate phenotype
		Alloantibodies (anti-E and -c) known elsewhere not taken into account during transfusion of 13 pRBC in total.	Laboratory
		pRBC with BG O ordered for patient X but not used was given to patient Y without performing a T&S. (Not by mistake, the BG BG-O_{neg} product was used intentionally)	Administration
		Patient with known anti-S, anti-E and anti-Bg(a) antibodies was given 2 untested O_{neg} emergency pRBC (one of them antigen S-positive) even though other pRBC had already been tested and supplied. (No signs of haemolysis after the transfusion)	Laboratory
		Incompatible Rh phenotype transfused to a patient with allo-Antibodies outside the Rh system (the known Antibody was taken into account)	Laboratory
Administration of a sub-optimal product	3	pRBC from a CMV-positive (antibodies) donor administered to pregnant woman	Administration (ordering)
		Administration of 1 FFP O to an O_{pos} infant less than 3 months of age (according to instructions, AB plasma should have been given)	Laboratory
		8-day-old infant was given BG A_{pos} instead of anstatt O_{pos}. Mother is O_{pos}	Laboratory
Total	**18**		

The transfusion errors presented here show that efficient, well-targeted processes still require considerable attention and that practical quality assurance measures for avoiding and identifying errors continue to be extremely important.

2.6.2 Near miss events

Definition: An error or deviation from standard operating procedures or directives that is discovered before initiating a transfusion and that could have resulted in a transfusion error or a transfusion reaction in the recipient if it had not been detected. Table 9 shows the reported near miss events, categorised by the stage in the transfusion chain at which they occurred and the location in which the error was discovered.

Of the 538 deviations at the preparation stage, 258 (48%) involved labelling/marking of the sample tubes. The analyses had to be repeated in 364 cases and the blood components that had been supplied had to be destroyed in 82.

Table 9: Classification of events by stage of the transfusion chain and location of discovery

Category			**Discovery**				**Most important examples**
Stage at which the deviation occurred	Number	of which process deviations	Laboratory	Ward/ theatre	Returns	Not stated	
Preparation	**538**	79	341	28	10	159	Wrong blood in sample tube Samples and/or order labelled incompletely, discrepantly (e.g. different patient names) or not at all, Ordering error
Laboratory	**55**	0	22	17	1	15	Wrong information entered
Administration	**8**	0	0	4	3	1	Products not transfused after all
Other	**163**	2	9	27	62	65	Handling & storage
Could not be determined	**20**	0	16	2	2	0	Blood group discrepancy with previous finding
Total	**784**	81	**388**	**78**	**78**	**240**	

In 2014, NM events were reported by 32 institutions (2013: 30; 2012: 14; in 2011 just 4). Although near misses are errors that actually occurred, near miss reports from a hospital are by no means indicative of quality assurance problems. On the contrary, we view near miss reports as a sign of an active quality assurance system and a structured approach to dealing with errors. In addition, if an error is reported, other individuals and teams can learn from it.

«A clever man doesn't make all the mistakes himself. He gives others a chance too.»
Winston Churchill

2.7 Donor reactions

The blood transfusion services in Switzerland are required to submit to Swissmedic individual case reports of serious donor reactions and an annual table (tally list) of the cumulative figures. The data will therefore be presented in two different tables. The first table shows the absolute number and a brief description of the serious adverse effects, while the second table (in Annex 1) gives the cumulative figures. The latter does not illustrate the situation for Switzerland as a whole since only three of the 13 blood transfusion services in operation at the time completed the table and submitted it. Based on the donor figures from these three blood transfusion services, however, the rates calculated permit to estimate the frequency and to draw comparisons, for example between whole blood and apheresis donations.

In 2014, 13 individual case reports of donor reactions were received. Nine of them were vasovagal reactions (Table 10).

Table 10: Individual case reports of donor reactions

Category	Number	of which serious	Brief description of the serious cases
A2.4 Unspecific arm pain	2	0	
B1 Immediate vasovagal reaction	3	1	After donating whole blood, unconscious for approx. 10 seconds, heavy perspiration, pallor, nausea and vomiting (5 times) in the following hour, after waiting for 3 hours the donor was admitted to the emergency department
B2 Immediate vasovagal reaction with injury	1	1	Collapse with suspected concussion, subsequently hospitalised
B3 Delayed vasovagal reaction	2	2	Approx. 90 minutes after donating whole blood, malaise, dizziness, nausea, then repeated vomiting. Following prolonged symptoms, admitted to nearest hospital where infusion was given, medical monitoring for approx. 2.5 hours. Then discharged home, patient symptom-free. Following donation of whole blood, vagal nausea after leaving the donation unit. Taken to the emergency department by ambulance.
B4 Delayed vasovagal reaction with injury	3	1	Evening donation in mobile unit. Got up rapidly the next morning at 7.00, went upstairs, dizzy, lost consciousness, fell on head. Son heard the noise and found mother unconscious on the floor. Emergency admission to hospital, broken jaw, lost tooth, cornea damaged by glasses. Osteosynthesis with plate.
C1 Citrate reaction during apheresis	2	1	Intermittent loss of consciousness and somnolence in spite of oral calcium, persistent symptoms led to admission to emergency department, lab work-up and ECG there, infusion, oral calcium, discharge after approx. 3 h.
Total	**13**	**6**	

The reaction rates can be calculated from the cumulative donor reactions reported by 3 regional blood transfusion services. The overall rate is 6.6 reactions per 1,000 donations (carried out by the three transfusion services). One striking feature is that at 18/1,000, the rate for apheresis is roughly three times higher than that for whole blood (6/1,000). This difference is due almost entirely to local reactions, mainly venous haematomas (Annex 1, Table cumulative reports of donor complications).

3. Preventive measures and conclusions

3.1 Pathogen inactivation of platelet concentrates (PC) using the Intercept® procedure

The ongoing evaluation of this measure was reported on in the 2013 Annual Report. In this Annual Report for 2014 we will therefore limit ourselves to providing a short update on the most important figures.

As in previous years, in 2014 there were again no reports of high-imputability transfusion reactions to bacterially contaminated PC. Since the pathogen inactivation (PI) process had been introduced for all PC in Switzerland, no more cases of sepsis due to PC have been reported.

In addition to reliably preventing septic transfusion reactions, the introduction of the PI process has led to a reduction in the number and severity of non-infection-related TR after PC transfusion (Table 12). The most likely explanation for this is the generally lower plasma content of PI-PC, which reduces allergic and febrile TR to plasma constituent.

The question of whether pathogen-inactivated PC constitute a higher risk of TRALI than conventional platelet concentrates is still subject to controversy [3, 4]. No high-imputability TRALI case was reported in Switzerland in 2014. Of the TRALI cases with imputability ‚possible', none occurred with a PC transfusion, but with other products. Continuous assessment of this potential risk, incorporating new findings and vigilance data, is extremely valuable. It is therefore important that everyone involved in the transfusion process continues to be aware of the possibility of severe transfusion reactions with respiratory symptoms and that they initiate investigations of suspected cases and send the reports to Swissmedic.

Possible effects of the PI process on platelet stability and functionality have long been the subject of research. There were no reports of lack of efficacy in 2014. Haemovigilance officers and doctors are also required to report cases in which blood products are suspected of not being effective if product-specific factors are thought to be the cause or if the lack of efficacy cannot be otherwise explained.

Table 12: Reported transfusion reactions involving conventional and pathogen-inactivated PC

Transfusion reactions	**2008–2011 cPC**		**2011–2014 PI-PC**		
Units transfused	93'600		130'800		
Risk = 1 reaction per x PC	Reports	Risk	Reports	Risk	
All high-imputability reports	344	~ 1 / 270	349	~ 1 / 375	P<0.001
High-imputability reports, Grade 3 & 4	33	~ 1 / 2800	15	~ 1 / 8700	P<0.001

cPC = conventional platelet concentrates
PI-PC = pathogen-inactivated platelet concentrates

3.2 Specificities of detectable alloantibodies

Alloantibody-formation may be induced by transfusions or pregnancy and are directed against antigens that the affected person does not have. Most of these antibodies could lead to (usually) delayed haemolytic reactions in the recipient in the course of a subsequent transfusion. If the recipient becomes pregnant, there is also the risk of some of these antibodies triggering haemolysis in the foetus or new-born child.

The reported alloantibodies were analysed not only for 2014 but also for the seven-year period 2008 – 2014 in order to produce a statistically robust evaluation. During this period, a total of 2,047 reports of one or several detectable alloantibodies were received. 2,363 specified antibodies were entered in the national HV database from these reports, as illustrated in Figure 9. The major alloantibodies C, c, E, e and K account for by far the largest proportion. Rh/K phenotype testing is used to test both blood products and recipients for these antigens to ensure that transfusions are compatible.

Girls and women under 50 years of age are particularly vulnerable to alloimmunisation because of the risk of foetal/neonatal haemolysis in a later pregnancy. The alloantibodies reported in this group are shown in Figure 10.

Figure 9: Specification of reported alloantibodies 2008–2014 (all patients)

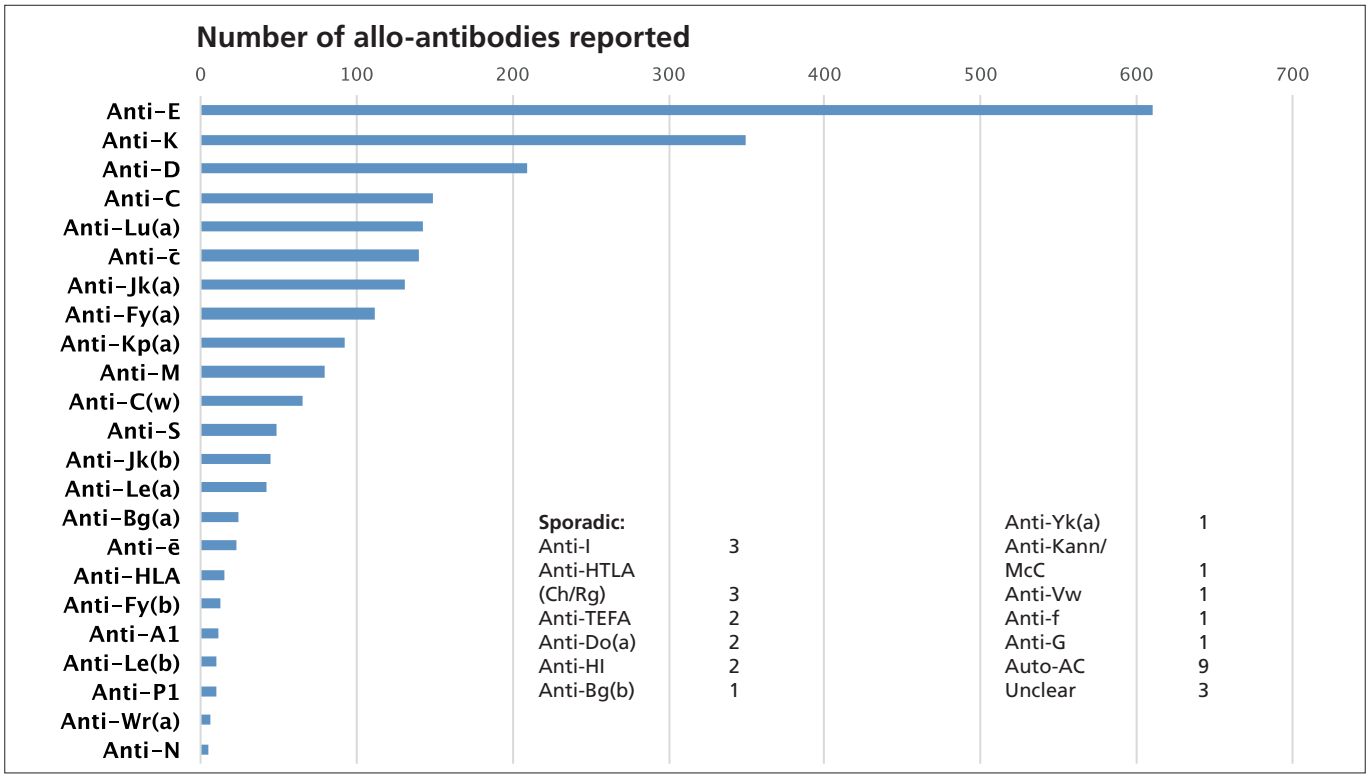
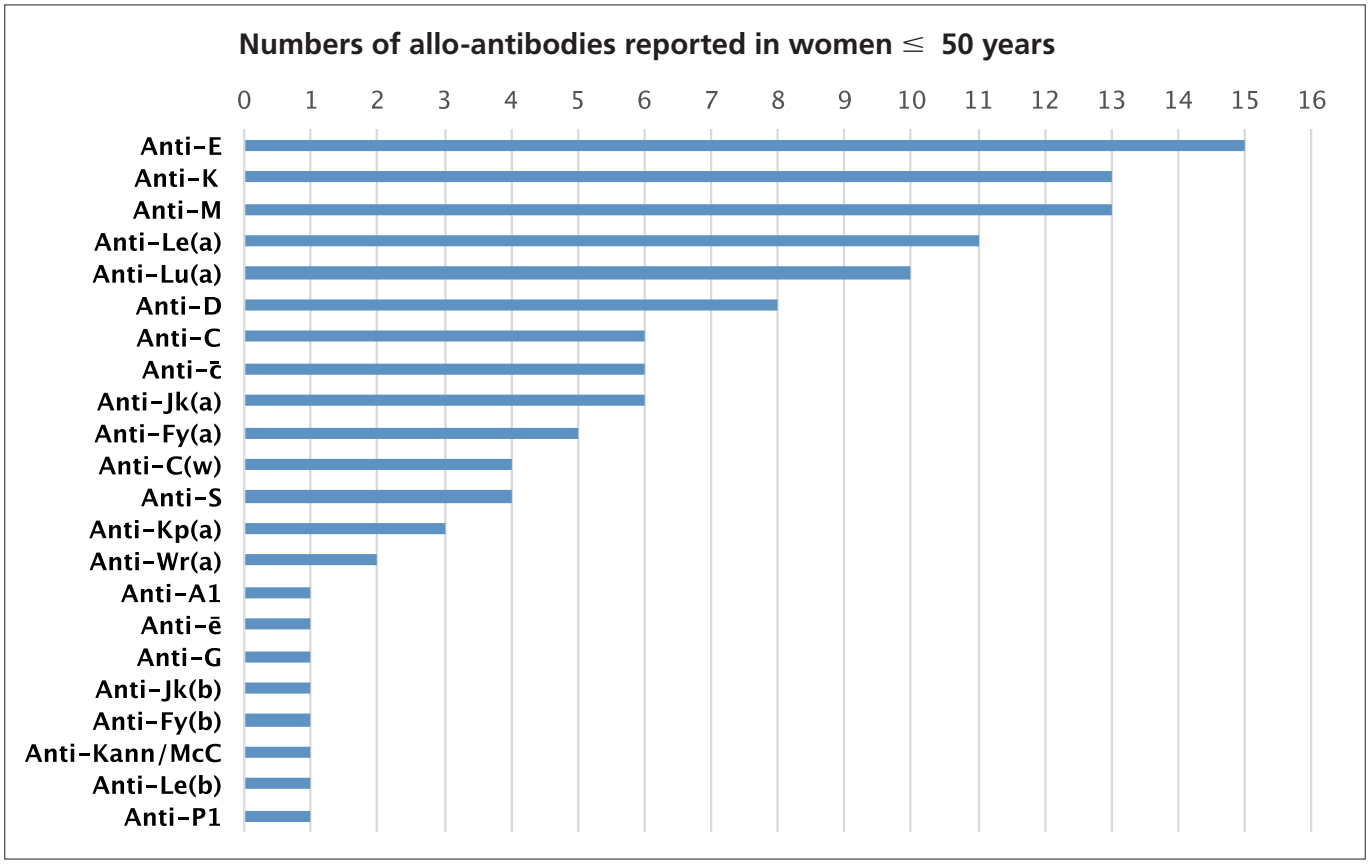
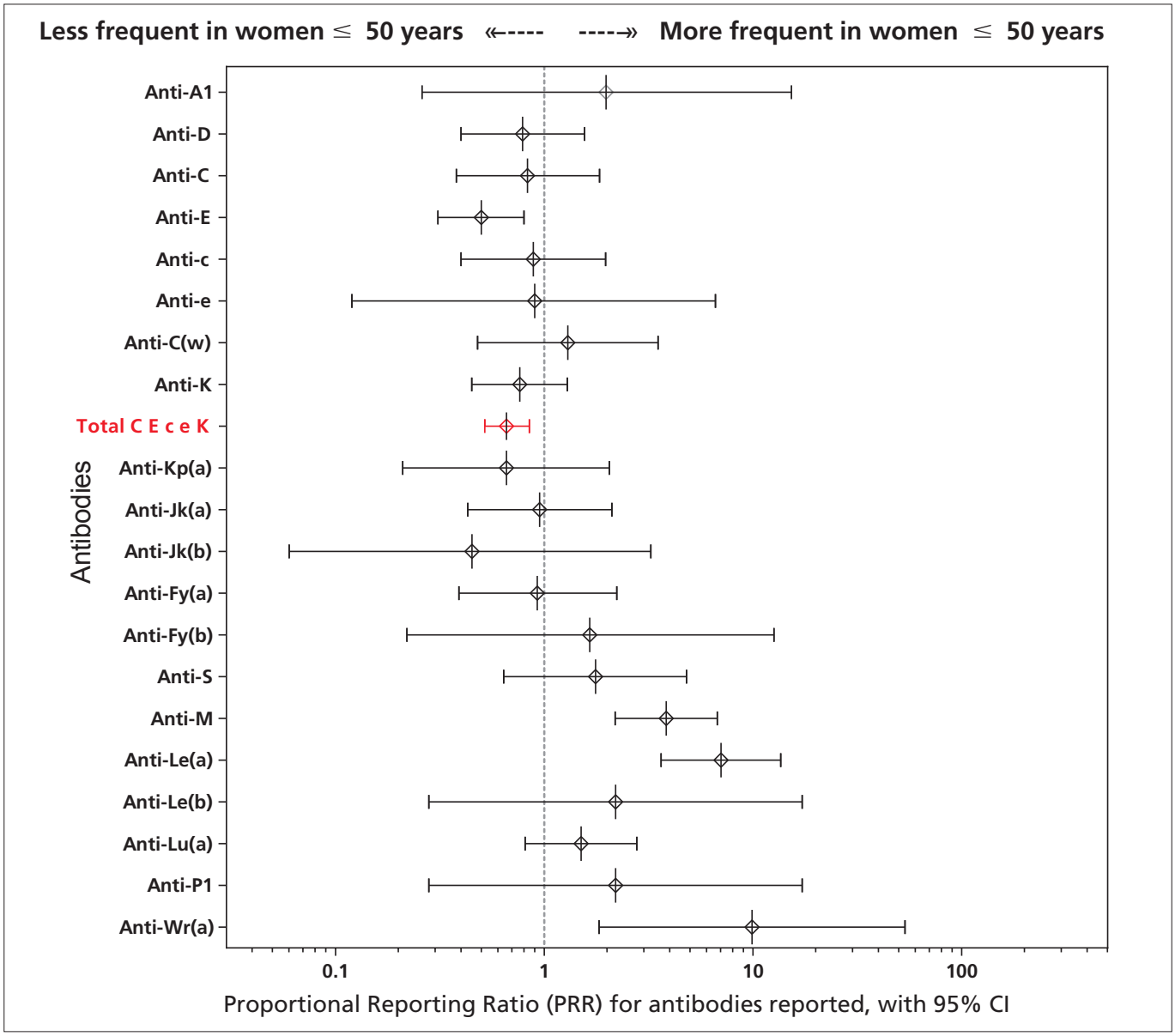


Figure 10: Specification of reported alloantibodies 2008–2014, only female patients ≤ 50



Apart from the substantially lower number of reports, one striking feature of Figure 10 is the different distribution compared to Figure 9. The ‚Rh/K phenotype' alloantibodies still account for the highest proportion in female patients ≤ 50, but the predominance is not as great as in the total population shown in Figure 9. One possible explanation for this smaller proportion of ‚Rh/K phenotype' antibody reports is compliance with the relevant Swiss recommendations [2]. The recommended state of the art is to give female patients ≤ 50 years of age transfusions of pRBC with a compatible Rh/K phenotype (the same is recommended for other special patient groups as well). The high proportion of anti-M or Anti-Le(a) antibodies, both of which can be formed during pregnancy, may also have contributed to the slightly different distribution among female patients ≤ 50. Figure 11 shows the proportion of Rh/K phenotype antibodies in female patients ≤ 50 in comparison with other patients (male patients and female patients over 50).

Figure 11:
Relative frequency of alloantibodies in female patients ≤ 50 in comparison with all other patients



Illustrative example for Figure 11: The proportion of anti-E in female patients ≤ 50 is 13% of all reported antibodies for this group. The proportion of anti-E in the comparator group is 26%. This gives a relative proportion of 0.5, or in other words the proportion is only half the size of that in the comparator group (beware the logarithmic x axis).

Figure 11 shows that immunisation with the antibodies that could prove problematic if the patient becomes pregnant at a later date is reported proportionally less often in female patients ≤ 50. This can be interpreted as a sign that the recommendations produced jointly by the Swiss Transfusion Medicine Association and Swiss Transfusion SRC are indeed being implemented. Systematic compliance with these recommendations should remain the goal in the future so that alloimmunisation of this type can continue to be avoided in this group of female patients.

4. Sample case reports

4.1 Deaths

Case 1 Acute haemolytic transfusion reaction, pRBC

A 68-year-old patient with stage B Waldenström's macroglobulinaemia with cold antibodies (anti-I), chronic haemolysis, severe acrocyanosis and pancytopenia under chemotherapy was given 2 pRBC each containing approx. 270 ml. Since the prewarmer for the pRBC was not available at that precise moment, the first pRBC was transfused using an improvised system to warm it (a urine bag filled with warm water through which the transfusion line was passed). While this insufficiently warmed pRBC was being transfused, the patient experienced pain in the kidney region and her blood pressure rose from 100/50 to 160/90 mmHg. Her body temperature dropped from 37.6 to 34.7°C. The reaction was initially not recognised as a haemolytic transfusion reaction. The second pRBC was warmed and administered correctly. The next day the patient's clinical condition deteriorated, with persistent pain in the kidney region, persistently elevated blood pressure and tachycardia. Dyspnoea subsequently occurred with hypoxaemia, headache and loss of haemodynamic stability with a drop in blood pressure, and oligo/anuria. That evening the patient was transferred to the ICU in a state of shock. She developed right-heart failure with no evidence of pulmonary embolism and disseminated intravascular coagulation, and died the next day.

In the laboratory, an anti-I titre of > 1/1000 and an anti-i of 1/64 were recorded 3 days before the reaction, anti-I was 1/32 at 22°C, negative at 37°C; IgM was 5.53 g/l. After the reaction, laboratory testing showed signs of acute exacerbation of the chronic haemolysis (e.g. LDH up to 5600 U/l). Clinically and radiologically there were no signs of ARDS, volume overload or lung toxicity due to chemotherapy. The reaction was classified as an acute haemolytic transfusion reaction due to insufficiently warmed erythrocytes in a patient with cold antibodies; the imputability was assessed as ‚probable'. The hospital concerned has implemented various fundamental measures to prevent similar events from happening. Among other things, transfusions are no longer performed in the evenings and at night, except in an emergency. In addition, the laboratory/blood bank has purchased a prewarmer that can be issued with the pRBC if required.

Case 2 Transfusion transmitted infection: Chagas disease, PC

Based on the Chagas screening for donors with respective exposure recently introduced in Switzerland, a donor was tested positive in 2013. A look-back has been performed for all products from his previous donations. Thereby, a patient was identified, who had received a PC from this donor in 2008, and who developed acute Chagas myocarditis two years later. The imputability was assessed as 'possible'. It is foreseen to publish the case report in a scientific journal soon. In order not to compromise this publication, we forego a detailed presentation here.

4.2 Life-threatening transfusion reactions

Case 3 Anaphylactic TR, PCb

A 24-year-old patient with dyskeratosis congenita and a myelodysplastic syndrome developed pruritis without urticaria approx. 15 minutes after the start of a transfusion of a pooled platelet concentrate. The transfusion was discontinued and symptomatic treatment with 2 mg clemastin was given. The patient developed an increasing sensation of constriction in the throat and 80 mg methylprednisolone was administered additionally, but with no improvement. There was no indication of bronchospasm on auscultation, oxygen saturation was over 95%. Dyspnoea led to the suspicion of larynx/glottis oedema due to an allergic transfusion reaction. Administration of 0.5 mg adrenaline i.v. (diluted 1/20, in 2 ml portions) produced only a slight improvement. In view of the moderate response to the measures taken, a resuscitation alarm was triggered and a further dose of adrenaline (1 mg) was given; this was followed by a substantial improvement in the symptoms and stress-induced hyperventilation. This decreased following administration of 5 mg midazolam i.v. During the reaction, the patient was tachycardic with normal to hypertensive blood pressure. After monitoring and transfusion of a

pRBC the patient was discharged home in an asymptomatic condition approx. 3 hours later.
The increase in platelets from 2 to 41 G/l was thought to be adequate and the transfusion reaction was not investigated further in view of the unequivocal clinical picture and the response to systematic antiallergic therapy.

Comments: The reaction described here was assessed as a mild allergic transfusion reaction in view of the exclusively cutaneous initial manifestation. Additional symptoms developed despite antiallergic therapy with antihistamines and corticosteroids, and it was initially not possible to control their severity adequately even with adrenaline. This and the subsequent decision to trigger a resuscitation alarm illustrate the clinical reassessment of the reaction as a life-threatening event. The take-home message of this case is the importance of monitoring the course thoroughly after symptomatic therapy, even in allergic reactions that initially appear to be mild.

Case 4 Transfusion-associated dyspnoea, PCa

A 58-year-old patient with AML experienced dyspnoea and hypoxia with no relevant haemodynamic changes 3 minutes after the start of a platelet transfusion. The symptoms resolved spontaneously a few seconds after the transfusion had been interrupted. A few minutes after the transfusion had been restarted, dyspnoea occurred again, accompanied by a drop in oxygen saturation to 80% in ambient air. The patient responded well to supplemental oxygen. Auscultation showed left basal hypoventilation and right basal crackles, assessed as being unchanged from the findings on the morning before the transfusion. Blood gas analysis under 2 litres of O_2 showed mild alkalosis, O_2 and CO_2 were both at the lower limit of the reference range, the chest x-ray showed the known left-sided pleural effusion. The ECG was unchanged from the previous findings. The patient had another episode of dyspnoea the following night. The chest x-ray showed no PE, an increase in the pleural effusion and thickened alveolar septa on both sides (more marked on the right).

Comments: We assessed this case as transfusion-associated dyspnoea. An allergic reaction with solely respiratory symptoms would have been possible, although the auscultation findings (with no evidence of broncho-obstructive involvement) and the rapid spontaneous resolution after the transfusion had been interrupted are not typical. Transfusion-associated volume overload is unlikely because of the short 3-minute infusion time and the absence of haemodynamic changes. The nearly normal blood gas analysis, the absence of ground-glass opacities on the chest x-ray and the rapid improvement are in disfavour of TRALI. The reporter and the haemovigilance officer assessed the causal connection as certain on the basis of the positive re-challenge (symptoms occurred again after the transfusion had been restarted). We also feel that the high imputability is definite. We agree with the assessment by the treating doctors that the event was life-threatening.

Case 5 Bacterial infection, pRBC

An 83-year-old patient with haemodynamically relevant upper GI bleeding while on oral anticoagulation resulting in anaemia developed a fever following transfusion of a pRBC. Immunohaematological testing revealed no evidence or hemolysis or immune haemoatlogical intolernce, Klebsiella pneumonia grew within 24 hours in residual material from the bag, no growth was observed in the initial blood cultures taken from the patient. Klebsiella pneumonia was also found in further blood cultures taken from the patient 3 days after the transfusion. Comparison of the results of sensitivity testing and molecular typing both bacterial isolates showed no differences between the two strains. Analysis of the sample from the serum bank and the plasma from the same donation produced no findings of interest, and a new, in-depth investigation of the donor's medical history produced no indication of a cause of bacteraemia through which the germ could have passed into the donation. Taking all the findings together, the blood transfusion service concerned and the haemovigilance officer classified the case as transfusion-associated sepsis with (very) probable imputability.

Comments: We can add nothing to the thorough and comprehensive investigation that was carried out, nor to the assessment by those involved. Although transfusion-associated bacteraemia due to pRBC is rare, it is still important to investigate the possibility of bacterial infection in patients with febrile, transfusion-associated reactions following pRBC transfusions, as this case demonstrates.

Case 6 TACO, pRBC

This 72-year-old patient was in acute renal failure due to thrombotic microangiopathy in the context of carcinoma of the pancreatic head being treated with chemotherapy, and had a pulmonary embolism. At the end of the erythrocyte transfusion, given over 90 minutes, dyspnoea, angina pectoris, loss of consciousness, an increase in heart rate from 96 to 124 bmp and a rise in blood pressure from 150/96 to 228/128 mmHg occurred. Administration of diuretics produced a substantial improvement.
The patient's temperature did not rise. A review of the documentation and immunohaematological investigation did not produce any conspicuous findings, culture of the product and the patient's blood showed no growth. The positive signs of haemolysis – elevated free haemoglobin in plasma at 7.7 µmol/l (reference value up to 3.5), haptoglobin < 0.08 g/l (normal 0.62-1.67) and LDH 689 U/l, (no baseline values available) – are viewed as being associated with the microangiopathy.
The reaction, assessed as life-threatening, was reported as volume overload with probable imputability, and we concur with this evaluation.

Comments: The transfusion rate of approx. 3 ml/min (based on the 90-minute duration of the transfusion and the pRBC volume of 275 ±75 ml in the specification) is clearly higher than the 1 ml per hour per kg bodyweight recommended for both risk factors pre-existing renal failure and age over 60. The course, with the symptoms occurring at the end of the transfusion and a substantial response to diuretics, also mitigate clearly in favour of this diagnosis.

Case 7 TACO, pRBC

After surgery for a total knee replacement, an 82-year-old patient with haemoglobin at 9.8 g/l was given a transfusion of pRBC over 1 hour on the instruction of the surgeon. He was then given 20 mg furosemide and a 2nd pRBC was transfused over 90 minutes. The patient experienced a sensation of retrosternal pressure with no subjective shortness of breath after an unspecified latency period. A clinical diagnosis of volume overload was made, subsequently pulmonary oedema developed with bilateral pleural effusion and an NT-pro-BNP of 4954 (the baseline value was not stated).

Comments: Transfusion of pRBC (275 ±75 ml) within one hour to a patient over 80 clearly exceeds the recommended rate of 1 ml/kg BW/h for patients with risk factors for volume overload. The administration of a diuretic between the two transfusions is a suitable means of preventing or treating volume overload, but the second transfusion was also given more rapidly than is recommended. It is also questionable whether the transfusion was indicated in a patient with a postoperative haemoglobin level of 9.8 g/l. Transfusion of pRBC is generally not recommended in patients with no signs of anaemic hypoxia and haemoglobin in excess of 8 g/l [7].

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Annex 1:
Table: Cumulative reports of donor complications from 3 regional blood transfusion services (the three tables have been combined)

Category	Number of events related to whole blood donations					Number of events related to apheresis					Number of events Total					
	Grade 1*	Grade 2	Grade 3	Sub-total	Rate: /1000 donations**	Grade 1	Grade 2	Grade 3	Sub-total	Rate: /1000 donations*	Total	Grade 1	Grade 2	Grade 3	Total	Rate: /1000 donations*
A Complications with local symptoms																
A1 Damaged vessels (blood outside the vessels)																
A1.1 Haematoma (bruise)	112	9	1	122	1.12	49	7		56	10.18	178	161	16	1	178	1.55
A1.2 Arterial puncture	4	2		6	0.05				0	0.00	6	4	2		6	0.05
A1.3 Delayed bleeding (haematoma delayed)	2	4		6	0.05				0	0.00	6	2	4		6	0.05
A2 Complications mainly characterized by pain																
A2.1 Nerve irritation	4	2		6	0.05				0	0.00	6	4	2		6	0.05
A2.2 Nerve injury	4	3		7	0.06				0	0.00	7	4	3		7	0.06
A2.3 Tendon injury				0	0.00				0	0.00	0				0	0.00
A2.4 Other Painful arm	30	1		31	0.28	7			7	1.27	38	37	1		38	0.33
A3 Localised infection/inflammation																
A3.1 Thrombophlebitis			3	3	0.03				0	0.00	3			3	3	0.03
A3.2 Local allergic reaction		1		1	0.01				0	0.00	1		1		1	0.01
Total local adverse events	156	22	4	182	1.67	56	7		63	11.45	245	212	29	4	245	2.14
B Complications mainly with generalized symptoms: vasovagal reactions (VVR)																
B1 VVR immediate	401	48	2	451	4.13	21	3		24	4.36	475	422	51	2	475	4.14
B2 VVR immediate with injury		9		9	0.08				0	0.00	9		9		9	0.08
B3 VVR delayed	8	5	3	16	0.15	1			1	0.18	17	9	5	3	17	0.15
B4 VVR delayed with injury		2		2	0.02				0	0.00	2		2		2	0.02
Total vasovagal reactions (VVR)	409	64	5	478	4.38	22	3		25	4.55	503	431	67	5	503	4.39
C Complications related to apheresis																
C1 Citrate reaction				0	0.00	4	6	1	11	2.00	11	4	6	1	11	0.10
C2 Haemolysis				0	0.00				0	0.00	0				0	0.00
C3 Generalised allergic reaction				0	0.00				0	0.00	0				0	0.00
C4 Air embolism				0	0.00				0	0.00	0				0	0.00
Total complications related to apheresis				0	0.00	4	6	1	11	2.00	11	4	6	1	11	0.10
D Other complications																
D1 Cardiovascular events																
D1.1 Angina pectoris				0	0.00				0	0.00	0				0	0.00
D1.2 Myocardial infarction				0	0.00				0	0.00	0				0	0.00
D1.3 TIA				0	0.00				0	0.00	0				0	0.00
D1.4 Cerebrovascular accident				0	0.00				0	0.00	0				0	0.00
Total Cardiovascular events				0	0.00				0	0.00	0				0	0.00
D2 Other complications, events rarely reported																
D2 Tachycardia/Fatigue	2			2	0.02				0	0.00	2	2			2	0.02
Total other complications	2			2	0.02				0	0.00	2	2			2	0.02
Total all events	567	86	9	662	6.06	82	16	1	99	18.0		649	102	10	761	6.63
Death				0	0.00				0	0.00	0				0	0.00

*Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe (see reporting form for details)
**Rate = Number of events per 1000 donations of the three reporting regional blood services