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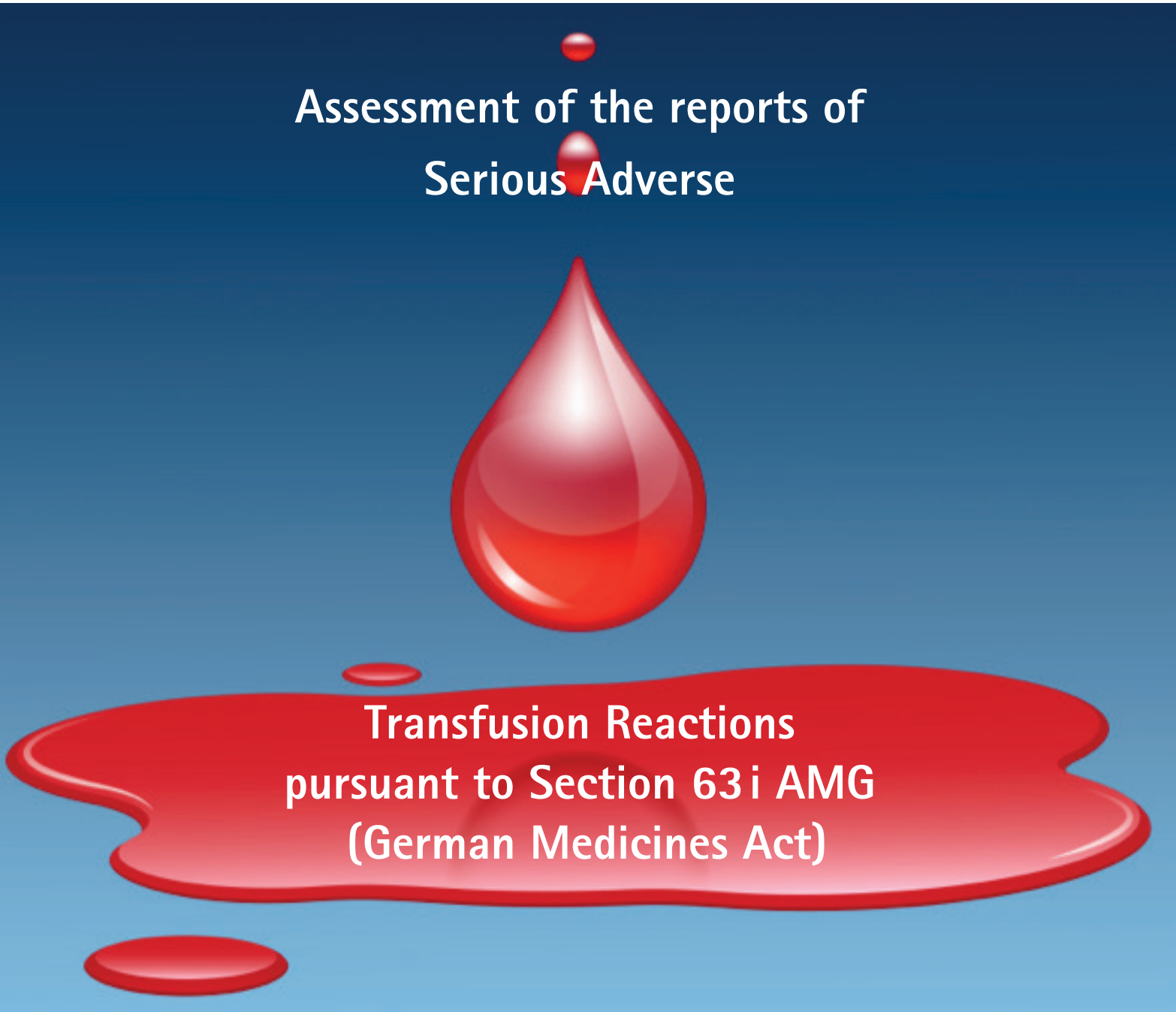
// HAEMOVIGILANCE REPORT OF THE PAUL-EHRLICH-INSTITUT //

2015



Assessment of the reports of Serious Adverse Transfusion Reactions pursuant to Section 63 i AMG (German Medicines Act)

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// Contents //

// 1. Introduction //

The current haemovigilance report from the Paul-Ehrlich-Institut summarises the reports of serious adverse transfusion reactions (SAR), serious adverse donor reactions (donor SAR), and serious adverse events (SAE) of 2015 and compares them with the reporting data from the years before that period (1997–2014). A direct comparison of the data from Germany with those of other haemovigilance systems (such as SHOT in the UK [1] and Switzerland [2]) is difficult, since different definitions are partly used as a basis.

The evaluation algorithm introduced in the haemovigilance report of the PEI of 2013-2014 [3] was maintained to obtain a more long-term comparison of the data und to be able to distinguish between possible and probable/certain immunogenic as well as non-immunogenic reactions.

To assess the benefit of anti-HBC screening [4], the number of deferral procedures on the basis of the donor look backs started due to a confirmed positive anti-HBc result was again presented here.

This haemovigilance report focuses on HEV transmissions reported as suspected transfusion reactions, on serious adverse donor reactions, and on incorrect transfusions to be reported as serious adverse events or serious adverse reactions since the amendment to the AMG (Arzneimittelgesetz, German Medicines Act).

As already emphasised in previous haemovigilance reports, the exact documentation of all adverse events by the physicians in charge and the blood donation centres affected, their correct report to the PEI, as well as the standardised and transparent evaluation of the data reported is essential for a better identification of previously undetected risks. Moreover, it is the basis for a discussion with the institutes affected on actions to be taken to increase the safety of the transfusion chain. The haemovigilance data collected are reported to the European Commission by the Paul-Ehrlich-Institut annually pursuant to Directive 2005/61/EC [5, 6].

// 2. Abbreviations //

Ab	Antibody
Ag	Antigen
AK Blut	National Advisory Committee Blood
AMG	Arzneimittelgesetz (German Medicines Act)
AML	Acute myeloid leukaemia
Anti-HBc	Antibodies against hepatitis B-core antigen
A-PC	Apheresis platelet concentrate(s)
ATR	Acute (allergic) transfusion reaction(s)
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies in Germany)
CJD/vCJD	Creutzfeldt-Jakob Disease/variant Creutzfeldt-Jakob Disease
CML	Chronic myeloid leukaemia
CMV	Cytomegaly virus
GvHD	Graft vs. Host Disease
HAV	Hepatitis-A virus
HBV	Hepatitis-B virus
HCV	Hepatitis-C virus
HEV	Hepatitis-E virus
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HNA	Human neutrophil antigen
HPA	Human platelet antigen
HTR	Haemolytic transfusion reaction(s)
IBCT	Incorrect blood component(s) transfused
ID-NAT	Individual Donor-NAT
IHN	International Haemovigilance Network
LDH	Lactate dehydrogenase
LOC	Loss of consciousness
NAT	Nucleic acid amplification technology
PC	Platelet concentrate(s)
PDI	Post donation information
PEI	Paul-Ehrlich-Institut
P-PC	Pool platelet concentrate(s)
PTP	Post-transfusion purpura
RBC	Red blood cell concentrate(s)
SAE	serious adverse event(s)
SAR	serious adverse reaction(s)
TACO	Transfusion-associated circulatory overload
TTBI	Transfusion-transmitted bacterial infection(s)
TTVI	Transfusion-transmitted viral infection(s)
TFG	Transfusionsgesetz (German Transfusion Act)
TPHA	Treponema pallidum haemagglutination
TRALI	Transfusion related acute lung-injury
WB	Whole blood

// 3. Methods //

3.1 Introduction

Each report of serious transfusion reactions in donors or recipients and all serious adverse events in the transfusion chain are captured at the PEI and assessed in accordance with the criteria of the International Haemovigilance Network (IHN). The SAE, donor and recipient SAR reported are grouped together and their ratio in comparison with the number of donations or transfusions/transfused blood components, as applicable, is determined. The legal basis for the reports on the part of the blood donation centres are laid down in the German Medicines Act (Section 63 i AMG) and for reports on the part of the responsible physicians in the German Transfusion Act (Section 16 (2) TFG). For this purpose, the PEI provides on its website the appropriate forms to be used for reporting [7]. In the reporting forms, the responsible physician documents the information on the transfusion such as time and type of the blood component administered, the course of the transfusion reaction and information on the recipient such as data of birth, sex, the underlying disease and the relevant concomitant diseases of the patient. The blood donation centres involved complete the data by specific information on the donors, the lab tests performed and look-back procedures, and, in the case of donor reactions, specify the type of reaction. Incorrect transfusions without transfusion reactions have to be reported to the PEI as serious adverse events pursuant to 63 i AMG (16th amendment of the AMG) by the pharmaceutical company. In the case of incorrect transfusions with a transfusion reaction, the treating doctor is also subject to a reporting obligation pursuant to Section 16 (2) TFG [8]. Since by law exclusively reports of serious reactions and events are required, only sporadic information on non-serious events is available to the PEI and is therefore not included in the evaluation.

3.2 Categorisation of transfusion reactions

Serious transfusion reactions are defined in accordance with the criteria of the International Haemovigilance Network (IHN) [9]. The classification and rating of the transfusion reactions was performed using the criteria presented in the box on page 7. Reported cases of acute (allergic) transfusion reactions were further subdivided with the aid of the classification according to Ring and Messmer [10] conceived by the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF, Association of the Scientific Medical Societies in Germany). Based on this classification, a distinction was made between allergic transfusion reactions Grades I and II, and serious allergic or anaphylactoid transfusion reactions, as the case may be, Grades III and IV. However, only serious acute allergic transfusion reactions were taken into account in the evaluation referenced here. Likewise, non-serious concomitant transfusion-related dyspnoea without bronchospasm as well as febrile, non-haemolytic transfusion reactions with a course of mild symptoms are not included.

In assessing suspected cases of TRALI, a distinction was made between possible and probable/certain TRALI events. The category of probable/certain cases was then subdivided into immunogenic and non-immunogenic events [11, 12].

The amount of blood components prepared by German blood donation centres as well as the loss at manufacturers and users has been reported to the PEI since 1998 pursuant to Section 21 TFG [8]. The annual

consumption of the individual blood components can be calculated as an approximate figure, and is also published on a regular basis in the report pursuant to Section 21 TFG of the PEI [13]. Table 1 (Page 36) summarises these data on the consumption of blood components; Figure 7 (Page 35) shows the trend for the consumption of the individual blood components since 2000. In Tables 3 to 6 (Pages 37-40) and 8 to 9 (Pages 42, 43), the reporting frequencies of the transfusion reactions referring to 10^6 transfused units of the appropriate blood component are determined for a period of four years each. In Table 10 (Page 43) and Figure 5 (Page 34), the reporting frequency is determined for the entire period, starting with reporting year 2000 for which robust data on the consumption pursuant to Section 21 TFG are available for the first time.

Box 1: Definition of serious transfusion reactions used for the assessment of the data (by IHN, AWMF criteria)

Acute (allergic) transfusion reaction (ATR):

Grade I/II: Skin rash, itching, hot flushes with redness of the skin, nettle rash, angio-oedema, nausea, cramps, dyspnoea, arrhythmia, drop in systolic blood pressure ≥20 mm Hg, rise in heart rate ≥20/min (definition of tachycardia); grade III/IV: Vomiting, defecation, bronchospasm, cyanosis, larynx oedema, shock, respiratory arrest, circulatory arrest.

Occurrence of the symptoms within 24 hours after transfusion, exclusion of other transfusion reactions.

Transfusion associated acute lung insufficiency (TRALI):

Acute respiratory distress (symptoms within six hours following transfusion start), dyspnoea, hypoxaemia, newly occurring bilateral lung oedema (confirmed radiological examination), exclusion of hypervolaemia (cardiac, renal, iatrogenic).

Haemolytic transfusion reaction (HTR):

Fever accompanied by other symptoms (respiratory distress, hypotension, tachycardia, pain in the region of the kidneys), macrohaematuria, inadequate rise in the haemoglobin level following transfusion, drop in the haemoglobin level >2g/dl within 24 hours, rise in the lactate dehydrogenase level (LDH level) >50% within 24 hours, rise in the bilirubin level, haemoglobinaemia, drop in haptoglobin in temporal connection with the transfusion. The reaction is confirmed by a positive antiglobulin test or a positive crossmatch-test, as applicable. Acute HTR manifests itself within 24 hours; delayed HTR manifests itself within a period of >24 hours to 28 days.

Transfusion transmitted bacterial infection (TTBI):

Occurrence of fever >39°C or a rise in body temperature by 2°C within 24 hours accompanied by chills and tachycardia. Suspected transfusion transmitted bacterial infections are verified by detection of the bacterium in the transfused blood product or in the recipient and confirmed by detection of the same bacteria strain in the blood of the recipient and the transfused blood components.

Transfusion transmitted viral infection (TTVI: HBV, HCV, HIV):

TTVI is suspected in the case of virus detection in the recipient or seroconversion of the recipient post transfusion, as applicable. To establish a causal relationship, the look-back procedure based on the recipient must be performed pursuant to Opinion 34/35 of the AK Blut for HIV, HBV, or HCV, or an appropriately adapted procedure based on these principles for other pathogens, as the case may be.

Transfusion associated circulatory overload (TACO):

Respiratory distress, tachycardia, hypertension, typical signs of cardiogenic lung oedema in the chest radiograph, evidence of a positive liquid balance and rise in blood pressure within six hours after the end of the transfusion, improvement of the condition after administration of diuretics.

Incorrect transfusion:

Treatment with ABO-incompatible blood components, transfusion of by chance ABO-compatible or ABO-identical blood components, of blood components the allo-Ab compatibility of which has not been confirmed, of blood components not manufactured conforming to the requirements (e.g.: no irradiation step was performed), of untested blood components, and transfusion of blood components without an indication for transfusion. Depending on the effects on the recipient, an incorrect transfusion must be reported by the pharmaceutical company as SAE or SAR (Section 63i (7) AMG).

Transfusion related dyspnoea:

Acute respiratory distress in temporal connection with a transfusion (within 24 hours) without any evidence of TRALI, without volume overload, or allergic respiratory distress.

Post-transfusion purpura (PTP):

Occurrence of purpura and thrombocytopenia within twelve days post transfusion. PTP is confirmed in the case of positive platelet crossmatch or if platelet specific antibodies (usually Anti-HPA-1a) are present in the blood of the recipient or the corresponding antigen can be detected on the platelets of the donor.

// 4. Results //

4.1 Serious adverse transfusion reactions (SAR) in accordance with the IHN criteria

559 suspected cases of serious transfusion reactions were reported to the PEI in 2015 (definition, see box, Pages 7, 8). The number of reports has thus remained constant in the past few years. Reports in detail referred to those concerning ATR, HTR, TACO and TTVI with the exception of the HEV transmissions reported for the first time as from 2013. Reporting figures for TRALI and TTBI showed a downward, SAR caused by incorrect blood components transfused (IBCT) showed an upward trend in the past four years. For 2012-2014, around 57-62 % of all reports were rated as confirmed serious adverse reactions compared with 63 % in 2015. Comparison: Swiss Medic rated around 52 % of the reports received as likely/probable or certain to be transfusion related cases.

The total of the 352 confirmed serious transfusion reactions in 2015 refer to 94 serious allergic reactions, Grade I and II, 152 anaphylactic reactions, Grade III and IV, 51 transfusion-associated volume overloads, 19 haemolytic reactions, five TRALI reactions, 24 incorrect transfusions, two transfusion-transmitted bacterial infections, one transfusion-transmitted HBV infection as well as four transfusion-transmitted HEV transmissions. One case of post-transfusion purpura and 16 other suspected cases were not confirmed to be transfusion reactions.

In 2015, the rates of the confirmed serious transfusion reactions per 10^6 transfused blood components for allergic/anaphylactic reactions, TACO and IBCT caused SAR were in the order of magnitude of the previous year. The rate of confirmed cases of HTR has decreased in 2015 compared with the previous year. Since 2013, up to now seven transmissions of HEV have been classified as likely/probable or certain.

In 2015, altogether four deaths due to transfusion reactions were documented; out of which three can be attributed to IBCT caused AB0 incompatibility and one can be attributed to volume overload (TACO). During the observation period of 19 years (1997–2015), 108 deaths can be attributed to the administration of blood components. Serious allergic and anaphylactic reactions (31 cases) were documented as the most frequent cause of death, followed by TRALI reactions (21 cases). 13 patients died because of haemolytic transfusion reactions, 14 because of transfusion-transmitted bacterial infections, and 13 because of IBCT. Besides, twelve deaths following TACO, three following viral infections, and one following GvHD were reported.

Table 4.1: Number of suspected cases of serious transfusion reactions (SAR), number of confirmed SAR and portion of SAR with fatal course from 2012–2015.

SAR	Suspected cases notified				Confirmed cases				Fatal cases thereof			
	2012	2013	2014	2015	2012	2013	2014	2015	2012	2013	2014	2015
ATR Grade I/II	62	85	147	98	61	79	130	94	0	0	0	0
ATR Grade III/IV	133	121	141	168	122	103	122	152	2	3	1	0
TRALI	61	54	58	46	1	10	7	5	0	1	0	0
HTR	37	36	60	62	8	17	39	19	0	0	2	0
TTBI	33	35	36	29	5	4	7	2	0	0	1	0
IBCT	5	16	22	25	5	16	22	24	0	0	2	3
HCV, HIV, HBV	46	56	68	51	1	0	0	1	0	0	0	0
HEV	0	1	6	10	0	1	2	4	0	0	1	0
PTP	5	0	6	1	3	0	2	0	0	0	0	0
TA-GvHD	0	0	0	0	0	0	0	0	0	0	0	0
TACO	41	50	42	53	40	49	36	51	3	1	3	1
Others	12	11	10	16	2	1	3	0	0	0	0	0
Total	**435**	**465**	**596**	**559**	**248**	**280**	**370**	**352**	**5**	**5**	**10**	**4**

4.2 Acute allergic transfusion reactions (ATR)

Since 2009, reported cases of acute allergic transfusion reactions (ATR) have been subdivided into allergic transfusion reactions Grades I and II and anaphylactic transfusion reactions Grade III and IV. This subdivision has its basis on the guidelines for the treatment of acute anaphylactic reactions drafted up by the AWMF according to Ring and Messmer [6].

ATR are defined by a set of clinical symptoms rather than laboratory parameters. In addition, the distinction between ATR and other transfusion-related reactions such as dyspnoea or febrile reactions is often difficult to make so that it is nearly impossible to classify an ATR as certain. All ATR classified as confirmed according to IHN are thus cases with possible or likely/probable causality.

Of the total of those 689 suspected cases of ATR reported between 2012 and 2014, 347 cases, corresponding to 50% were confirmed as Grade III/IV. Of the 266 suspected cases reported in 2015, 152 cases of ATR, corresponding to 57% were classified as of possible or likely/probable causality. This is equivalent to the order of magnitude of 2012–2014. In addition, it confirms that serious allergic transfusion reactions occur more frequently after the administration of PC than after the administration of other blood components. There was no fatality among the cases of 2015 with confirmed causality.

Table 4.2 a: Number of suspected cases of ATR grade I/II and III/IV and confirmed cases after the administration of RBC, PC, plasma or combined administration from 2012–2015.

ATR		2012	2013	2014*	2015*
Reported cases		195	206	288	266
Confirmed cases	grade I/II	47	64	56	94
	grade III/IV	122	103	122	152
	total	169	167	178	246
ATR following RBC transfusion	grade I/II	30	35	33	57
	grade III/IV	68	65	55	89
	fatal cases	2	2	0	0
ATR following PC transfusion	grade I/II	10	18	14	26
	grade III/IV	25	15	36	32
	fatal cases	0	1	0	0
ATR following plasma transfusion	grade I/II	4	8	5	5
	grade III/IV	17	14	12	14
ATR following combined transfusions	grade I/II	3	3	4	6
	grade III/IV	12	9	19	17
	fatal cases	0	0	1	0

*As from 2014, all reports by the Drug Commission of the German Medical Association (DCGMA) were forwarded to the PEI.

The table presenting the rates per 10^6 transfused units below only takes into account anaphylactic reactions of Grades III and IV.

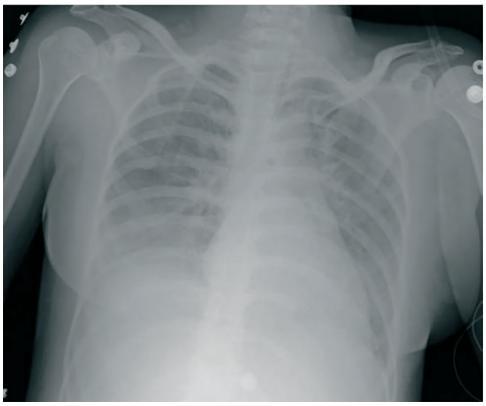
Table 4.2 b: Rates of confirmed ATR grade III/IV cases per 10^6 transfused units RBC, PC or plasma from 2012–2015.

ATR III/IV per 10^6 units	2012	2013	2014	2015
RBC	15.67	15.77	13.80	23.70
PC	48.49	29.95	72.26	63.02
Plasma	17.03	16.22	14.34	18.55

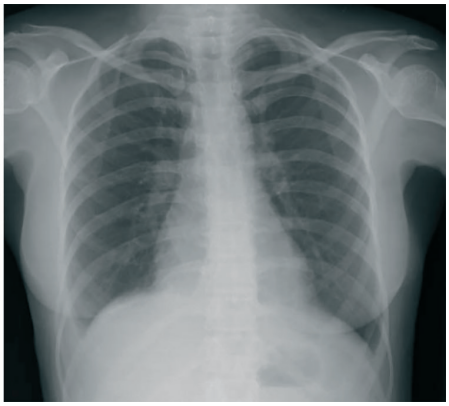
4.3 Transfusion-associated circulatory overload (TACO)

TACO (Transfusion associated circulatory overload) [14] has only been recorded at the PEI systematically as transfusion complication since 2009. Here, too, clinical parameters are the criteria for the evaluation of the complication reported. The distinction between TACO and transfusion reactions with similar symptoms is made by the detection of a cardiogenic lung oedema in the chest x-ray.

Radiological diagnosis: Lung oedema



Monitoring of the course post diuresis



http://www.mevis-research.de/~hhj/Lunge/HG.html

Table 4.3 a: Number of suspected cases of transfusion associated circulatory overload (TACO) and confirmed cases after the administration of RBC, PC, plasma, or a combined administration from 2012–2015.

TACO	2012	2013	2014	2015
Reported cases	41	50	42	53
Confirmed cases	40	49	36	51
TACO following RBC transfusion	33	36	30	47
TACO following PC transfusion	3	3	2	0
TACO following plasma transfusion	0	4	2	0
TACO following combined transfusions	4	6	2	4
Fatal cases thereof	1	1	3	1
Main underlying diseases: cardio-vascular, renal and lung damage, septicaemia, liver cirrhosis, malignancies	31 (77.5%)	29 (59%)	26 (72.2%)	38 (74.5%)
Recipients' age: median (range)	68.5 (6–92)	68.8 (7–94)	69.7 (13–92)	67.7 (23–86)

Table 4.3 b: Rates of confirmed cases of TACO per 10^6 transfused units of RBC, PC, and plasma from 2012–2015.

TACO per 10^6 units	2012	2013	2014	2015
RBC	7.60	8.73	7.53	12.52
PC	5.82	5.99	4.01	0.00
Plasma	0.00	4.63	2.39	0.00

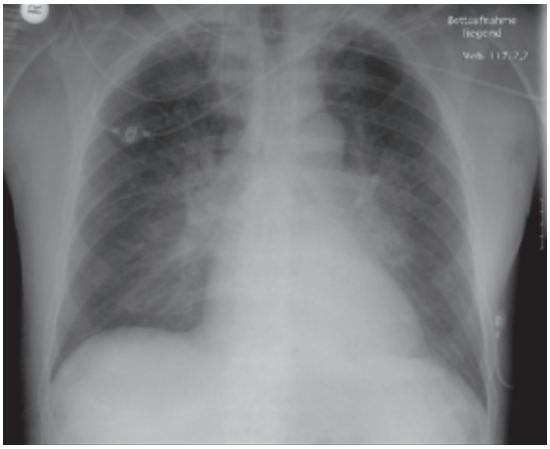
The total number of TACO cases reported was in the same order of magnitude in the past few years as in the preceding years. The underlying disease of the patients was provided in nearly all the reports. As also described in the literature, the majority of the patients affected (38 of 51) had predisposing underlying diseases such as cardiovascular diseases, kidney and lung damage, sepsis, known liver cirrhosis, malignancies, etc. [14].

4.4 Transfusion-related acute lung injury (TRALI)

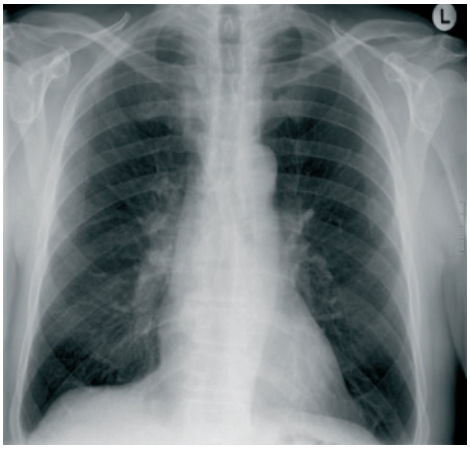
TRALI is characterised by rapid occurrence of respiratory distress (within six hours after the end of the transfusion) and the exclusion of disorders that can cause acute lung injury (e.g. cardiologic disorders etc.). In contrast to TACO, no radiological signs of lung oedema can be found in a TRALI reaction, but acute bilaterally occurring perihilary lung infiltrates. Immunogenic TRALI is confirmed by providing evidence of specific antibodies in the donor and the corresponding antigen in the recipient.

Radiological findings: TRALI following administration of plasma

Bilateral lung infiltrates



Control (day 5) after machine-assisted ventilation



For the current assessment of suspected cases of TRALI reactions, the algorithm [3] described above was therefore used in which symptoms were examined first and possible other causes were ruled out. An examination of the donors for any relevant HLA or HNA antibodies will then follow as well as (in isolated cases) an examination of the recipient for any corresponding antigens. Depending on the result, the reaction will be subdivided into immunogenic or non-immunogenic TRALI.

Table 4.4 a: Assessment of the suspected cases of TRALI reported in 2015

TRALI	Assessment			
	unlikely	possible	probable/likely	certain
RBC	16	7	0	1
PC	2	3	1	1
Plasma	1	2	0	1
Combined transfusion	4	6	1	0
Total	23	18	2	3

In 2015, a total of 46 suspected cases of TRALI were reported to the PEI. In five cases, a TRALI reaction could be confirmed. In three cases, HLA Class II antibodies were detected in the donors and the corresponding antigens were detected in the patients. The diagnosis was thus certain. The two donors of the plasma and P-PC concerned did not have a history of immunisation. The donor of the RBC had indicated that she had been pregnant eight years before. Another case of HLA Class II antibodies in a donor of A-PC who had also indicated a previous pregnancy (two years before) was classified as likely/probable, since no corresponding antigens were described in the patient. Another case after combined administration of RBC and plasma was also classified as non-immunogenic TRALI.

Table 4.4 b: Listing of TRALI cases in 2015

TRALI	Donor			Patients	
Evaluation	Antibody	Compo-nent	Sex	Correspon-ding Ag	Underlying disease
Confirmed; immunogenic	HLA class II DR 17	plasma	Male, without immunisation in the history	HLA class II DR 17	Cardio surgical bypass operation
Confirmed; immunogenic	Various HLA class II Ab with 3 of the donors, out of these 1 anti-HLA-DQ9	P-PC	Male, without immunisation in the history	HLA class II DQ9	Cardio surgical bypass operation
Confirmed; immunogenic	HLA class II Ab DR 13,8,11,12, 17,18,DQ5, 6,2	RBC	Female, pregnancy in the history	HLA class II DRB1,01,13, DQ 1,5,6	GI bleeding with multimorbid status, acute renal failure, cardiac insufficiency
Likely; not immunogenic	1 plasma slightly positive in the LIFT	4 RBC, 4 plasma	Not applicable	Without	Atonous bleeding of the uterus, hae-morrhagic shock after secondary section
Likely; not immunogenic	HLA class II Ab DR5,6,3,8,52, slightly DP	A-PC	Female, pregnancy in the history	Slightly pos. HLA class I Ab A3, no corresponding Ag findings	MDS

Table 4.4 c: Rates of confirmed cases of TRALI per 10^6 transfused units of RBC, PC or plasma from 2012–2015.

TRALI per 10^6 unit	2012	2013	2014	2015
RBC	0.23	1.21	1.25	0.27
PC	0	3.99	0	3.94
Plasma	0	1.16	1.19	1.32

Altogether two male and two female donors were involved in the immunogenic cases of TRALI. In two cases (plasma, P-PC), the donors had denied that they had risk factors (transfusions) in the donor interview, so that the reason for the development of antibodies remained unclear. The two female donors involved had indicated previous pregnancies, however, were admitted to the donation, since the donations involved were a donation of whole blood and a donation of platelet apheresis. In the reporting year of 2015, no case of death was reported in connection with a TRALI reaction.

4.5 Transfusion-related dyspnoea

Transfusion related dyspnoea refers to respiratory distress in temporal relation to a blood transfusion without any signs of TRALI, allergy-related dyspnoea, or TACO.

Table 4.5: Number of reports of suspected cases of transfusion related dyspnoea and confirmed cases after administration of RBC, PC or plasma or combined administration from 2012–2015.

Dyspnoe	2012	2013	2014	2015
Reported cases	14	19	25	14
Confirmed cases	6	13	19	13
RBC	3	9	17	9
PC	1	2	0	2
Plasma	0	1	0	1
Combined transfusion	2	1	2	1
Fatal cases thereof	0	0	0	0
Recipients' age: median (range)	67 (48–68)	63 (45–93)	70 (38–89)	63 (47–80)

In previous haemovigilance reports of the PEI, the cases of dyspnoea were not assigned to serious transfusion reactions. The PEI continues to document the frequency of the reports. If required, a more precise definition will serve to facilitate the distinction from transfusion reactions with similar clinical symptoms in future.

4.6 Haemolytic transfusion reactions (HTR)

The association of an HTR with a transfusion is rated as likely/probable if, besides the typical clinical symptoms, the laboratory findings speak in favour of a haemolysis and other causes for this can be ruled out. The association with the transfusion is considered as certain if the antiglobulin test or the cross-match is positive.

Table 4.6 a: Number of reports of suspected cases of haemolytic transfusion reactions (HTR) and confirmed cases after administration of RBC, PC or combined administration from 2012–2015.

HTR	2012	2013	2014	2015
Reported cases	37	36	60	62
Confirmed cases	8	17	39	19
Acute HTR	5	11	36	17
Delayed HTR*	3	6	3	2
HTR following RBC transfusion	7	16	33	15
HTR following PC transfusion	1	0	1	1
HTR following combined transfusion	0	1	5	3
Fatal cases thereof	0	0	2	0
Fatal cases thereof following RBC transfusion	0	0	2	0

*with evidence of irregular erythrocyte Ab

Table 4.6 b: HTR rate per 10^6 transfused units of RBC or PC from 2012–2015.

HTR per 10^6 units	2012	2013	2014	2015
RBC	1.61	3.88	8.28	3.99
PC	1.94	0.00	2.01	1.97

The number of reports of 2015 was comparable with that of the reports from the previous year while the number of confirmed cases had decreased compared with 2014. Most cases were acute haemolytic reactions. In contrast to the data of other haemovigilance systems (SHOT, Swissmedic), the portion of reports on delayed reactions with evidence of irregular erythrocyte Ab is low. For instance, for the period from 2008-2013 Swiss Medic documented [2] an average portion of delayed haemolytic reactions of 41% (20-56%).

Table 4.6 c: Delayed HTR with evidence of irregular erythrocyte antibodies, 2015.

Case	Symptoms	Underlying disease	Laboratory findings	Cause	Outcome
1	Increase in RR, Increase in temperature (38.4°C)	Female, 56, alcohol toxic liver cirrhosis, anaemia	Increase in LDH, Decrease in Hb, serum haemolytic	Anti-E and anti-Jk(a)	Restored
2	No data available	Female, 63 bleeding from gastroduodenal artery	Evidence of anti-Kidd-Ab and pos. DCT in the laboratory findings	Anti-JK(b)	Restored

4.7 Transfusion-transmitted bacterial infections (TTBI)

TTBI reports for which no evidence of pathogen was available or the time interval was exceeded, were classified as cases of unlikely causality. If the pathogen was identified only in the blood component but not in the recipient, the causality was classified as "possible". If the same pathogen was detected in the product and in the patient, the causal relationship was classified as likely/probable. A TTBI was classified as certain in cases with proven homology of the pathogens, e.g. by an identical antibiogram. In practice, consistent testing of the recipient and the blood components is not always feasible. The data in the follow-up reports are therefore often incomplete. As in the report for 2013/2014, the cases below are all cases of transfusion-transmitted bacterial infections which fall into the category "possible", as well as all cases recorded as confirmed which fall into the categories "likely/probable" and "certain".

In the reporting year of 2015, altogether 29 cases of suspected TTBI were reported to the PEI. For 19 reports for RBC, five for PC and two for the combined administration of blood components, the causal relationship was classified as unlikely or not assessable, for one transfusion with RBC as possible, for one RBC transfusion as likely/probable, and for one PC transfusion as certain.

Achromobacter spp. was found in the suspected case classified as possible after RBC transfusion. Since the patient recovered again after five minutes of chills and tachycardia, however, no blood culture was performed on him.

In the suspected case classified as likely/probable, *Acinetobacter pittii* was detected in the RBC. In addition, Enterococcus faecium was found in the recipient. A HTR could be ruled out; however, no comparative tests were performed to confirm the identity of the pathogen *Acinetobacter pittii* in the product and the patient.

In the suspected case after the administration of PC, the causal relationship was classified as certain, since the *Streptococcus dysgalactiae* found in the P-PC transfused (third day after manufacture) and in the recipient showed nearly identical antibiograms. A HTR was ruled out in the recipient. The cause of the contamination in the P-PC affected could not be detected; the corresponding RBC were negative in the culture.

The last fatality caused by a contaminated RBC was reported in 2014.

Table 4.7 a: Transfusion-transmitted bacterial infections with possible causality from 2012–2015.

Year	Pathogen	Blood component	Evidence of pathogen Recipient/product	Outcome
2012	*Propionibacterium acnes*	A-PC	Product	Restored
2013	*Citrobacter freundii*	RBC	Recipient	Restored
	Enterococcus faecium	RBC	Product	Restored
	Enterococcus faecium and *Staphylococcus hominis*	Plasma	Product	Restored
2014	*Staphylococcus hominis*	RBC	Product	Restored
	Staphylococcus aureus	RBC	Product	Restored
	Enterobacter cloacae	RBC	Recipient	Restored
	Bacillus cereus	PC	Product	Fatal
	Staphylococcus warneri	RBC	Product	Restored
	Propionibacterium acnes	RBC	Product	Restored
	Propionibacterium acnes	PC	Product	Restored
	Acinetobacter baumannii	RBC	Product	Restored
	Escherichia coli	RBC	Recipient	Restored
2015	*Achromobacter spp.*	RBC	Product	Restored

Table 4.7 b: Transfusion-transmitted bacterial infections with confirmed causality from 2012-2015.

Year	Product	Pathogen	Evaluation	Outcome
2012	RBC	*Staphylococcus saprophyticus*	Likely/probable	Restored
	A-PC	*Staphylococcus epidermidis*	Likely/probable	Restored
	A-PC	*Streptococcus pneumoniae*	certain	Restored
	A-PC	*Streptococcus pneumoniae*	certain	Restored
2013	RBC	*Klebsiella pneumoniae*	Likely/probable	Restored
	RBC	*Staphylococcus aureus*	Likely/probable	Restored
	A-PC, 4 days old	*Staphylococcus epidermidis*	certain	Restored
	A-PC, 4 days old	*Staphylococcus epidermidis*	certain	Restored
2014	A-PC, 4 days old	*Escherichia coli*	Likely/probable	Restored
	A-PC, 4 days old	*Staphylococcus aureus*	Likely/probable	Restored
	A-PC, 4 days old	*Staphylococcus aureus*	Likely/probable	Fatal
	RBC	*Staphylococcus aureus*	Likely/probable	Restored
	RBC	*Klebsiella pneumoniae*	Likely/probable	Restored
	RBC	*Klebsiella oxytoca*	Likely/probable	Restored
	A-PC, irradiated	*Escherichia coli*	certain	Restored
2015	A-PC, 3 days old	*Streptococcus dysgalactiae*	certain	Restored
	RBC	*Acinetobacter pittii* in RBC and recipient *Enterococcus faecium* only in recipient	Likely/probable	Restored

Table 4.7 c: Number of suspected cases of transfusion-transmitted bacterial infections (TTBI) and confirmed cases after the administration of RBC, PC, and plasma from 2012–2015.

TTBI	2012	2013	2014	2015
Reported cases	33	35	36	29
Confirmed	5	4	7	2
RBC	2	2	3	1
P-PC	0	0	0	1
A-PC	3	2	4	0
Plasma	0	0	0	0
Fatal cases thereof	0	0	1	0

Table 4.7 d: Rate of confirmed cases of transfusion-transmitted bacterial infections per 10^6 transfused units of RBC, PC, and plasma from 2012–2015.

TTBI per 10^6 units	2012	2013	2014	2015
RBC	0.46	0.49	0.75	0.27
PC	5.82	3.99	8.03	1.97
Plasma	0.00	0.00	0.00	0.00

4.8 Transfusion-transmitted viral infections (TTVI: HBV, HCV, HIV, HEV)

Viral transmission was confirmed by means of the criteria conforming to Opinion 34, 35, and 42 AK Blut for HBV, HCV, and HIV [15] or comparable criteria for other viruses.

Table 4.8 a: Number of suspected cases of transfusion-transmitted viral infections (TTVI) and confirmed cases after the administration of RBC, PC, and plasma from 2012–2015.

TTVI	2012	2013	2014	2015
Reported cases (HIV, HCV, HBV, HAV, HEV)*	47	50	69	61
Reported cases **HBV**	20	20	30	19
Confirmed **HBV infections** by				
RBC	0	0	0	1
PC	1	0	0	0
Plasma	0	0	0	0
Reported cases **HEV**	0	1	6	10
Confirmed **HEV infections** by				
RBC	0	0	1	2
PC	0	1	1	2
Plasma	0	0	0	0
Total confirmed TTVI	1	1	2	5

*Combined suspected cases are only recorded as one case for each report.

Transfusion-transmitted Hepatitis C and HIV infections

After the introduction of HCV- and HIV-NAT donor screening, three cases of transmission by blood components were documented, one case of HCV transmission (2004) and two cases of HIV transmission (2007 and 2010). In all cases transmission was caused by RBC of whole blood donors in whom the infections were not detected in the NAT pool test [16]. From 2012–2015, there were no cases of transfusion-related HCV and HIV transmission.

Transfusion-transmitted Hepatitis B infections

From 1997-2006, transfusion-transmitted HBV infections on average accounted for two transmissions per year. Since the introduction of donor screening for anti-HBc antibodies (10/2006) altogether five cases of transfusion-transmitted HBV infection were confirmed, out of which two occurred in the last four-year reporting period (2012 and 2015). The cause for the HBV transmission in 2015 was the RBC of a donor in the window phase with serologically negative findings and a viral load of 15 IU/ml found in the follow-up test sample by means of ID-NAT. Eight months after the index donation, the donor was ID-NAT negative, anti-HBc-positive, and had an anti-HBsAg titre > 1,000 IU/L. A confirmation of the result by sequence homology was not possible due to the low viral load in the follow-up test sample of the donation. Since other donors could be ruled out as causing the HBV infection and the recipient showed a fresh HBV infection, causality was classified as likely/probable. The recipient, a patient with a condition after CLL and chemotherapy was tested for HBV as part of the look-back procedure. Four months after transfusion, he was HBsAg and ID-NAT positive, anti-HBc negative with normal transaminases, and was treated with ribavirin due to his high viral load. One year later, no virus genome could be detected in the recipient. His values for anti-HBC were negative until that time.

Since the introduction of anti-HBc testing as donor screening test in September 2006 [17], the number of confirmed transfusion-transmitted HBV transmissions has declined (Figure 4, page 33). As some major blood donation centres introduced HBV pool NAT in their donor screening only a short time later, the retrospective trend cannot be seen entirely as the effect of anti HBc testing.

Table 4.8 b: Rate of confirmed cases of HBV transmissions per 10^6 transfused units from 2012–2015.

HBV per 10^6 units	2012	2013	2014	2015
RBC	0.00	0.00	0.00	0.27
PC	1.94	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00

Transfusion-transmitted Hepatitis E infections

From 1912-2015, a total of 17 suspected cases of transfusion-transmitted HEV infections were reported out of which seven transmissions could be confirmed. Four of the seven patients did not show any clinical signs of hepatitis, two patients had temporally limited symptoms and one patient experienced an exacerbation of his underlying disease due to the hepatitis.

Table 4.8 c: Number of suspected cases of transfusion-transmitted HEV infections reported as SAR (look-back procedures based on recipients' infection) or as donor look-back (based on donors' infection) from 2012–2015.

Reporting year	Relation to transfusion assessed as:			Patients involved	Donors involved	Blood compo-nents involved
	Probable/ likely or certain	possible	Not assessable/ unlikely			
2013	1	0	0	1	1 WB donor	1 P-PC
2014	2	1	7	10	1 WB donor 1 Apheresis donor	1 RBC 4 A-PC
2015	4	1	9	14	2 WB donors 2 Apheresis donors	2 RBC 7 A-PC
Total	7	2	16	25	4 WB donors 3 Apheresis donors	3 RBC, 1 P-PC 11 A-PC

Table 4.8 d: Rate of confirmed cases of HEV transmissions per 10^6 transfused units from 2012–2015.

HEV per 10^6 units	2012	2013	2014	2015
RBC	0.00	0.00	0.25	0.53
PC	0.00	2.00	2.01	3.94
Plasma	0.00	0.00	0.00	0.00

CMV infections

In 2015, two cases of transfusion-transmitted CMV infections were reported to the PEI which could not be confirmed.

Other transfusion-transmitted infections

Up to the reporting period, no suspected reports of transmissions were received for viral pathogens such as WNV, Chikungunya virus, Dengue virus, Zika virus or other pathogens transmittable by arthropods. Since transfusion reactions have been recorded by the PEI from 1997 through to 2015, six HIV, 20 HCV, 25 HBV, two HAV, seven HEV and one malaria transmission by transfusions have been confirmed.

4.9 Post-transfusion purpura (PTP)

One case of post-transfusion purpura was reported in 2015, the causality of which was classified as unlikely.

4.10 Number of look-back procedures based on a donor infection (donor look-back)

Table 4.10 a: Reports of donor look-back procedures from 2012–2015.

	2012	2013	2014	2015
Total reported cases	906	815	798	904
HEV	0	2	7	20
HBV	702	548	489	571
HCV	102	131	168	174
HAV	1	0	1	0
HIV	58	69	53	48
CMV	2	0	5	11
Parvovirus B19	0	7	2	8
Lues, HEV, HAV, HBV, HCV, HIV*	3	6	4	2
Lues	34	52	68	69
CJK	3	0	0	0
Toxoplasmosis	1	0	0	0
Lyme disease	0	0	0	1
Malaria	0	0	1	0

*combined reports

With 904 look-back procedures resulting from the donor, the number of reports of suspected cases was in the order of magnitude of the past four years. Eight reports erroneously affected first time donors. 571 of the look-back procedures resulting from the donors concerned HBV and were thus in an order of magnitude compared with that of previous years. Out of these, a confirmed, isolated positive anti-HBc result was detected in 504 procedures (without simultaneous detection of HBs-Ag and/or HBV genome), which was by far the most frequent reason for performing a look-back procedure also in 2015. The downward trend suggested since 2012 could therefore not be confirmed in 2015.

Table 4.10 b: Look-back procedures based on donors with HBV-positive screening tests in 2015.

HBV look-back procedures	2015
Total reported cases*	571
HBsAg-positive	59
Pool-NAT only positive	3
Unclear	3
Anti-HBc-Ab only positive	504
thereof anti-HBs > 100 IU/L	78
thereof anti-HBs < 100 > 10 IU/L	54
thereof anti-HBs < 10 IU/L bzw. negativ	186
thereof no information regarding anti-HBs	186

*Two reports erroneously concerned first time donors.

Altogether, in 2015 look-back procedures were induced based on 569 repeat donors due to suspected HBV transmission by a previous donation of the donor. This concerned 59 HBsAg positive donations, two isolated cases of NAT (pool testing) positive, 504 isolated anti-HBc positive donations and three other donations with unclear findings.

The retain sample of the previous donation of one of the 59 HBsAg positive donors showed a weak positive result in the ID-NAT; the negative results in the recipient ruled out an HBV transmission.

Three donations showed an isolated positive result in the HBV-NAT pool test. One case referred to a donor who had donated exclusively plasma for fractionation, so that an HBV transmission by a transfused blood component can be ruled out. Based on the relatively short donation intervals, it could be shown that the ID-NAT was positive up to 20 days before the index donation; retain samples from earlier donations as from 21 days prior to the index donation revealed ID-NAT negative results. In the two other cases of isolated HBV-NAT pool testing-positive donations, the retain samples of the previous donations revealed negative results for all HBV parameters, so that an HBV transmission by these donations can also be ruled out.

In four out of 504 anti-HBc only positive donations from repeat donors, the HBV infection was confirmed by a positive ID-NAT in the index donation or in the retain sample of previous donations. For one donor whose index donation was HBV-ID-NAT negative, the look-back procedure showed an HBV-ID-NAT positive result from a retain sample. The recipient concerned died of multiple organ failure caused by his underlying disease. No data on its HBV status were available.

A further anti-HBc isolated positive donor was tested negative in the NAT pool test; the ID-NAT was weak positive in the index donation. The results from the retain samples of the previous donations, which were all negative, rule out an HBV transmission.

The index donation of the third anti-HBc only positive donor was ID-NAT negative, the retain sample of the previous donation, on the other hand, was HBV-ID-NAT only positive. The anti-HBc-IgM negative finding of the recipient speaks against a HBV transmission by this donation.

The fourth index donation which tested anti-HBc only positive revealed an anti-HBs titre > 100 IU/L. The retain samples from two previous donations were anti-HBs negative; one of these two previous donations was weak HBV-ID-NAT positive. Both recipients died of their underlying diseases. Their HBV status is unknown.

In 78 of the 132 donors with known anti-HBs titre, the titre was > 100 IU/L so that, in accordance with the

restriction of the PEI on anti-HBs testing of 7 February 2014 [4] a blocking of the donor and the donation did not have to be applied. In nine of these donors, who had anti-HBS titres > 1,000 IU/L, a history of vaccination was assumed, which was confirmed in one case.

For 186 donors, no information is available on anti-HBs titres. Many blood donation centres defer all donors with confirmed reactive anti-HBc findings, a measure which is stricter than laid down in the above edition, so that subsequent testing for anti-HBs antibodies could be dispensed with.

The number of look-back procedures regarding Treponema pallidum (lues) infections in donors was at the same level in 2015 as in the previous year. An infection in the recipient could not be confirmed in any of the cases. In the case of involved RBC which were kept cool at 4°C for more than five days, a transmission of the pathogen can be ruled out so that no follow-up testing was performed in the recipients [18]. In two cases, the recipients of a donation that had tested positive for lues had already died so that it was no longer possible to establish a transmission.

4.11 Serious adverse events (SAE)

Since 2012, reporting of serious adverse events (SAE) by blood donation centres has been compulsory pursuant to Section 63i AMG. These adverse events include mainly the marketing of defective products, repeatedly occurring events which give rise to the assumption of a faulty working procedure, critical events also without the products being supplied, and incorrect transfusions without serious reactions in the recipient (see also [7]).

Pursuant to Directive 2005/61/EC [5], serious adverse events are categorised by their occurrence in the transfusion chain (collection, processing, storage, and marketing) and by type of adverse event (error in the material or equipment, and human error).

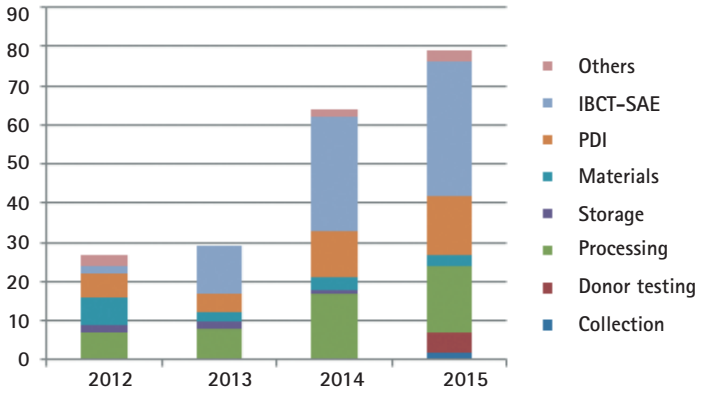
The number of reporting blood donation centres has continuously risen since the 16th amendment of the AMG came into force in 2012.

Table 4.11 a: Reports of serious adverse events (SAE) from 2012–2015.

SAE reported due to errors at:	2012	2013	2014	2015
Donation (WB and apheresis collection)	0	0	0	2
Testing of donations	0	0	0	5
Processing	7	8	17	17
Storage (e.g. cooling break)	2	2	1	0
Materials (e.g. bag leakages)	7	2	3	3
Others: contamination prior to distribution	3	0	2	3
PDI on donor deferral criteria	6	5	12	15
IBCT without SAR	1	12	29	34
Total	**26**	**29**	**64**	**79**

The table shows the absolute number of reports. A presentation of the frequency of specific adverse events referring to the number of donations, the number of components prepared or the number of components transfused is difficult due to the different denominators. Figure 4.11 therefore shows the absolute numbers of adverse events from 2012-2015 referring to the respective source of error.

Figure 4.11: SAE from 2012–2015 by source of error.



The total number of reports of adverse events has tripled since 2012. The number of donations, blood components prepared and transfused, has declined by ten to 17% within the same period [9]. After the 16th amendment of the AMG came into force, the number of reports on incorrect transfusions without donor reaction increased. The breakdown of the reports for reporting year 2015 also shows that human error was the main cause for SAE of which again the major share was incorrect transfusions.

Table 4.11 b: SAE in 2015.

SAE at/due to	Product defect	Equipment/ software failure	Human error	Others	Total
Donation (WB, pheresis)	1		1		**2**
Testing of donations		3	2		**5**
Processing	1	2	13	1	**17**
Storage	3				**3**
Distribution*			34		**34**
Material	3				**3**
Others (PDI)**				15	**15**
Total	**8**	**5**	**50**	**16**	**79**

* Incorrect blood components transfused (IBCT)
** Post Donation Information (PDI): 3 x genetic relatives with CJD, 1 x donor with suspected CJD, 8 x donor infections, 3 x incorrect information provided at donor interview

4.12 Incorrect blood components transfused (IBCT)

Incorrect transfusions include procedures in which blood components have been assigned or already administered to the wrong patient. This usually results in a transfusion of components with a non-identical blood group. Incorrect transfusions also include the administration of non-irradiated blood components despite the respective request to do so or blood group compatible transfusions to patients without an indication for a transfusion.

The section below summarises incorrect transfusions which caused a serious reaction in the recipient and were to be reported as SAR as well as incorrect transfusions that did not cause health impairment in the recipient based on the transfusion and which were reported as SAE (see also Section 4.11 SAE).
The table below presents IBCT reported as SAE without serious adverse reactions in the recipient in 2015.

Table 4.12 a: IBCT without any serious reactions in the recipients (SAE) in 2015.

IBCT	Blood group compatible (by chance)	ABO incompatible	Rhesus incompatible	Other	Total
RBC	17	8	4	1**	30
PC				1*	1
Plasma	1	2			3
	Case descriptions				
RBC	30 IBCT: 17 IBCT ABO and/or Rh compatible (once despite the discrepancy in the bedside test); 8 ABO incompatible IBCT, partly only some ml, once prevented by bedside test; 4 Rh incompatible IBCT (once a young woman, once with known anti-D-Ab); 1 ABO compatible IBCT without irradiation requested				
PC	1 IBCT: Compatible transfusion without indication				
Plasma	3 IBCT: 2 incompatible, 1 compatible transfusions				

One RBC was transfused despite a discrepancy in the bedside test, one transfusion of an incompatible RBC was prevented by a bedside test that showed a discrepancy, one ABO compatible RBC was not irradiated even though this was required**, and one compatible PC was transfused to a patient without an indication*. One young woman received an Rh incompatible RBC, and one patient with known anti-D antibodies also received Rh incompatible RBC. Out of most of the ABO incompatible RBC, only few millilitres were transfused before the error was detected so that a SAR could be avoided.

In 2015, 25 suspected cases of SAR were reported based on incorrect transfusions. For 24 reports with 22 transfused RBC and one PC and one FFP each, the causality was classified as likely/probable and certain, respectively. Three of the four deaths reported during this reporting year are due to incorrect transfusions of RBC.

Altogether, it can be stated that since reports of incorrect transfusions have become legally binding, above all the number of incorrect transfusions without serious adverse reactions in recipients have risen sharply.

To date it cannot yet be estimated when the number of reports will be consolidated. In the reporting year of 2015, 13.58 incorrect transfusions per 10^6 transfused RBC were recorded. The table shows the rate of incorrect transfusions for RBC only, since only a tenth maximum of all reports so far refers to PC and plasma. In the period from 2012-2015, three incorrect transfusions with serious reactions were reported for plasma (2013, 2014, and 2015) and one for PC (2015).

Since the haemovigilance system is based on recording of spontaneous reports, an analysis of sources of error in the blood establishments or the health care facilities cannot be performed based on these data.

Table 4.12 b: Confirmed IBCT with and without SAR and rates per 10^6 transfused RBC during the period from 2012-2015.

IBCT	2012	2013	2014	2015
IBCT: SAR	5	16	22	24
IBCT: SAE	2	12	29	34
total (SAR+SAE)	7	28	51	58
transfused	4.339.700	4.122.190	3.985.415	3.754.760
IBCT – RBC: SAR	5	15	21	22
SAR/10^6 RBC	1.15	3.64	5.27	5.86
IBCT – RBC: SAE	2	9	25	30
SAE/10^6 RBC	0.46	2.18	6.27	7.99
Total IBCT (SAR+SAE) / 10^6 RBC	1.61	5.82	11.54	13.85

4.13 Serious adverse donor reactions (donor SAR)

The number of reports of serious adverse donor reactions has risen to 531 suspected cases in 2015, 154 as spontaneous reports and 377 as part of an enquiry from the PEI. Seven of the cases reported were classified as being of possible and 523 as being of likely causality. For the characterisation of serious donor reactions, the PEI also recommended the publication by Diekamp et al. to evaluate donor SAR, in addition to the IHN criteria [20].

Table 4.13 a: Number of donor SAR reported from 2011-2014.

	2011	2012	2013	2014	2015
Donor SAR	1	3	13	24	531

Altogether 35 of the 82 German blood donation centres (around 40%) have submitted reports on donor SAR. Out of these, ten blood donation centres had not observed any donor SAR; two did not show the degree of severity of the donor SAR, and for 23 blood donation centres, the complete data were available.

Only those reports were included in the further evaluation in which a distinction was clearly made between serious and non-serious cases, and for which an allocation to the type of donation was available. The total number of whole blood, plasmapheresis, and cytapheresis donations from the blood donation centres which had reported perfect donor SAR data were included in the calculation of the SAR rate per 10^6 donations.

Multicomponent apheresis, thrombocytapheresis and erythrocytapheresis donations are merged as cytapheresis donations.

The result was 406, 182 and 30 serious donor reactions per 10^6 cytapheresis, whole blood and plasma donations, respectively, in 2015. Major differences existed between the donation centres with regard to the reports. These were probably due to different judgements of the severity of the reaction.

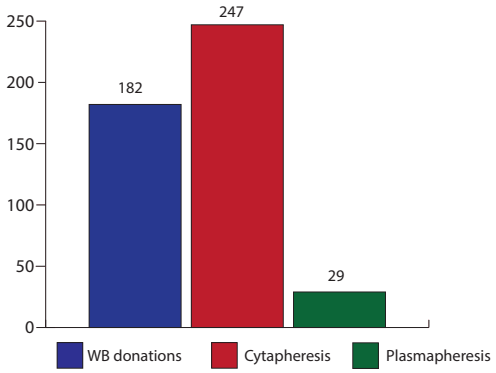


Figure 4.13 a: Rate of donor SAR per million donations referred to the respective type of donation reported in 2015.
(Cytapheresis comprises thrombocytapheresis, multi-component donations, and erythrocytapheresis.)

Table 4.13 b: All donor SAR reports fulfilling the above mentioned criteria were categorised by their IHN subdivisions of donor reactions.

A – Local symptoms (needle prick related)	
A1	Blood loss: Haematoma, punctured artery
A2	Arm pain: Paraesthesia, non-specific arm pain
A3	Local inflammation/infection: Thrombophlebitis, non-specific tissue reaction
A4	Other major vessel injuries: venous thrombosis, arteriovenous fistula, compartment-syndrome, pseudo aneurism of the upper arm artery
B – Generalised symptoms	
B1	Vasovagal reactions without LOC
B2	Vasovagal reactions with LOC at donation
B3	Vasovagal reactions with LOC after donation
C – Complications at apheresis	
C1	Citrate reaction
C2	Haemolysis
C3	Air embolism
C4	Tissue infiltration
D – Allergic reactions	
D1	Local
D2	Generalised (anaphylactic)
E – Cardio vascular events: AMI, cardiac arrest, TIA, apoplexy, other acute cardiac symptoms (angina pectoris, TAA), death	
F – Other	

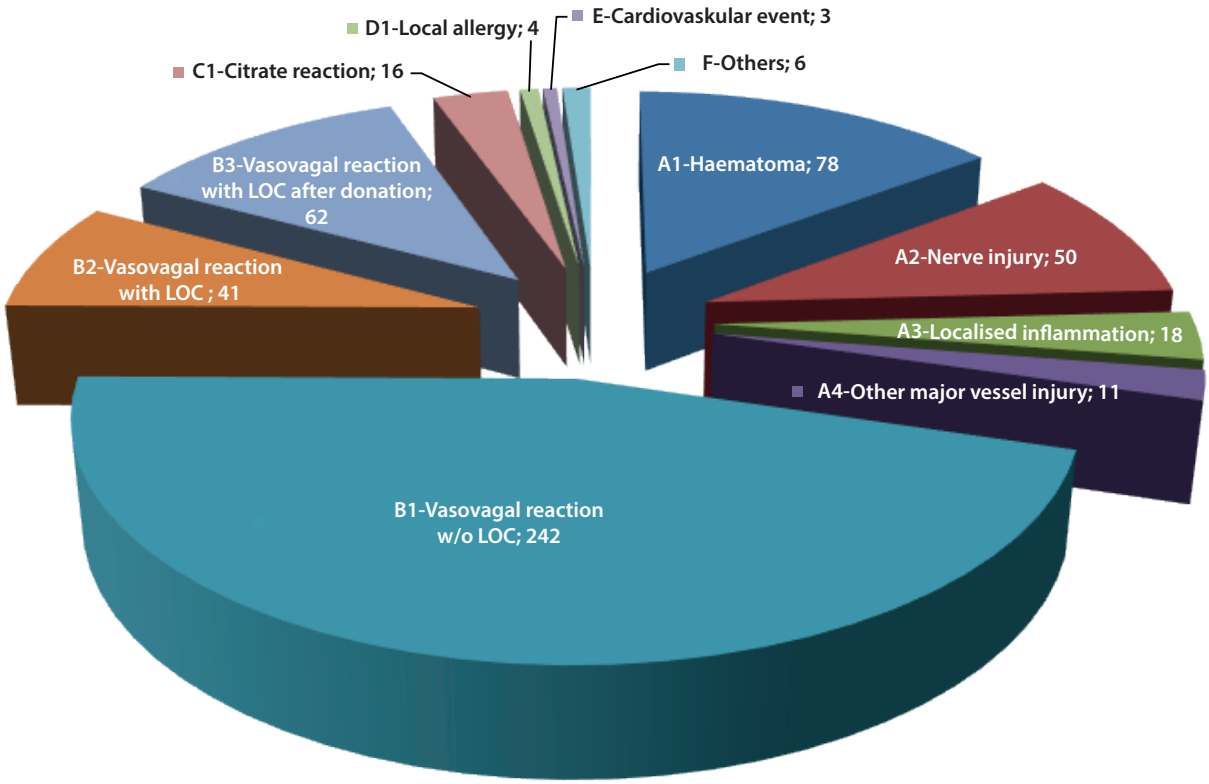


Figure 4.13 b: Donor SAR in 2015, categorised in accordance with the IHN classification.

Altogether, vasovagal reactions without loss of consciousness (LOC) were the most frequent donor reactions with 46%. Taken together, the portion of local symptoms was 29%, the portion of vasovagal reactions with LOC was 20% of the donor SAR evaluated.

Although the data volume available is still small, the evaluation of the donor reactions as rates points to differences in the frequency of reactions depending on the type of donation, as was also observed by Daurat et al. [21].

// 5. Summary/Conclusion //

- Taken together, it can be stated that haemovigilance data based on spontaneous reports will only allow us to determine the reporting frequency, not the incidence of serious transfusion reactions.
- Acute allergic/anaphylactic reactions were the most frequently occurring serious transfusion reactions with rates of 63.02 for PC, 23.70 for RBC, and 18.55 for plasma, in each case referred to 10^6 transfused units.
- Transfusion associated deaths in 2015 were caused by one volume overload and three incorrect blood components transfused.
- The high number of look-back procedures induced by confirmed positive anti-HBc only findings has remained unchanged, even after the amendment of the requirement for the introduction of anti-HBc testing [4, 17]. In one out of 59 HBV-infectious donors an ID-NAT positive retain sample of a previous donation was shown without infection of the recipient. Three HBV-NAT (pool testing) only positive window phase donations each resulted in negative findings in the retain samples of the previous donations. Four of 504 donors with anti-HBc only positive findings could be confirmed by a positive HBV-ID-NAT in the index donation or the retain sample.
- Reports of serious adverse events have continued to increase in 2015. Since 2013, the major share of these events has been accounted for by incidents of human error, predominantly process errors or incorrect transfusions.
- The reports on serious adverse donor reactions have increased significantly in the reporting year of 2015 compared with previous years thanks to the requests from the PEI.
- The general trend points to a higher rate of serious donor reactions for cytapheresis compared with whole blood and plasmapheresis donations. However, the data are very preliminary because reports are still incomplete.

// 6. References //

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// 7. Figures and tables //

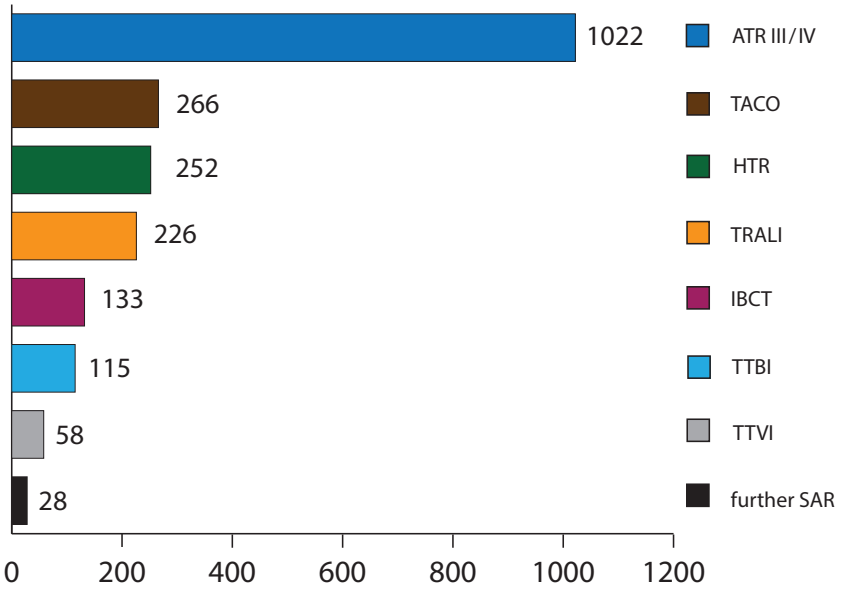

Figure 1: Cumulative number of confirmed SAR 1997–2015 graded by frequency.
The transfusions included here up to 2012 exclusively refer to ABO incompatibilities as incorrect blood component transfused (IBCT) with serious reactions in the recipient; as from 2009 exclusively to Grade III and Grade IV reactions as serious allergic transfusion reactions (ATR); as from 2013 exclusively to cases of a transfusion associated acute lung insufficiency (TRALI) rated as likely/probable and certain in accordance with the IHN criteria, and as from 2009 systematically to transfusion associated volume overload as serious transfusion reaction.

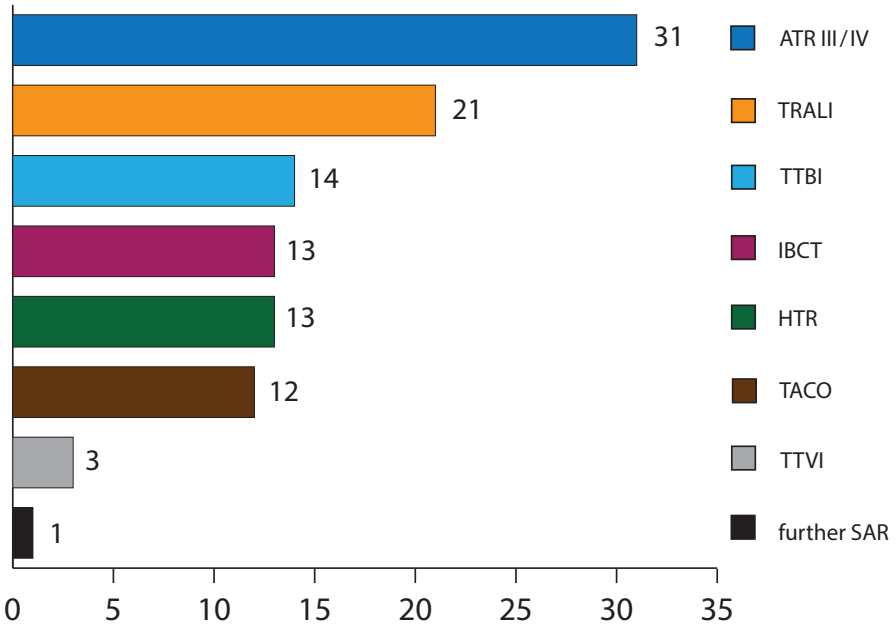

Figure 2: Cumulative number of deaths due to SAR 1997–2015 graded by frequency.

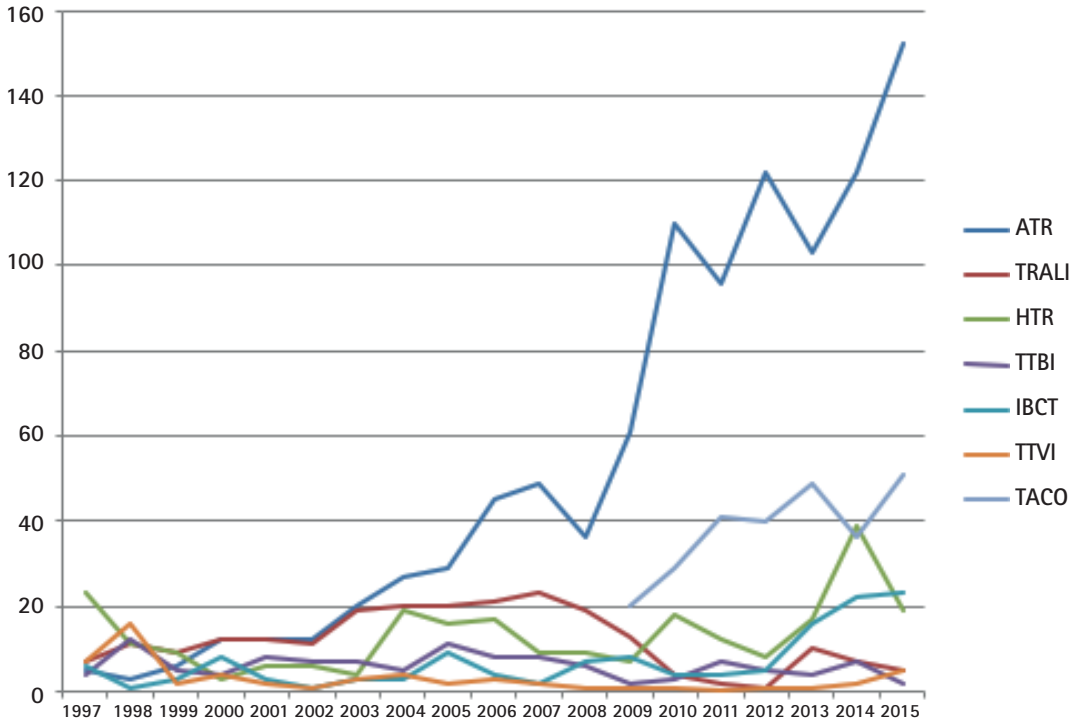

Figure 3: Number of confirmed SAR per year (1997–2015).
As from 2013, the TRALI curve includes only likely/probable and certain cases (new definition); TACO has been recorded systematically ever since 2009; as from 2010, only ATR of Grade III/IV have been included.

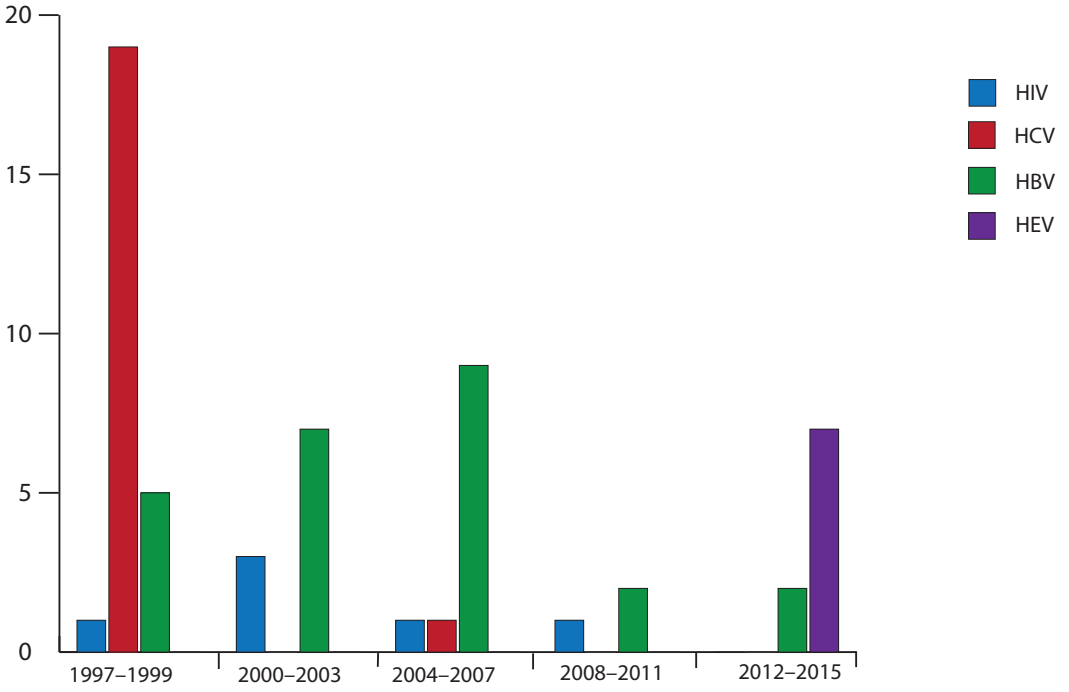

Figure 4: Number of confirmed transfusion-transmitted HIV, HCV, HBV, and HEV infections (1997–2015).

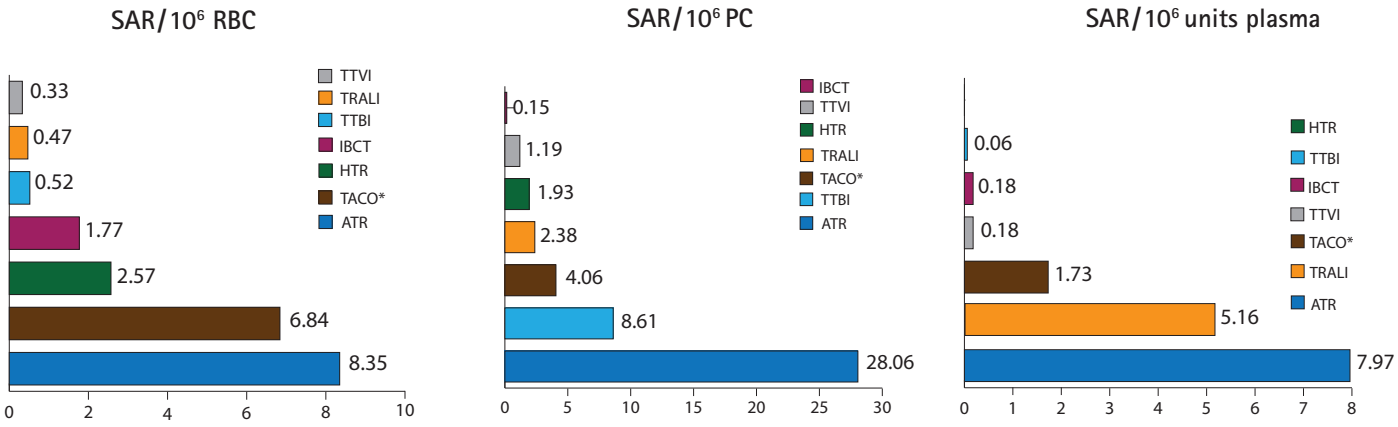

Figure 5: Rates of confirmed SAR for each 10^6 transfused units of RBC, PC and plasma (2000–2015).
*TACO: 2009–2015

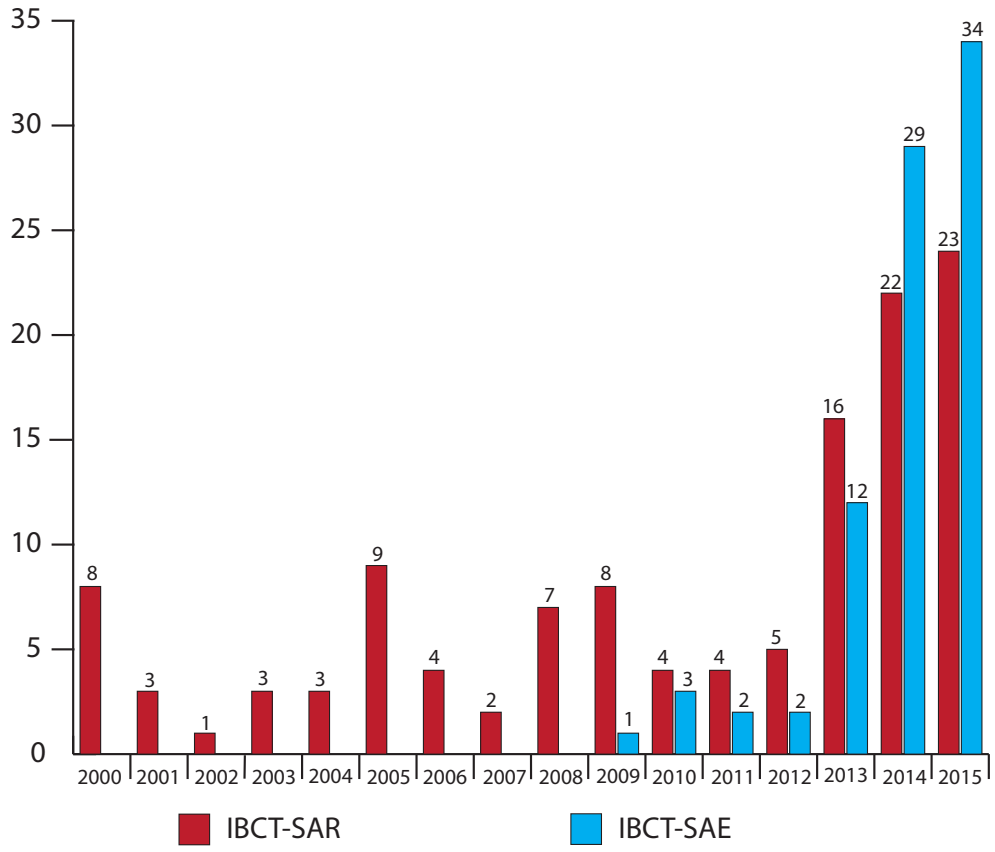

Figure 6: Number of confirmed IBCT (2000–2015).
IBCT without serious adverse reactions in the recipient recorded as SAE (blue) and with serious reactions in the recipient recorded as SAR (red).

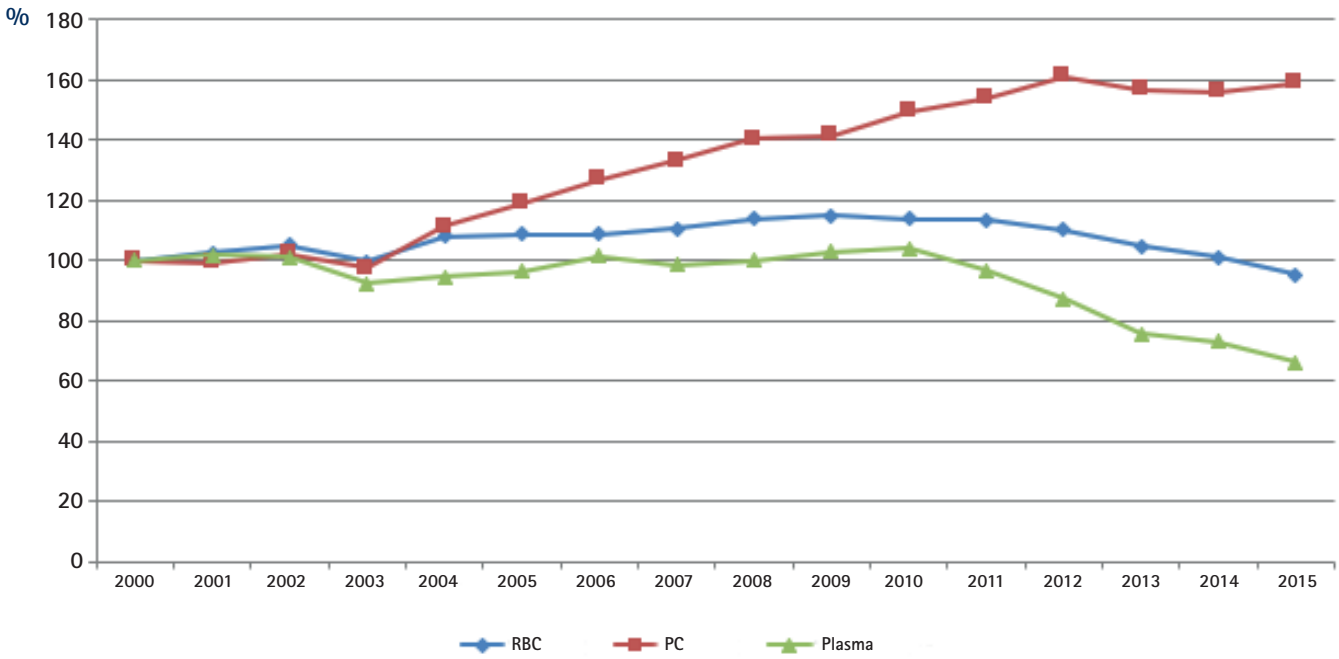

Figure 7: Percentage change of the consumption of blood components from 2000 to 2015.
The consumption in 2000 is equivalent to 100 percent.

Table 1: Consumption of blood components 2000–2005, calculated from the data reported pursuant to Section 21 TFG.
Manufacturer data on the number of red blood cell concentrates (RBC), platelet concentrates (PC), and units plasma distributed minus number of units expired/disposed at the user site – presented per year and per quarter.

	2000	2001	2002	2003	2004	2005	2006	2007
RBC	3,941,157	4,046,190	4,135,720	3,928,403	4,259,097	4,279,104	4,284,180	4,350,750
PC	319,701	317,265	326,130	311,563	355,979	379,758	405,711	425,425
Plasma	1,143,722	1,162,685	1,154,278	1,055,033	1,079,987	1,103,480	1,160,805	1,125,226

	2008	2009	2010	2011	2012	2013	2014	2015
RBC	4,482,667	4,522,312	4,490,929	4,468,918	4,339,700	4,122,190	3,985,415	3,754,760
PC	449,139	452,129	477,456	492,188	515,534	500,874	498,230	507,814
Plasma	1,143,646	1,177,488	1,190,599	1,104,371	998,008	863,261	837,099	754,896

	2000–2003	2004–2007	2008–2011	2012–2015	2000–2015
RBC	16,051,470	17,173,130	17,964,825	16,202,065	67,391,491
PC	1,274,659	1,566,873	1,870,911	2,022,453	6,734,896
Plasma	4,515,718	4,469,498	4,616,104	3,453,264	17,054,584

Table 2: Total number of reported transfusion reactions, confirmed transfusion reactions and the portion of deaths (1997–2015).

Serious adverse reaction (SAR) 1997–2015	Reported cases	Confirmed cases	Thereof fatal cases
Acute allergic/anaphylactic transfusion reaction (ATR) grades I–IV*	2,982	1,022	31
Transfusion related acute lung injury (TRALI)	1,028	226	21
Haemolytic transfusion reaction (HTR)	518	252	13
Transfusion transmitted bacterial infection (TTBI)	398	115	14
Incorrect blood component transfused (IBCT)	134	133	13
Transfusion transmitted viral infection (TTVI)**	3,476	58	3
Post-transfusion Purpura (PTP)	25	17	0
Transfusion-associated GVHD (TA-GVHD)	4	3	1
Transfusion-associated circulatory overload (TACO)	282	266	12
Others	100	8	0
Total	8,947	2,100	108

* As from 2009 only ATR Grade III and IV were included in the assessment
**Includes HCV, HIV, HBV transmissions, as from 2013 also HEV transmissions with one case of death in 2013

Table 3: Confirmed cases of serious allergic transfusion reactions Grades III and IV, associated deaths and rate of confirmed reactions referring to 10^6 units transfused (before 2009: including serious reactions Grade II).

	1997–1999	2000–2003	2004–2007	2008–2011	2012–2015	1997–2015
Confirmed serious allergic transfusion reactions						
RBC	7	27	99	160	277	570
PC	2	12	20	49	108	191
Plasma	1	9	16	54	57	137
Combined transfusion	4	8	15	40	57	124
Total	**14**	**56**	**150**	**303**	**499**	**1,022**
Thereof fatal cases						
RBC	0	4	2	6	4	16
PC	0	1	1	2	1	5
Plasma	0	1	1	2	0	4
Combined transfusion	2	2	0	1	1	6
Total	**2**	**8**	**4**	**11****	**6**	**31**

Rates of confirmed serious allergic transfusion reactions

	2000–2003		2004–2007		2008–2011		2012–2015	
	Units transfused	ATR per 10^6 units	Units transfused	ATR per 10^6 units	Units transfused	ATR per 10^6 units	Units transfused	ATR per 10^6 units
RBC	16,051,470	1.68	17,173,130	5.76	17,964,825	8.91	16,202,065	17.10
PC	1,274,659	9.41	1,566,873	12.76	1,870,911	26.19	2,022,453	53.40
Plasma	4,515,718	1.99	4,469,498	3.58	4,616,104	11.70	3,453,264	16.51

As of 2009 acute transfusion reactions are subdivided in allergic (ATR I/II) and anaphylactic (ATR III/IV) transfusion reactions.
** The cases from 2009 refer to patients with serious underlying diseases. A connection between transfusion reactions and fatal outcome cannot be ruled out.

Table 4: Confirmed cases of serious immunogenic and non-immunogenic TRALI, associated deaths, and rate of immunogenic TRALI referring to 10^6 transfused units.

	1997–1999	2000–2003	2004–2007	2008–2011	2012–2015	1997–2015
TRALI-cases, search for HLA-/HNA-antibodies						
Negative	1	9	18	12	3	43
Donors positive	12	24	60	26	20	142
Not done	14	21	6	0	0	41
Total	**27**	**54**	**84**	**38**	**23**	**226**
TRALI-cases, search for HLA-/HNA-antibodies positive in						
RBC-donors	5	5	9	5	13	37
PC-donors	1	2	3	5	6	17
Plasma-donors	6	17	48	18	5	94
Total	**12**	**24**	**60**	**28**	**24**	**148**
Thereof fatal TRALI-cases due to transfusion of						
RBC	0	1	2	0	0	**3**
PC	0	0	0	1	1	**2**
Plasma	0	1	10	5	0	**16**
Total	**0**	**2**	**12**	**6**	**1**	**21**

Rates of confirmed immunogenic TRALI-cases

	2000–2003		2004–2007		2008–2011		2012–2015	
	Units transfused	TRALI per 10^6 units	Units transfused	TRALI per 10^6 units	Units transfused	TRALI per 10^6 units	Units transfused	TRALI per 10^6 units
RBC	16,051,470	0.31	17,173,130	0.52	17,964,825	0.28	16,202,065	0.74
PC	1,274,659	1.57	1,566,873	1.91	1,870,911	2.67	2,022,453	1.98
Plasma	4,515,718	3.76	4,469,498	10.74	4,616,104	3.90	3,453,264	0.87

*The total number of positive donors may differ from the number of confirmed cases of immunogenic TRALI, if a recipient has received several different blood components of AB positive donors.
A specific donor selection, i.e. screening applies as per 1 Sept. 2009 if plasma for transfusion is manufactured from the donation.

Table 5: Confirmed cases of HTR, associated deaths and rate of serious HTR referring to 10^6 transfused units.

	1997–1999	2000–2003	2004–2007	2008–2011	2012–2015	1997–2015
Haemolytic transfusion reactions						
RBC	40	11	50	41	71	**213**
PC	0	2	4	4	3	**13**
Combined transfusion	3	6	7	1	9	**26**
Total	**43**	**19**	**61**	**46**	**83**	**252**
Thereof acute HTR, delayed HTR, and HTR with proof of irregular antibodies						
Acute HTR	37	16	55	25	69	**202**
Delayed HTR	6	3	6	21	14	**50**
Irregular antibodies	4	2	4	28	14	**52**
Thereof fatal cases						
RBC	4	0	3	2	2	**11**
Combined transfusion	1	0	1	0	0	**2**
Total	**5**	**0**	**4**	**2**	**2**	**13**

Rates of confirmed haemolytic transfusion reactions								
	2000–2003		2004–2007		2008–2011		2012–2015	
	Units transfused	HTR per 10^6 units	Units transfused	HTR per 10^6 units	Units transfused	HTR per 10^6 units	Units transfused	HTR per 10^6 units
RBC	16,051,470	0.69	17,173,130	2.91	17,964,825	2.28	16,202,065	4.38
PC	1,274,659	1.57	1,566,873	2.55	1,870,911	2.14	2,022,453	1.48

Table 6: Confirmed cases of TTBI, associated deaths and rate of TTBI referring to 10^6 transfused units.

	1997–1999	2000–2003	2004–2007	2008–2011	2012–2015	1997–2015
TTBI						
RBC	10	7	13	7	8	45
P-PC	6	8	9	5	1	29
A-PC	1	11	9	6	9	36
Plasma	4	0	1	0	0	5
Total	**21**	**26**	**32**	**18**	**18**	**115**
Thereof fatal cases						
RBC	4	0	0	0	0	4
P-PC	1	1	1	2	0	5
A-PC	0	2	2	0	1	5
Plasma	0	0	0	0	0	0
Total	**5**	**3**	**3**	**2**	**1**	**14**

Rates of confirmed TTBI

	2000–2003		2004–2007		2008–2011		2012–2015	
	Units transfused	TTBI per 10^6 units	Units transfused	TTBI per 10^6 units	Units transfused	TTBI per 10^6 units	Units transfused	TTBI per 10^6 units
RBC	16,051,470	0.44	17,173,130	0.76	17,964,825	0.39	16,202,065	0.49
PC	1,274,659	14.91	1,566,873	11.49	1,870,911	5.88	2,022,453	4.94
Plasma	4,515,718	0.00	4,469,498	0.22	4,616,104	0.00	3,453,264	0.00

Table 7: Results of microbiological examinations of confirmed cases of TTBI (1997–2015).

TTBI confirmed by pathogen detection in component/recipient	Number of blood components with evidence of pathogen in the recipient/blood product				Course of disease in the recipient		Deaths after administration of	
Genus/species	RBC	PC	Plasma	Total	Non-fatal	Fatal	RBC	PC
With low (human) pathogenicity								
Staphylococcus capitis, epidermidis, hominis, saprophyticus und spp. *Micrococcus luteus, Corynebacterium spp.* *Propionibacterium acnes*	18	27	2	47	46	1	0	1
With medium and high (human) pathogenicity								
Staphylococcus aureus *Streptococcus pyogenes und agalactiae* *Bacillus cereus, Escherichia coli* *Enterobacter aerogenes, amnigenus* *Klebsiella oxytoca, pneumoniae* *Pantoea agglomerans, Serratia marcescens,* *Yersinia enterocolitica, Enterococcus spp.* *Acinetobacter lwoffii, Pseudomonas aeruginosa* *Stenotrophomonas maltophilia*	27	38	3	68	55	13	4	9
Total	45	65	5	115	101	14	4	10*

* Transfusion of the platelet concentrates on the 4th or 5th day, as applicable, after manufacture

Table 8: Confirmed cases of TTVI and rate of TTVI referring to 10^6 transfused units.

	1997–1999	2000–2003	2004–2007	2008–2011	2012–2015	1997–2015
HIV-Infections following transfusion of						
RBC	1	3	1	1	0	**6**
PC	0	0	0	0	0	**0**
Plasma	0	0	0	0	0	**0**
Total	1	3	1	1	0	**6**
HCV-Infections following transfusion of						
RBC	7	0	1	0	0	**8**
P-PC	1	0	0	0	0	**1**
A-PC	2	0	0	0	0	**2**
Plasma	9	0	0	0	0	**9**
Total	**19**	**0**	**1**	**0**	**0**	**20**
HBV-Infections following transfusion of						
RBC	4	3	8	1	1	**17**
P-PC	0	0	0	0	0	**0**
A-PC	1	2	0	1	1	**5**
Plasma	0	2	1	0	0	**3**
Total	**5**	**7**	**9**	**2**	**2**	**25**
HEV-Infections following transfusion of						
RBC					3	**3**
P-PC					1	**1**
A-PC					3	**3**
Plasma					0	**0**
Total					7	**7**

Rates of confirmed transfusion transmitted HIV-, HCV-, and HBV-Infections

	2000–2003		2004–2007		2008–2011		2012–2015	
	Units transfused	TTVI per 10^6 units	Units transfused	TTVI per 10^6 units	Units transfused	TTVI per 10^6 units	Units transfused	TTVI per 10^6 units
RBC	16,051,470	0.37	17,173,130	0.58	17,964,825	0.11	16,202,065	0.06
PC	1,274,659	1.57	1,566,873	0.00	1,870,911	0.53	2,022,453	0.49
Plasma	4,515,718	0.44	4,469,498	0.22	4,616,104	0.00	3,453,264	0.00

Rates of confirmed transfusion transmitted HEV-Infections

							2012–2015	
							Units transfused	TTVI per 10^6 units
RBC							16,202,065	0.19
PC							2,022,453	1.98
Plasma							3,453,264	0.00

Table 9: Confirmed cases of IBCT with serious adverse reactions (SAR) and cases of IBCT without serious adverse reactions (SAE) in the recipient.

	1997–1999	2000–2003	2004–2007	2008–2011	2012–2015	1997–2015
SAR RBC	10	15	18	23	63	129
SAR PC				0	1	1
SAR Plasma				0	3	3
SAR total	10	15	18	23	67	133
Thereof fatal	3	0	1	4	5	13
SAE RBC				6	66	72
SAE PC				1	4	5
SAE Plasma				0	7	7
SAE total				7	77	84
IBCT (SAE plus SAR) total	10	15	18	30	144	217

*Notifiable for SAE (IBCT without SAR) since 2012
Up to 2013, reports of IBCT with serious reactions (SAR) were indicated as ABO incompatibilities.

Table 10: Rates of the most common SAR (2000–2015) for each 10^6 transfused units of RBC, PC and plasma.

SAR Rates per 10^6 units:	ATR	HTR	TRALI	TACO*	TTBI	TTVI	IBCT	Units transfused 2000–2015	Units transfused 2009–2015*
RBC	8.35	2.57	0.47	6.84	0.52	0.33	1.77	67,391,491	29,684,224
PC	28.06	1.93	2.38	4.06	8.61	1.19	0.15	6,734,896	3,444,225
Plasma	7.97	0.00	5.16	1.73	0.06	0.18	0.18	17,054,584	6,925,722

*Rates for TACO based on units transfused between 2009 and 2015.