Bundesinstitut für Impfstoffe
und biomedizinische Arzneimittel

Paul-Ehrlich-Institut

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

2016/2017

Assessment of the Reports of Serious Adverse

Transfusion Reactions and Events

pursuant to Section 63 i AMG
(German Medicines Act)

// Publication details //

Published by

Paul-Ehrlich-Institut (PEI, Langen)
Federal Institute for Vaccines
and Biomedicines
Paul-Ehrlich-Straße 51–59
63225 Langen, Germany

Editors

Professor Dr Markus Funk
Dr Margarethe Heiden
Dr Susanne Müller
Pharmacovigilance II, PEI
Phone: +49 (0)6103/77–3116
Email: pharmakovigilanz2@pei.de

Dr Corinna Volz-Zang
Press Office PEI
Phone: +49 (0)6103/77–1093
Email: Corinna.Volz-Zang@pei.de

Proof-reading and Layout

Kirsten Külker, Berlin

The pdf version can be viewed on or downloaded from the website of the Paul-Ehrlich-Institut (www.pei.de/haemovigilance-report). Alternatively, you can take out a subscription to receive updates by sending an email to presse@pei.de

ISSN (Internet) 2192-2314

The Paul-Ehrlich-Institut reports to the German Federal Ministry of Health.

Other co-workers contributing to the haemovigilance report:

Cornelia Witzenhausen[1], Dr Sonja Schönefeld[1], Dr Gabriele Ruppert-Seipp[1], Dr Philipp Berg[1], Klaudia Wesp[1], Olaf Henseler[2], Jochen Halbauer[1], Sarah Fiedler[1], Constanze Taylor[3], and Dr Brigitte Keller-Stanislawski[1]

[1]Division S: Safety of Medicinal Products and Medical Devices
[2]Division 7: Haematology/Transfusion Medicine
[3]Division L: Translation Service

Titel graphics: www.shutterstock.com, Stock Vektor graphics: 217752715

// Contents //

// 1. Introduction //

The haemovigilance report 2016/17 of the Paul-Ehrlich-Institut (PEI) summarises all spontaneous reports from 2016 and 2017 on serious adverse transfusion reactions (SAR), serious adverse donor reactions (donor SAR), and serious adverse events (SAE). It continues the analysis and compares the new data to the reports of 2000-2015. The assessment algorithm introduced in the haemovigilance report 2013-2014 [1] for transfusion-related acute lung insufficiency (TRALI) was retained, thus permitting a comparison of the data on confirmed immunogenic as well as non-immunogenic reactions over the last 5 years.

As in previous reports, the number of donor-initiated look-back procedures for viral pathogens is compared with the confirmed infectious donations with special focus on HBV.

The suspected cases reported of HEV transmission from 2013 to 2017 are presented with information on the underlying diseases as well as on the clinical symptoms of hepatitis that occurred in donors or recipients. Special focus of the current reports is on the serious adverse donor reactions and on the serious adverse events occurring in the transfusion chain. The serious adverse events also include errors in the identification of the donation or the recipient which could have led to the transfusion of an incorrect blood component as well as incorrect blood components transfused (IBCT) without serious reactions in the recipient. Those IBCT reported as serious adverse events are compared with IBCT causing serious reactions.

As has been emphasised in previous haemovigilance reports, an appropriate and correct evaluation of the data reported can only take place if all adverse events are documented in sufficient detail by the treating physicians and the blood establishments (BE) involved. The reports should therefore at least include the information required in Section 14 Transfusion Act [2]. In the case of complex situations and, in particular, in the case of transfusion reactions leading to death, a more detailed documentation (e.g. anonymised transfer report/epicrisis) is desirable. Reliable data of sufficient quality form the indispensable basis for an adequate scientific evaluation and the subsequent assessment of risks within the transfusion chain. The haemovigilance data collected are reported by the Paul-Ehrlich-Institut to the European Commission pursuant to Directive 2005/61/EC [3] [4].

// 2. Abbreviations //

Ab	Antibody
Ag	Antigen
AK Blut	National Advisory Committee Blood of the German Federal Ministry of Health
AkdÄ	Arzneimittelkommission der deutschen Ärzteschaft (Drug Commission of the German Medical Association)
AMG	Arzneimittelgesetz (German Medicines Act)
AML	Acute myeloid leukaemia
Anti-HBc	Antibodies against hepatitis B-core antigen
A-PC	Apheresis platelet concentrate(s)
ARDS	Acute Respiratory Distress Syndrome
ATR	Acute allergic/anaphylactic transfusion reaction(s)
BE	Blood establishment(s)
BNP	Brain natriuretic peptide or B-type natriuretic peptide
CVL	Central venous line
HAV	Hepatitis-A virus
HBV	Hepatitis-B virus
HCMV	Human cytomegalovirus
HCV	Hepatitis-C virus
HEV	Hepatitis-E virus
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen(s)
HNA	Human neutrophil antigen(s)
HPA	Human platelet antigen(s)
HTR	Haemolytic transfusion reaction(s)
IBCT	Incorrect blood component transfused
ID-NAT	Individual Donor-Nucleic Acid Testing
ISBT	International Society of Blood Transfusion
NAT	Nucleic acid amplification technology
PC	Platelet concentrate(s)
PEI	Paul-Ehrlich-Institut
PDI	Post Donation Information
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)
TRALI	Transfusion-related acute lung-injury
WB	Whole blood

// 3. Methods //

3.1 Introduction

Each report of a suspected SAR in a donor or recipient is captured in the PEI database and completed by means of additional information requests if necessary. Table 3.1 provides an overview with examples of how the connection of SAR with the transfusion is evaluated in accordance with the criteria in Annex II Part B "Imputability levels to assess serious adverse reactions" of Directive 2005/61/EC 2005/61/EG [3]. A SAR is considered as confirmed if it has been categorised as certain or likely/probable, and if the SAR refers to a TRALI, a transfusion-transmitted bacterial infection (TTBI), a transfusion-transmitted viral infection (TTVI), or an IBCT. Since, in particular for allergic and anaphylactic transfusion reactions (ATR), febrile non-haemolytic transfusion reactions (FNHTR) and transfusion associated dyspnoea, partly also for haemolytic transfusion reactions (HTR) and transfusion associated circulatory overload, unique clinical parameters are missing, which could unambiguously provide proof for the relationship between a SAR and the transfusion, confirmed serious transfusion reactions also include SAR categorised as having a possible connection with the transfusion. Reported deaths are considered as confirmed only if the clinical course of the SAR and additional laboratory parameters captured or post-mortem findings point to a certain or likely/probable causal relationship with the product transfused.

The confirmed SAR are grouped and their ratio is calculated by comparing them with the number of blood components determined as transfused in accordance with Section 21 Transfusion Act (Transfusionsgesetz, TFG) [5]. Donor SAR reported by the BE as due to whole-blood or apheresis donations are grouped by type of

Table 3.1: Rating of serious adverse transfusion reactions

Relationship to transfusion	Criteria
Not assessable	Insufficient data available e.g. because no data are available on the donor or recipient any longer.
Excluded or unlikely	Data, the temporal relationship, or the underlying disease rule out or speak against the transfused blood component as being the cause of the reaction.
Possible	The clinical course of the reaction and the temporal relationship to the transfusion point to the transfusion as the cause of the reaction. However, other factors such as the underlying disease of the patient, a known septicaemia prior to the transfusion, or a different source of contamination cannot safely be ruled out as factors being or contributing to the cause of the reaction.
Likely, probable	Clinical course of the reaction and data point to the transfusion as the cause of the SAR, but the data do not provide proof, e.g. because a comparative antibiogram of the bacterial strain found in the product and the recipient is missing, or proof of sequence homology of the virus found in the donor and the recipient, or proof of corresponding antigens or antibodies could not be provided due to insufficient testing material.
Certain	Clinical course of the SAR and laboratory data provide proof or the relationship.

reaction on the one hand, and presented by type of donation as the rate of confirmed SAR per number of the respective donations on the other hand. The frequency of SAE which did not cause a reaction in the donor or the recipient are listed and presented from their occurrence in the transfusion chain from the donation up to their use.

The legal basis for reports of SAE and SAR required from the blood donation centre is laid down in Section 63i, German Medicines Act (Arzneimittelgesetz, AMG) [6], and the legal basis for those required from treating doctors is laid down in Sections 14 and 16 Transfusion Act (TFG) [2]. For this type of reporting, the PEI provides standardised forms on its homepage [7]. Reports can be submitted via an online submission platform as well (https://humanweb.pei.de). In the report, the physician shall document all essential information on the transfusion, such as time and type of the blood component administered, data on the recipient such as date of birth, gender, underlying disease, and all relevant concomitant diseases as well as adjuvant medicines taken by the patient. The BE involved in the production of the blood components concerned shall complete this information by specific data on the respective donors as well as additional blood products that may have been produced from the donations. Besides, the BE shall report the results of lab tests performed and the initiation of a look-back procedure, if applicable [8–10]. In the event of an adverse donor reaction, the type of donation and donor reaction shall be reported too. Incorrect blood components transfused (IBCT) without transfusion reactions and errors in the transfusion chain that could have led to IBCT must be reported by the pharmaceutical companies to the senior federal authority as SAE pursuant to Section 63i AMG [6] (16th amendment of the AMG). A reporting obligation pursuant to Section 16 (2) TGF [2, 7, 10] also applies to the treating doctor in the event of an IBCT involving an adverse transfusion reaction. Since the legal obligation to notify the authorities exclusively applies to serious adverse reactions and events, the PEI receives only sporadic information on non-serious ones. These are, therefore, not included in the evaluation. Since 2014, the Drug Commission of the German Medical Association (AkdÄ) has been forwarding all available reports to the PEI, which have been included in the evaluation accordingly.

3.2 Categorisation of transfusion reactions

The definitions of serious adverse transfusion reactions in accordance with the Haemovigilance Working Party of the International Society of Blood Transfusion (ISBT) [11] are presented in Table 3.2. The distinction between allergic transfusion reactions Grades I and II from serious allergic or anaphylactic (as applicable) transfusion reactions Grades III and IV is made according to Ring and Messmer [12]. As has been common practice since 2009, only serious acute allergic/anaphylactic transfusion reactions Grads III and IV have been included in this evaluation. Suspected cases of TRALI that have been confirmed have been categorised into immunogenic and non-immunogenic TRALI [13, 14].

Reports pursuant to Section 21 TFG on the sale and loss of red blood cell concentrates (RBC), platelet concentrates (PC), and plasma were used for calculating the number of transfused units (deadline 15 Jan. 2019 [5]), which served as the basis to determine the frequencies of confirmed SAR.

The first part of the haemovigilance report presents the data captured in the reporting period. The tables and figures of the annex continue the summary collection of haemovigilance data since the year 2000.

Table 3.2: Definitions of suspected serious adverse transfusion reactions

Acute allergic/anaphylactic 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 post 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 post transfusion, drop in the haemoglobin level >2 g/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, positive antiglobulin test or positive crossmatch-test. 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 and detection of the same bacterial strain in the recipient, as applicable.

Transfusion transmitted viral infection (TBVI):

Detection of the virus or seroconversion of the recipient post transfusion, negative finding before the transfusion.

Transfusion associated respiratory 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, strongly increased concentration of brain natriuretic peptides (BNP), improvement of the condition after administration of diuretics.

Incorrect blood component transfused (IBCT):

Treatment with ABO-incompatible blood components, transfusion of accidentally 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. An incorrect blood component transfused without any reactions in the recipient is subject to SAE reporting (definition see Section 63i [6] AMG).

Transfusion related dyspnoe:

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; detection of platelet-specific antibodies. PTP is considered as 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)

Out of the 547 suspected cases of serious adverse transfusion reactions reported in total in 2016 and of 535 reported in 2017, 362 and 359, respectively, were assessed as confirmed (for definitions, see Table 3.2). Thus, the spontaneous reports of adverse transfusion reactions as well as the number of confirmed cases have been in the same order of magnitude since 2014 (see Table 4.1 a).

Table 4.1 a: Suspected, confirmed and fatal cases of SAR (2012–2017)

SAR	Reported	Confirmed	Fatal cases
2012	435	248	5
2013	465	280	5
2014	596	370	10
2015	559	352	4
2016	547	362	5
2017	535	359	11

This applies specifically to confirmed cases of TRALI, TTBI, and TTVI, and, since 2015, to ATR. In contrast, confirmed cases of TACO have increased by almost 80% from 36 in 2014 to 64 in 2017 (see also Annex, Fig.1). There has been a slight upward trend (with fluctuations) for confirmed cases of HTR and incorrect blood components transfused since 2014.

Deaths:

The following adverse transfusion reactions contributed as cause of altogether 16 deaths reported in 2016 and 2017:

- three anaphylactic reactions after administration of RBC, PC, or plasma
- three TTBI caused by bacterially contaminated PC,
- three HTR after administration of RBC, out of these two with irregular red blood cell Ab,
- three IBCT due to incorrectly transfused RBC with ABO incompatibility,
- three TACO after administration of RBC, and
- one immunogenic TRALI after administration of RBC.

In summary, 124 fatalities have been linked to the administration of blood components in the observation period of 21 years (1997–2017). As the most frequent cause of death, serious allergic/anaphylactic reactions (34 cases) were documented, followed by TRALI (22 cases). Seventeen deaths occurred due to TTBI, 16 patients died each due to HTR and IBCT, and 15 due to TACO. In addition, three deaths were reported after viral infections and one death after a GvHD reaction (see Figure 4.1 and Annex Table 2).

Figure 4.1: Number of serious adverse reactions with fatal outcome (1997–2017)

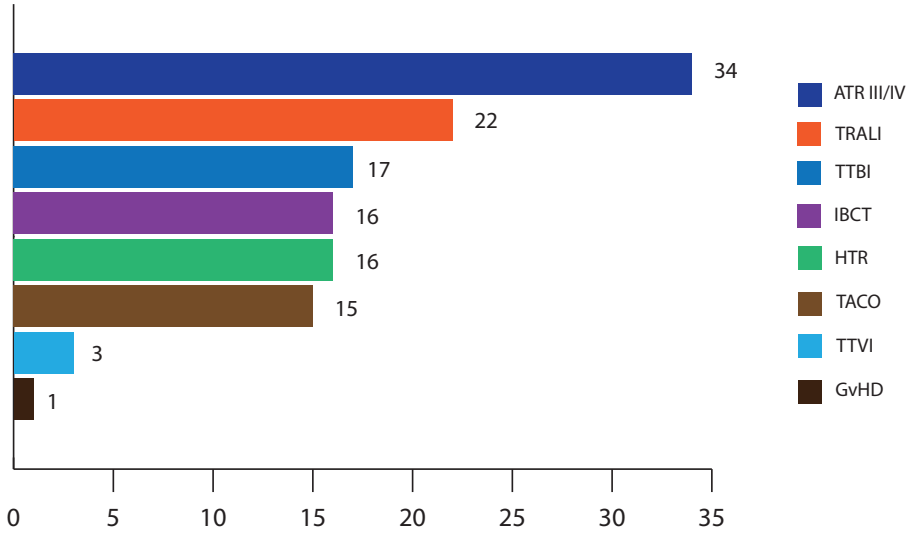


Table 4.1 b: Number of suspected cases of serious transfusion reactions (SAR), number of confirmed SAR as well as fatal cases due to a transfusion reported in 2016 and 2017

SAR	Suspected cases notified		Confirmed cases		Fatal cases thereof with causal connection	
	2016	2017	2016	2017	2016	2017
ATR Grade I/II	71	59	70	57	0	0
ATR Grade III/IV	173	158	160	149	1	2
TRALI	62	44	6	4	0	1
HTR	44	64	28	46	0	3
TTBI	40	50	3	6	1	2
IBCT	29	27	28	27	2	1
HCV, HIV, HBV	39	37	0	0	0	0
HEV	9	6	3	1	0	0
PTP	4	1	0	1	0	0
TACO	56	68	54	64	1	2
Other	20	21	10	4	0	0
Total	**547**	**535**	**362**	**359**	**5**	**11**

4.2 Acute allergic/anaphylactic transfusion reactions (ATR)

Since 2009, only ATR Grade III and IV are used as the basis for calculating the SAR rates out of the total number of acute allergic/anaphylactic reaction cases reported.

ATR are defined by a set of clinical symptoms rather than laboratory parameters. Many symptoms can be unspecific – apart from the development of urticaria or itching – and can overlap with symptoms of other transfusion reactions such as dyspnoea or febrile reactions. Therefore, it is almost impossible to rate individual cases of ATR as "certain", which is why for ATR classified as confirmed, the causality assessment has almost exclusively been assessed as "likely/probable" or "possible".

In line with previous haemovigilance reports, serious allergic/anaphylactic transfusion reactions have been reported more frequently following the administration of PC than following the administration of other blood components (see Annex Tables 3 and 11).

Table 4.2: Number of suspected cases of ATR Grade I/II and III/IV, confirmed cases, and fatal cases after the administration of RBC, PC, plasma or combined administration (2016–2017)

ATR		2016	2017
Reported cases	Grade I/II	71	59
	Grade III/IV	173	158
	Total	244	217
Confirmed ATR	Grade I/II	70	57
	Grade III/IV	160	149
	Total	230	206
Following administration of RBC	Grade I/II	37	35
	Grade III/IV	90	91
	Fatal cases thereof	0	1
Following administration of PC	Grade I/II	14	10
	Grade III/IV	43	34
	Fatal cases thereof	0	1
Following administration of plasma	Grade I/II	10	8
	Grade III/IV	15	14
	Fatal cases thereof	1	0
Following administration of combined products	Grade I/II	9	4
	Grade III/IV	12	10
	Fatal cases thereof	0	0

Deaths:

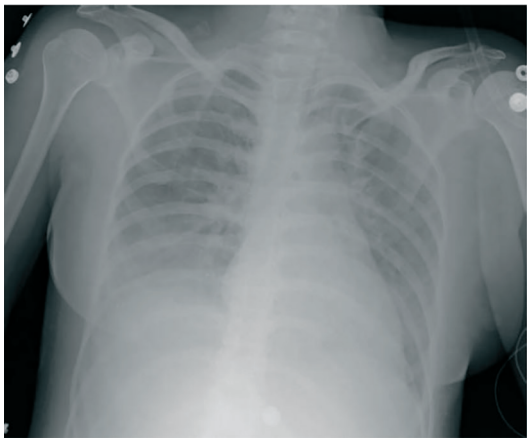
In 2016, one fatal outcome of an ATR following plasma transfusion was reported and confirmed. For 2017, one fatal outcome was reported and confirmed after an RBC and one after a PC transfusion.

4.3 Transfusion-associated circulatory overload (TACO)

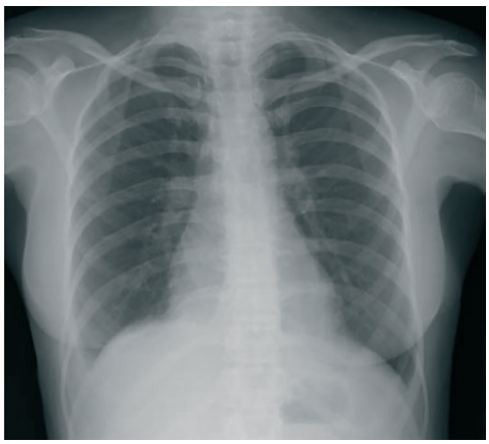
As with ATR, clinical parameters are the decisive factors for the assessment of a suspected case of TACO [15] and the differentiation from non-immunogenic or possible TRALI or ARDS is complex inasmuch as the differences in the symptoms may be blurred. The respective findings in a thorax x-ray, as shown below, and rapid recovery after the administration of diuretics are diagnostic criteria pointing to circulatory overload. Another diagnostic parameter, which has been established for some time, is the BNP value, especially for a distinction to non-immunogenic TRALI. A strong increase in the BNP (brain natriuretic peptide) levels during the course of the observation can support the TACO diagnosis.

Radiological findings:

Lung oedema



Post diuresis follow-up



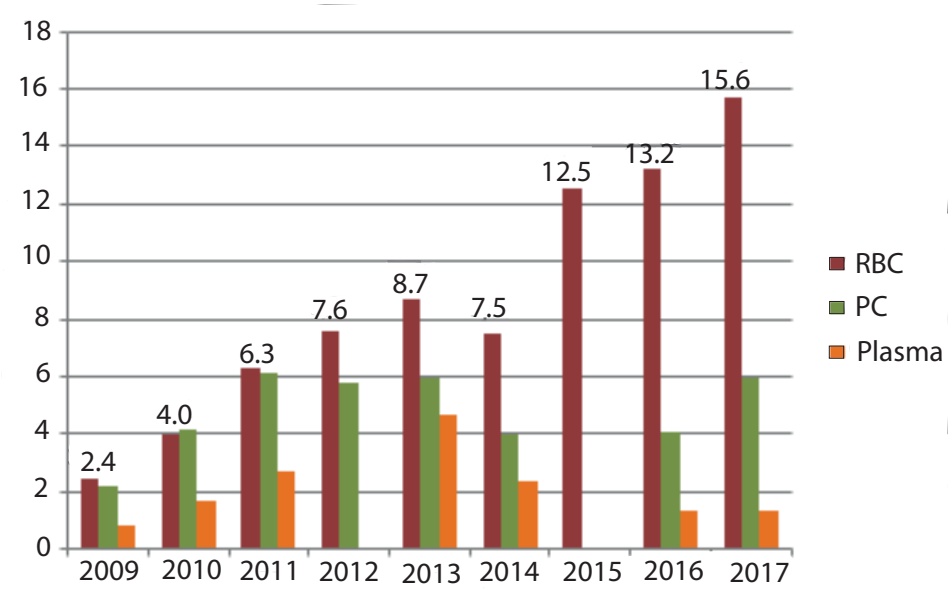
http://www.mevis-research.de/~hhj/Lunge/HG.html

Table 4.3: Number of suspected cases reported for transfusion-associated circulatory overload (TACO), confirmed cases as well as fatal cases after the administration of RBC, PC, plasma, or combined administration (2016–2017)

TACO	2016	2017
Reported cases	56	68
Confirmed cases	54	64
Following administration of RBC	47	55
Fatal cases thereof	1	2
Following administration of PC	2	3
Fatal cases thereof	0	0
Following administration of Plasma	1	1
Fatal cases thereof	0	0
Following combined administration	4	5
Fatal cases thereof	0	0

Since the systematic capture of TACO has started in 2009, the number of cases assessed as confirmed has tripled from 20 to 64 up to 2017 (see Annex Figure 1 and Table 4). For the frequency per 10^6 transfused RBC units, the increase is almost seven-fold (Figure 4.3). The rise in the number of reports can most likely be attributed to more awareness of the clinical picture of TACO but partly also to the steadily increasing portion of patients with medical conditions, which favour a development of TACO (such as coronary heart disease, kidney and liver insufficiency, etc.).

Figure 4.3: Rate of confirmed TACO referred to 10^6 transfused units of RBC, PC, and plasma, respectively, from 2009 (beginning of systematic capture) to 2017



Deaths:

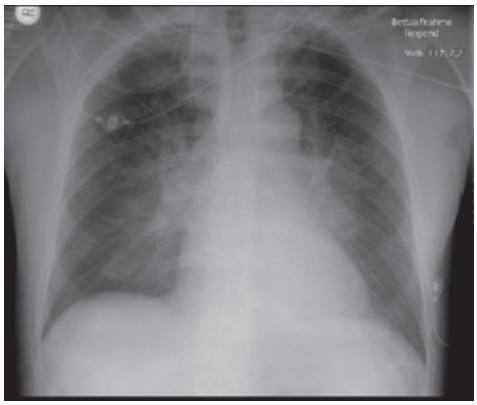
Altogether 14 patients have died due to transfusion-associated circulatory overload in the 9 years since the beginning of the systematic capture of TACO; out of these, one after administration of RBC in 2016 and two, also after administration of RBC in 2017.

4.4 4.4 Transfusion-related acute lung injury (TRALI)

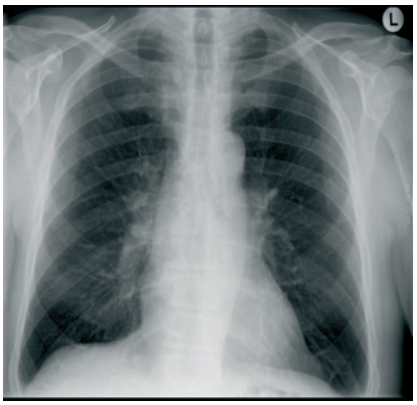
TRALI is characterised by the rapid occurrence of respiratory distress within a maximum of six hours following the end of the transfusion. At the same time, other diseases that may also cause lung insufficiency (e.g. cardiologic diseases, etc.) must be ruled out. Unlike in TACO, no radiological signs of lung oedema can be found in TRALI, but bilateral acute perihilar lung infiltrates. Immunogenic TRALI is confirmed by evidence of specific antibodies (Ab) in the donor and the corresponding antigen (Ag) in the recipient.

Radiological findings: TRALI following the administration of FFP in patients following prostatectomy

Bilateral lung infiltrates



Control (day 5) after machine-assisted ventilation



The algorithm already described [1] was used for the current assessment of the suspected cases of TRALI, in which symptoms are tested and possible other causes ruled out initially. Then, the donors are tested for relevant HLA-Ab or HNA-Ab and recipients are tested for corresponding antigens. Depending on the result, the reaction is then subdivided into immunogenic or non-immunogenic TRALI. Based on new medical and scientific findings, these algorithms are currently reassessed, in particular with regard to a distinction between immunogenic and non-immunogenic TRALI [14]. Unfortunately, testing of the recipients for corresponding antigens is performed very rarely, and is practically the exception for the reports of suspected TRALI. However, in the future information on the corresponding antigens in the recipient could be essential for an assessment on the basis of a revised algorithm.

Especially in those cases that, due to missing evidence of corresponding Ab, cannot easily be distinguished from TACO, in which the latency until onset of symptoms points to TRALI, but at the same time pre-existing medical conditions point to the TACO, the BNP levels can be used as a diagnostic decision criterion.

In 2016, the PEI received 62 and in 2017 a total of 44 reports of suspected cases of TRALI, out of which 6 and 4 cases, respectively, could be confirmed (see Table 4.4 a). The cases reported were exclusively immunogenic TRALI; HLA class II or HNA-Ab in the donors were confirmed in all cases. In the four cases rated as certain, corresponding Ag could be detected in the recipients. No further details were available for the other six patients. Three previous pregnancies are reported for the whole-blood (WB) donor of a TRALI-triggering RBC. Out of nine of the other donors involved, five did not have any history of immunisation; no data is available on four donors (see Table 4.4 b). Six out of the ten TRALI cases confirmed for 2016 and 2017 were caused by RBC, two by PC and two cases by plasma transfusions.

Table 4.4 a: Number of reports of suspected cases of transfusion-related acute lung insufficiency (TRALI), confirmed cases, and fatal cases after administration of RCB, PC, plasma, and combined administrations (2016–2017)

TRALI	2016	2017
Cases reported	62	44
Confirmed cases	6	4
Immunogenic cases thereof	6	4
After administration of RBC	4	2
Fatal cases thereof	0	1
After administration of PC	1	1
Fatal cases thereof	0	0
After administration of plasma	1	1
Fatal cases thereof	0	0
After combined administrations	0	0
Fatal cases thereof	0	0

Table 4.4 b: Listing of confirmed cases of TRALI from 2016 and 2017

TRALI	Donor			Recipient	
Evaluation	Antibody (Ab)	Blood component	Sex	Correspon-ding antigen (Ag)	Underlying disease
2016					
Likely/ probable	WB donor HLA-Ab class II DR4,16,18 positive	RBC	Male, without immunisation in the history	No data	Anaemia
Likely/ probable	WB donor HNA-Ab positive	RBC	Female, no pregnancy in the history	No data*	ALL, chemo
Certain	Female WB donor, HLA-Ab class II positive	RBC	Female, no pregnancy in the history	Yes	Malignoma
Certain	WB donor HLA-Ab class II positive (DR04, week DQ08)	RBC	Male, without immunisation in the history	Yes	Congenital vitium cordis, OP with HLM

TRALI	Donor			Recipient	
Evaluation	Antibody (Ab)	Blood component	Sex	Corresponding antigen (Ag)	Underlying disease
Certain	2 WB donors HLA-Ab class I and II positive, 1 with corresponding ag (DRB1*13) in the female recipient	PTC	Male, n. d. on immunisation history	Yes	Coronary heart disease, endocarditis, cardiac surgery with HLM
Likely/ probable	Plasma donor HLA-Ab class I and II positive, also panreactive HNA-Ab	Plasma	Male, n. d. on immunisation history	No data	TTP
2017					
Likely/ probable	Female WB donor HLA-Ab class II (DQ8) positive	RBC	Female, n. d. on pregnancies in the history	No data	OP: Spinal alignment for the treatment of scoliosis
Likely/ probable (death)	Female WB donor HLA Ab class I and II positive	RBC	Female, 3 pregnancies	No data on ag but anti-HLA-Ab class I (B57,58)	SLE
Likely/ probable	1 female WB donor HLA-Ab class II positive	PPC	Female, no pregnancies in the history	No data	AML
Certain	1 donor HLA-Ab class I (CW10) and II (DR4) positive; female recipient with corresponding ag; 3 other donors also HLA-Ab positive, without corresponding ag in the female recipient	Plasma	Male, n. d. on immunisation history	Yes	Autoimmune encephalitis, plasma exchange

* Additional diagnosis: *Pseudomonas aeruginosa* in pleura effusion

Deaths:

In 2017, one RBC was confirmed as the cause of a TRALI with fatal outcome. The donor of the whole blood donation was tested positive for HLA-Ab class I and II following three previous pregnancies.

4.5 Transfusions-related dyspnoea

For 2016, eleven and for 2017, 22 suspected cases of transfusion-associated dyspnoea were reported as serious adverse transfusion reactions; in nine and 20 cases, respectively, a connection with the transfusion was confirmed.

In previous haemovigilance reports of the PEI, cases of dyspnoea were not assigned to the serious adverse transfusion reactions. The frequency of reports will be documented from now on.

Table 4.5: Number of suspected cases of dyspnoea and of confirmed cases after administration of RBC, PC, plasma, or combined administration from 2016 to 2017

Dyspnoea	2016	2017
Reported cases	11	22
Confirmed cases	9	20
After administration of RBC	8	16
After administration of PC	1	3
After administration of plasma	0	1
After combined administration	0	0

Deaths:

No fatal courses were reported.

4.6 Haemolytic transfusion reactions (HTR)

The association of a haemolytic reaction with a transfusion is rated as possible or likely/probable if, besides the typical clinical symptoms, supported by laboratory findings. The causality is considered as certain if the antiglobulin test or the cross-matching is positive.

Both the number of reports and the number of cases with confirmed connection to the transfusion varies from year to year (see Annex Figure 1). In 2016-2017, the largely thoroughly performed documentation of HTR provided evidence of irregular red blood cell Ab in 42 (57%) of the total of 74 confirmed cases, out of which half the cases were due to E, Jk (b) and Fy (a) incompatibilities. It is worth mentioning that around a quarter of all confirmed cases (19) were delayed haemolytic reactions. The reports on delayed HTR are, thus, in the same order of magnitude as described for other countries for the first time [16, 17].

Table 4.6: Number of reports of suspected cases of haemolytic transfusion reactions (HTR), confirmed cases, and fatal cases after administration of RBC (2016–2017)

HTR	2016	2017
Reported cases	44	64
Confirmed cases	28	46
After administration of RBC	26	44
Out of these, delayed HTR	9	10
Out of these, non-ABO	17	25
Out of these, deaths	0	3
After combined administration	2	2
Out of these, deaths	0	0

Deaths:

Two patients died in 2017 after transfusion of RBC due to an acute HTR; one patient died of delayed HTR.

4.7 Post-transfusion purpura (PTP)

In the reporting period, 5 suspected cases were reported of PTP out of which one was rated as confirmed, and 4 were rated as unlikely.

4.8 Transfusion-transmitted bacterial infections (TTBI)

The number of confirmed bacterial infections due to a transfusion with RBC or PC has been low for about 10 years. Based on the data available, the connection with the transfusion could be assessed as likely/probable or certain, and thus as confirmed, only in 10% of the suspected cases reported. In 2016 and 2017, 2 RBC and 7 PC (see Table 4.8 a) were identified as the contamination sources of the confirmed transmissions of a bacterial infection. Thus, due to the storage temperature of the PC that favour bacterial growth, TTBI most frequently occur following transfusions with PC. Since 2000, only one TTBI caused by the transfusion of plasma has been reported.

Table 4.8 a: Number of suspected cases on transfusion-associated bacterial infections (TTBI), confirmed cases, as well as fatal cases after the administration of RBC and PC (2016–2017)

TTBI	2016	2017	Total 2016 and 2017
Reported cases	40	50	90
Confirmed cases	3	6	9
After administration of RBC	1	1	2
Fatal cases thereof	0	0	0
After administration of PC	2	5	7
Fatal cases thereof	1	2	3
After administration of plasm	0	0	0
After combined administration	0	0	0

Reports of suspected TTBI were rated as cases without sufficient causality (unlikely) if no evidence of pathogen was provided and/or the time interval was exceeded. In case the pathogen was detected only in the blood component but not in the recipient, causality was rated as "possible". If the confirmatory testing showed inconsistent results, or if a contamination of the bag containing the preparation at the patient bed could not be ruled out, the causality of the observed septic reactions with the transfusion were also only rated as "possible". If the same pathogen was detected in the product and in the patient, the causal connection was considered as likely/probable. To classify a TTBI as certain, it is necessary to provide proof of the homology of the pathogens, e.g. by an identical antibiogram. In practice, consistent testing of the recipient and the blood component is not always feasible; for this reason, the data in the follow-up reports are often incomplete. Therefore, the contaminated product was considered as the possible cause of the septic reaction in two reported cases without providing proof of the pathogen, since the clinical course spoke in favour of this assumption. As in previous reports, Table 4.8 b lists all cases of transfusion-transmitted bacterial infection that fall into the category "possible", and Table 4.8 c lists all recorded cases confirmed in the categories "likely/probable" and "certain".

Deaths:

One death in 2016 after transfusion of a PC was due to contamination with *Streptococcus dysgalactiae equisimilis;* two deaths in 2017 were also caused by transfusion of PC, in one case contaminated with *Escherichia coli,* in the second case with *Staphylococcus aureus.* All fatal cases were caused by PC transfused on day 4 after donation. Interestingly, a sister-apheresis-PC of the above-mentioned *Escherichia coli*-contaminated PC, was given to a second patient only one hour later, causing a septic transfusion reaction from which this patient recovered.

Tabelle 4.8 b: Transfusion-transmitted bacterial infections with possible causality (2016–2017)

Year	Pathogen	Product	Evidence of pathogen Recipient/Products	Outcome
2016	*Staphylococcus aureus* in RBC, *Escherichia coli* in patient	RBC	Both	Restored
	Staphylococcus aureus	RBC	Product	Restored
	Klebsiella pneumoniae, gram rods	RBC	Recipient	Restored
	No microbiological findings, but clinical signs of a septic reaction	RBC	N.d.	Restored
	Streptococcus dysgalactiae; ß-haemolysing	PC	Both, but secondary contamination of the PC possible	Restored
	Staphylococcus epidermidis	RBC	Recipient	Restored
	Propionibacterium acnes	RBC	Product	Restored
	Staphylococcus epidermidis, however, differences in the antibiogram	PC	Both, however differences in the antibiogram	Restored
	Proteus mirabilis	RBC	Both, antibiotic resistance profile identical but sample collection from CVL	Restored
	Corynebacteriales gram-pos. rods	RBC	Product (rinse fluid)	Restored
	gram-pos. rods	RBC	Recipient	Restored
	Escherichia coli from transfusion tube and in patient, *Acinetobacter pittii* from rinse fluid, *Brevundimonas diminuta* in second culture	RBC	Both, but inconsistent results	Restored
	Escherichia coli	RBC	Product	Restored
	gram-pos. bacteria	RBC	Unclear whether detecti-on in recipient or product	Restored
2017	No material for examination but typical symptoms of sepsis (2 days after TF)	RBC	N.d.	Restored
	No material for examination but typical symptoms of sepsis	RBC	N.d.	Restored
	Propionibacterium acnes	RBC	Product	Restored
	gram-pos. rods	RBC	Recipient	Restored
	Enterobacter kobei and *Klebsiella oxytoca*	RBC	Recipient	Restored
	Escherichia coli	RBC	Recipient	Restored
	Propionibacterium acnes	RBC	Product	Restored
	Staphylococcus haemolyticus	RBC	Product	Restored
	Staphylococcus saprophyticus in the product; *Escherichia coli, Streptococcus oralis* and *Streptococcus salivaris* in the recipient	P-PC	Both	Restored
	Corynebacterium striatum, Enterococcus faecalis, Staphylococ-cus haemolyticus, Streptococcus vestibularis, Escherichia coli	RBC	Product	Restored

P-PC = Pool PC; CVL = central venous line

Table 4.8 c: Transfusion-transmitted bacterial infections with confirmed causality (2016–2017)

Year	Product	Pathogen	Imputability level	Outcome
2016	RBC	*Escherichia coli* and *Enterococcus faecalis*	Likely/probable	Restored
	P-PC	*Streptococcus dysgalactiae equisimilis*	Likely/probable	Fatal
	P-PC	*Staphylococcus warneri*	Likely/probable	Restored
2017	A-PC	*Escherichia coli*	Likely/probable	Fatal
	A-PC*	*Escherichia coli*	Likely/probable	Restored
	RBC	Aerobic spore former	Likely/probable	Restored
	P-PC	*Staphylococcus aureus* wide-spread sensitivity	Certain	Fatal
	A-PC	*Streptococcus gallolyticus*	Likely/probable	Restored
	A-PC	*Serratia marcescens*	Likely/probable	Restored

A-PC = Apheresis platelet concentrate
P-PC = Pool platelet concentrate
*split products from a single contaminated plateletpheresis unit

4.9 Transfusion-transmitted viral infections (TTVI)

Viral transmission was confirmed by means of the criteria in agreement with Opinion 34, 35, and 42 of the AK Blut for Hepatitis B (HBV), Hepatitis C (HCV) and human Immune deficiency virus (HIV) [8, 9] or using comparable criteria for other viruses.

Table 4.9 a: Number of suspected cases of transfusion-transmitted viral infections (TTVI) and confirmed cases after the administration of RBC, PC, plasma or combined administration in 2016 and 2017

TVVI (HIV, HCV, HBV, HEV)	2016		2017	
	Reports	Confirmed	Reports	Confirmed
After administration of RBC	33	1	29	0
After administration of RBC	2	1	0	0
After administration of plasma	1	1	1	0
After combined administration	12	0	13	1
Total	**48**	**3**	**43**	**1**

Transfusion-transmitted HIV, HCV, and HBV infections

In the period 2016 and 2017, none of the suspected case reports of a transfusion-related transmission of HIV, HCV, or HBV was rated as likely/probable or certain.

Since the introduction of the HCV and HIV-1-NAT donor screening, three cases of transmission by blood components have been documented so far, namely one case of HCV transmission (2004) and two cases of HIV transmission (2007 and 2010). In all these cases, the transmission was caused by RBC from whole-blood donors in whom the infections could not be detected in the NAT pool testing [18]. Since the introduction of the donor screening for anti-HBC (10/2006), altogether five cases of transfusion-related HBV infection have been confirmed, all caused by donations in the early window phase of an HBV infection of the donors (one RBC each in 2007, 2008, and 2015, one A-PC each in 2009, and 2012).

Deaths:

No cases of confirmed transfusion-related transmissions of HIV, HCV, or HBV occurred in 2016 and 2017. Thus, no deaths have been reported for these periods.

Transfusion-related HEV infections

All confirmed virus transmissions reported for 2016 and 2017 (see Table 4.9 a) were caused by HEV. The transmission in 2017, which was listed as combined administration, refers to a patient who received two A-PC and one RBC from three donors who were tested positive for the HEV genome at the time of the donation. The sister products of the two contaminated A-PC also led to a HEV transmission, which, however, was reported only as late as 2018. For the purpose of calculating the SAR rates per 106 transfused units, the 2017-case was assigned to the PC (see Annex Tab. 9).

Table 4.9 b lists all suspected cases of transfusion-related HEV transmissions reported to the PEI, in whom a viraemia in the donor was detected at the time of the donation.

Table 4.9 b: Description of suspected cases of HEV transmission by viraemic donors reported from 2013 to 2017. Where more than one patient was involved in the look-back procedures, the transmission leading to the look-back procedure is marked as index case.

(n.d.=no data, TF=transfusion, SC-TX=stem cell transplantation, MDS=myelodysplastic syndrome, GI bleed=gastrointestinal bleeding)

Reporting year	Look-back procedure initiated by HEV in	Donor	Product	Imputability level	Patient
2013	Donor	WB donor jaundice	P-PC	**Certain**	Underlying disease unknown. Clinical presentation: n.d.; 1 month after TF NAT positive, 2 months after TF NAT negative. **Identical genotype 3c, sequence homology.**
2014	Recipient	Apheresis donor	1 A-PC	**Certain**	*Index case:* Mantle cell lymphoma, SC-TX. Jaundice with increase in transaminases, NAT negative before and NAT positive after TF. HEV infection co-factor for death. **Identical genotype 3f, sequence homology.**
			1 A-PC	Not assessable	Symptom-free, no laboratory data, death caused by septicaemia
			1 A-PC	Possible	Vascular surgery, clinical presentation: n.d.; IgG positive 7 months after TF
			1 A-PC	Not assessable	Without symptoms, no laboratory data, death by cardiac arrhythmia
			1 A-PC	Unlikely	NAT negative 3 weeks after TF
2014	Recipient	WB donor	RBC	**Likely/probable**	Jaundice, NAT positive 6 weeks after TF
2015	Donor	Apheresis donor, Laboratory findings	2 A-PC	**Certain**	Leukaemia, SC-TX. Clinical presentation: n.d.; NAT negative before and positive 2 months after TF. **Identical genotype.**
			1 A-PC	Possible	MDS, clinical presentation: n.d.; 3.5 months after TF IgG positive
			2 A-PC	Unlikely	Pancytopenia, aplastic anaemia: symptom-free, 6 months after TF NAT, IgG, IgM negative.
2015	Donor	WB donor, jaundice	RBC	**Likely/probable**	GI bleed, increase in transaminases after TF, after 4 months normalized and NAT negative
2015	Recipient	Apheresis donor	2 A-PC	**Likely/probable**	*Index case:* Thalassaemia, SC-TX. NAT negative before and positive 1 month after TF
			1 A-PC	Not assessable	Symptom-free, no laboratory data, death caused by malignant underlying disease

Repor-ting year	Look-back procedure initiated by HEV in	Donor	Pro-duct	Imputability level	Patient
2015	Recipient	WB donor	RBC	**Likely/probable**	*Index case:* Grey cell lymphoma, SC-TX. Clinical presentation: n.d. NAT negative before and positive after TF
			P-PC	Unlikely	Allogenic SC-TX. NAT negative, IgG positive before and after TF
2016			Plasma	**Likely/probable**	Heart-TX, clinical presentation: n.d.; NAT negative before and positive after TF
2016	Recipient	WB donor	RBC	**Certain**	MDS, SC-TX, NAT negative before TF, increase in transaminases and NAT (identical genotype) positive 5 months after TF. **Identical genotype 3c, 3 regions identical with donor HEV.**
2016	Recipient	WB donor	P-PC	**Likely/probable**	*Index case:* Liver-TX after chronic hepatitis B, jaundice, NAT negative before and positive 1 month after TF
			RBC	Unlikely	MDS, RAEB-II: Symptom-free, NAT, IgM, IgG negative 4 months after TF
2017	Donor	WB donor, Laboratory findings	RBC	Possible	Underlying disease unknown, IgG and IgM positive approx. 3 months after TF
2017	Donor	WB donor, jaundice	RBC	Possible	GI bleed. Clinical presentation: n.d.; 5 months after TF IgG and IgM positive
2017	Recipient	WB donor	RBC	**Likely/probable**	Immune deficiency, SC-TX. NAT positive 7 months after TF
		Apheresis donor	1 A-PC		
		Apheresis donor	1 A-PC		

A-PC = Apheresis platelet concentrate
P-PC = Pool platelet concentrate

Twenty-two recipients were involved in the above listed suspected cases of a transfusion-related HEV transmission, who had received 8 RBC, 3 P-PC and 1 plasma from 9 WB donors as well as 14 A-PC from 5 A-PC donors.

In 3 out of the 5 donor-triggered look-back procedures clinical symptoms in the donors occurred after donation; in 2 cases, the infection of the donor was established exclusively based on the laboratory findings. In 3 out of the 7 recipient-triggered look-back procedures, the infection was at first detected solely on the basis of clinical symptoms, and in 4 cases by the detection of HEV in the laboratory diagnostics (Table 4.8 b). In 3 cases, a possible HEV transmission could not be assessed conclusively.

Tabelle 4.9 c: Causality assessment for the blood components included in the HEV transmission in the period from 2013 to 2017

	Confirmed	Possible	Unlikely	Not assessable	Total
Recipients	11	4	4	3	22
RBC	5	2	1	0	8
PPC	2	0	1	0	3
Plasma	1	0	0	0	1
APC	7	2	2	3	14
Total products	15	4	4	3	26

Deaths:

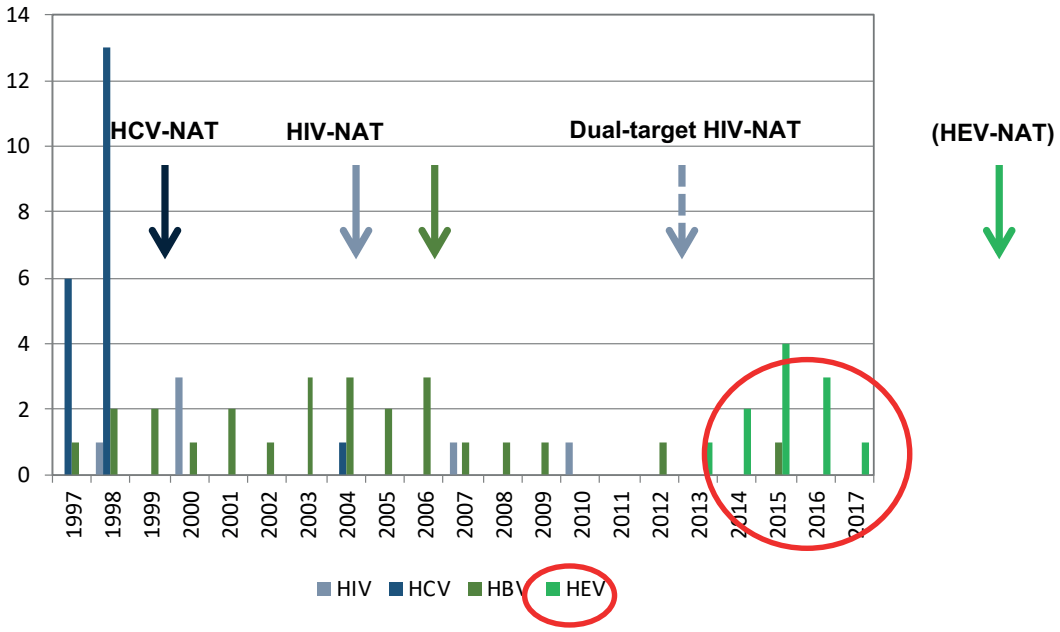
No fatal cases were reported in connection with a transmission of HEV in 2016 and 2017.

Other transfusion-transmitted infections

In 2016 and 2017, the PEI received reports on 5 suspected cases of a transfusion-related CMV infection and one case of parvovirus B19 infection, which could not be confirmed.

Since the PEI started recording transfusion reactions in 1997 up to and including 2017, no suspected transmissions of viral pathogens such as WNV, chikungunya virus, dengue virus, Zika virus, or other arthropod-borne viruses were reported. During this period, a total of six HIV, 20 HCV, 25 HBV, two HAV, 11 HEV, and 1 malaria transmission due to transfusions were confirmed.

Figure 4.9: Transfusion-related HIV, HBV, HCV and HEV infections in the period from 1997–2017 and risk prevention measures introduced for donor testing



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

Table 4.10 a: Donor look-back procedures in the period from 20016–2017 triggered by infections confirmed according to AK Blut Opinions 34 and 42 (or analogue procedures) or by first-time specifically positive (i.e. confirmed) anti-HBc findings and/or ambiguous results in laboratory diagnostics

	2016				2017			
Patho-gen	Reported	Confirmed (*out of these, ID-NAT neg.)	Un-deter-mined	% Confir-med	Reported	Confirmed (*out of these, ID-NAT neg.)	Un-deter-mined	% Confir-med
HEV	35	35 (0)	0	100	119	116 (0)	3	97.5
HBV	398	51 (40)	**347	12.8	497	62 (52)	**435	12.5
HCV	146	32 (11)	114	21.9	152	35 (13)	117	23.0
HIV	47	42 (0)	5	89.4	44	31 (4)	13	70.5
CMV	17	17 (0)	0	100	13	13 (0)	0	100
Parvo-virus B19	9	9 (0)	0	100	8	8 (0)	0	100
HAV	0	-	-	-	4	4 (0)	0	100
EBV	1	1(0)	0	100	0	-	-	-
WNV	1	0	1	0	0	-	-	-
Lues	70	68	2	97.1	74	65	9	87.8
Total	**724**	**255**	**469**	**35.2**	**911**	**334**	**577**	**36.7**

* Definition "Infection confirmed" with ID-NAT negative results, see AK Blut, Opinions 34 and 42 [8, 9]
** Isolated anti-HBc specific reactive donations

Both the number of suspected cases of an infection in repeat donors, triggering donor look-backs, and the share of confirmed donor infections were in the order of magnitude of previous years. Six reports in 2016 and 3 in 2017 referred to first-time donors. Ambiguous test results caused 3 donor look-backs for HEV, 18 for HIV, 241 for HCV, and 11 for syphilis, in 2016 and 2017. In these cases, the infection of the donors could not be confirmed by either a follow-up examination of the donor or testing of the retained samples from previous donations, or the donors were no longer available for a follow-up. Out of the suspected HBV donor infections rated as confirmed for the periods of 2016 and 2017, the HBV genome could be detected only in 11 and 10 donors, respectively, using ID-NAT (see Table 4.10 b). The 782 suspected cases of an infectious donation that could not be confirmed were due to first-time specifically positive anti-HBc results.

Table 4.10 b: Donor look-backs with justified suspected HBV infection or a first-time specifically positive anti-HBc (2016–2017)

(PDI = post donation information)

HBV	2016		2017	
	Reports	Confirmation by pos. ID-NAT	Reports	Confirmation by pos. ID-NAT
HBsAg isolated confirmed reactive	**36**	**0**	**47**	**0**
Anti-HBc isolated specifically reactive	350	**4**	436	**1**
MP-NAT isolated positive	0	**0**	2	**2**
HBsAg and anti-HBc confirmed/ specifically reactive	4	**0**	5	**0**
MP-NAT positive, HBsAg confirmed reactive, anti-HBc negative	2	**2**	5	**5**
MP-NAT positive, anti-HBc specific reactive, HBsAg negative	2	**1**	1	**1**
MP-NAT positive, HBsAg confirmed reactive, Anti-HBc specific reactive	4	**4**	0	**–**
PDI: acute Hepatitis B	0	**–**	1	**1**
Total	**398**	**11**	**497**	**10**

In the reporting period of 2016-2017, altogether 895 reports were received for suspected HBV infections in the donor that resulted in donor look-back procedures. A HBV infection was confirmed in 21 donors by means of ID-NAT in the up-to-date donation or in a retained sample from the look-back period. This concerned 5 of the 768 isolated anti-HBc specifically reactive donations, 2 isolated MP-NAT positive donations, and one case of hepatitis in a donor, which became known after the donation. The 13 other cases of ID-NAT confirmed infections were also HBV-screening-NAT positive. The HBV genome was not detected in any of the cases in which isolated HBsAg reactivity was confirmed. For 13 of the confirmed isolated HBsAg reactive donors in 2016 and for 24 of those confirmed in 2017, a suspected vaccination history was reported. A non-specific reaction can be assumed as a cause for the isolated HBsAg reactivity without evidence of the HBV genome by ID-NAT and without a confirmed vaccination history, as described by Fiedler et al. [19].

4.11 Incorrect blood components transfused (IBCT)

The term IBCT refers to transfusions in which the blood component to be transfused was assigned or administered to the wrong patient, which usually results in a transfusion of components with non-identical blood groups. IBCT also include the administration of non-irradiated blood components despite an applicable requirement or blood-group compatible transfusions in patients without an indication for a transfusion.

Table 4.11 a summarises the incorrect blood components transfused reported since 2012, which caused a serious adverse reaction in the recipient and had to be reported as SAR, as well as near-IBCT and IBCT that did not cause a health impairment in the recipient due to the transfusion and were reported as SAE (see Section 4.12 SAE).

Table 4.11 a: IBCT with (SAR) and without serious transfusion reactions (SAE) in the recipient (2012–2017)

	2012	2013	2014	2015	2016	2017
IBCT SAR	5	16	22	24	28	27
IBCT SAE	2	12	29	34	41	55
Total	**7**	**28**	**51**	**58**	**69**	**82**

The number of reports on IBCT that caused a serious transfusion reaction stagnated in 2016/2017, while the number of reports on IBCT without any transfusion reactions continued to increase. Nevertheless, the German Transfusion Act does not require reporting of an IBCT by physicians if it did not cause a severe transfusion reaction. In consequence, the haemovigilance report presents cases of IBCT SAE that became known to BE and had been reported to the PEI and most likely does not represent the real number of IBCT occurring without transfusion reactions.

56 suspected cases of SAR due to IBCT were reported in 2016 and 2017, and 55 of the suspected cases were confirmed. By far the greatest portion of these was accounted for by incorrectly transfused RBC (see Table 4.11 b).

Table 4.11 b: SAR due to an IBCT (2016–2017)

IBCT SAR	2016	2017
RBC	27	24
Fatal cases thereof	2	1
PC	0	2
Fatal cases thereof	0	0
Plasma	1	1
Fatal cases thereof	0	0
Total	28	27

Deaths:

Two deaths in 2016 and one death in 2017 were caused by incorrectly transfused RBC.

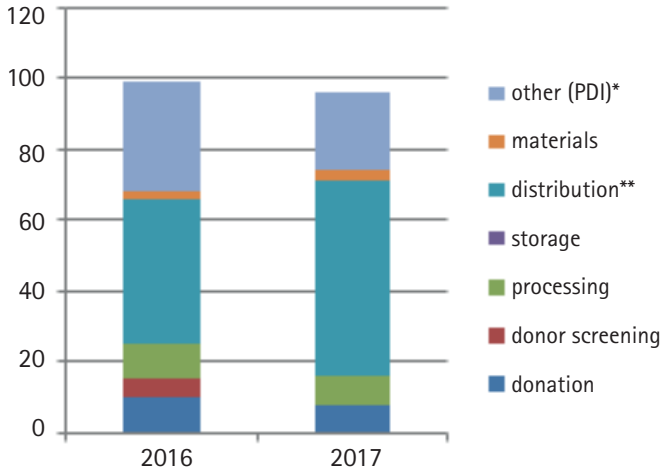
4.12 Serious adverse events

Serious adverse events pursuant to Section 63i Abs. 6 AMG [6] include above all the marketing of defective products; repeatedly occurring adverse events, which give rise to the assumption of a faulty working procedure; critical events, also without the products being supplied; and incorrect blood components transfused without any serious reactions in the recipient.

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 SAE reports has nearly quadrupled since the coming into force of the 16th amendment of the AMG in 2012 up to the reporting period. During the same period, the number of blood components transfused has decreased by almost 20% (see Annex Figure 2).

Figure 4.12: Number and distribution of serious adverse events (SAE) shown by their occurrence in the transfusion chain (2016–2017)



* PDI = Post Donation Information (exclusion criteria that became known in retrospect)

** IBCT without SAR or prevented IBCT (as applicable)

In 2016 and 2017, no adverse events were reported that were due to a mistake in storage. Altogether 86 transfusions without any serious transfusion reactions in the recipient were reported in which a serious adverse event became known in retrospect. These referred to confusions caused by human or software errors, errors in processing (accidental failure to irradiate the products) or suspected cases of a donor contamination (PDI) (see Table 4.12), which became known in retrospect. Incorrect blood components transfused or events that could have led to the transfusion of an incorrect blood component (as applicable) were mainly caused by human error both in 2016 and in 2017, like in previous years.

Table 4.12: Transfusion of blood components that did not cause any SAR in the recipient but in which a serious adverse event became known in retrospect.

Sources of error	2016	2017
IBCT due to confusion of blood components, patients, test tubes, labels, etc.	29	40
TF of possible faulty blood components (PDI, processing)	9	6
IBCT due to software errors	0	2
Total	**38**	**48**

The data on IBCT is still insufficient. An analysis of the sources of error, in the BE or medical care facilities, leading to IBCT is not possible based on the available data from spontaneous reports. However, after further completion of the reporting data in the future this could constitute a foundation for quality assurance purposes and error analysis in donation centres and health facilities performing transfusions.

4.13 Serious adverse donor reactions

According to a query performed separately by the PEI in 2015, the number of reports of serious donor reactions has significantly risen.

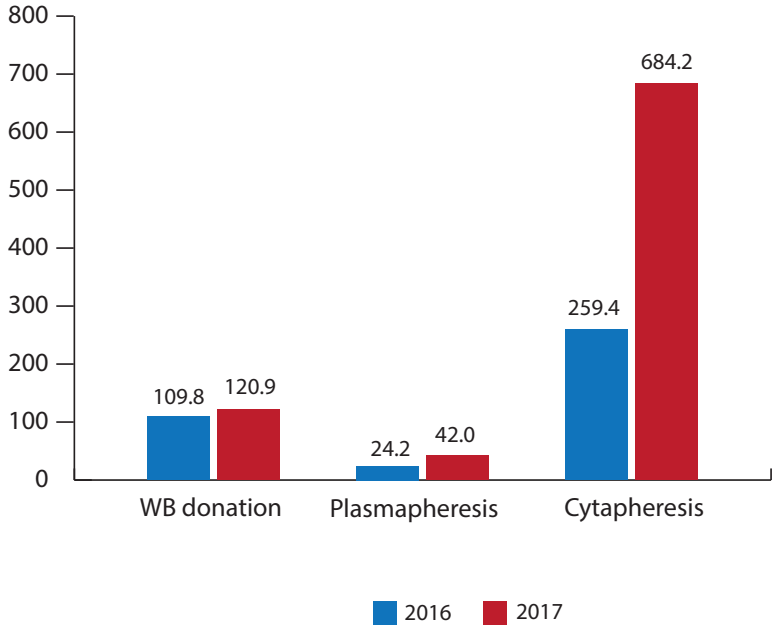
Table 4.13 a: Development of the reporting figures of serious adverse donor reactions (donor SAR) from 2011 to 2017

	2011	2012	2013	2014	2015	2016	2017
Number of confirmed donor SAR	1	3	13	24	531	459	527
Number of reporting BE	1	1	3	5	35	40	26

Even though the number of reporting BE decreased significantly in 2017, the number of confirmed donor SAR has increased slightly. The reports include direct reports by BE as well as reports by the competent federal authorities about blood centres, which exclusively produce plasma for fractionation. Only in 9 cases the assignment to the type of donation was missing; in 2016, seven BE reported that they had not observed any donor SAR. The figures thus point to marked differences between the reporting behaviours of the BE in Germany and make it more difficult to capture the actual frequency of serious donor reactions. For the calculation of the number of donor SAR per type of donation, only the donation figures of the 40 or 26 reporting centres, as applicable, were used. For 2016 and 2017, thrombocytaphereses (90.4%), granulocytaphereses (90.4%), and erythrocytaphereses (0.2%) were grouped under cytaphereses. For granulocytaphereses no donor SAR and for erythrocytaphereses one donor SAR in 2016 and 2017, respectively, were reported and confirmed. Out of all donor SAR reported in 2017, a causal relationship could be confirmed, and out of the 459 suspected cases of a donor reaction reported in 2016, the causality in relation to the donation was confirmed or reported as likely in 456 of the cases. Nausea and stomach troubles of a donor during thromocytapheresis, which led to the donation being terminated early, were attributed to an acute

hepatitis based on laboratory findings; a circulatory reaction with newly occurring pain in the chest area in a WB donor was diagnosed as the consequence of Scheuermann's disease; arterial hypertension was considered as the cause of tachyarrhythmia in a plasmapheresis donor.

Figure 4.13 a: Rates of confirmed donor SAR per 1 million donations referring to the number of donations from the reporting BE from 2016–2017. Cytaphereses include thrombocytaphereses, granulocytaphereses, and erythrocytaphereses.



Similarly to the definition by the Haemovigilance Working Party ISBT [20], the donor SAR were categorised as follows: local and generalised symptoms, allergic reactions, cardiovascular events, and complications exclusively observed in apheresis donations (see Table 4.13 b).

Table 4.13 b: Donor SAR, categorised in line with the definition by the Haemovigilance Working Party of the ISBT

A – Local symptoms (pin-prick related)	
A1	Leaked blood: Haematoma, artery punctured
A2	Arm pain: Paraesthesia, unspecific arm pain
A3	Local inflammation/infection: Thrombophlebitis, unspecific tissue reaction
A4	Other blood vessel damage: Venous thrombosis, arteriovenous fistula, compartment syndrome, pseudoaneurysm of the bracheal artery
B – Generalised symptoms	
B1	Vasovagal reactions without syncopes
B2	Vasovagal reactions with syncopes at donation
B3	Vasovagal reactions with syncopes after donation
C – Complications during apheresis	
C1	Citrate reaction
C2	Haemolysis
C3	Air embolism
C4	Tissue infiltration
D – Allergic reactions	
D1	Local
D2	Generalised (anaphylactic)
E – Cardiovascular events: AMI, cardiac arrest, TIA, stroke, other acute cardiac symptoms (angina pectoris, tachyarrhythmia), death	
F – Other	

Figure 13 b: Distribution of donor SAR 2016

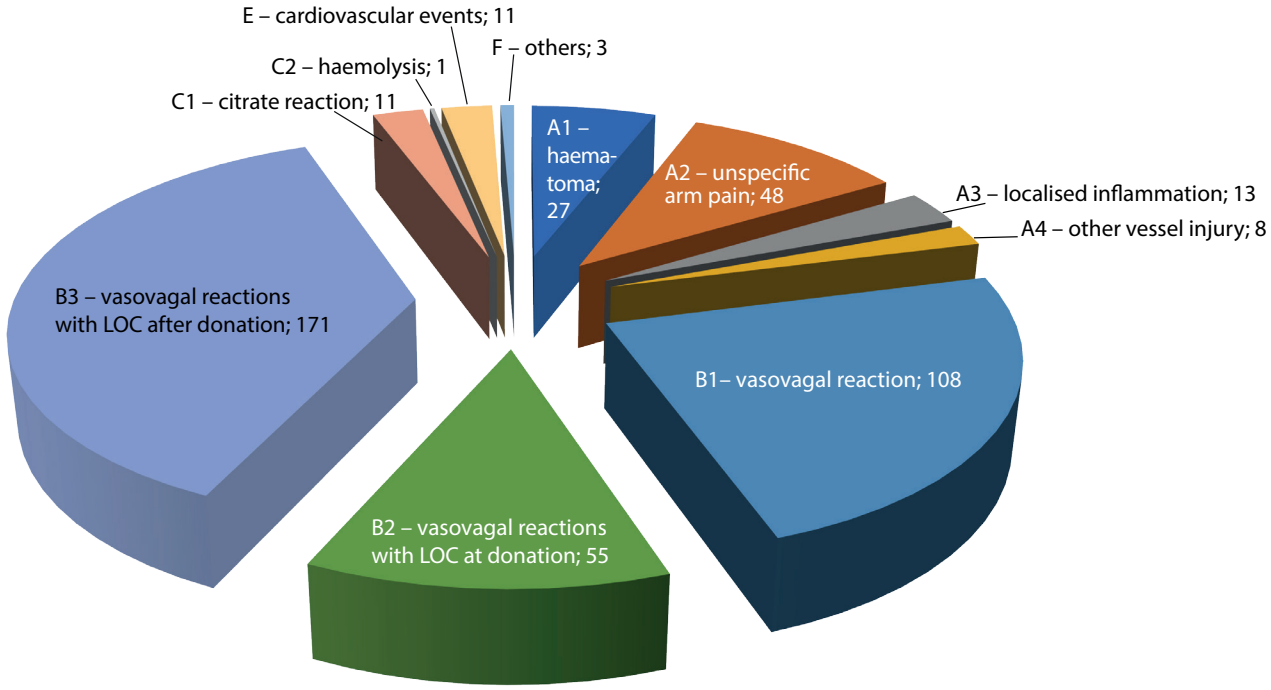
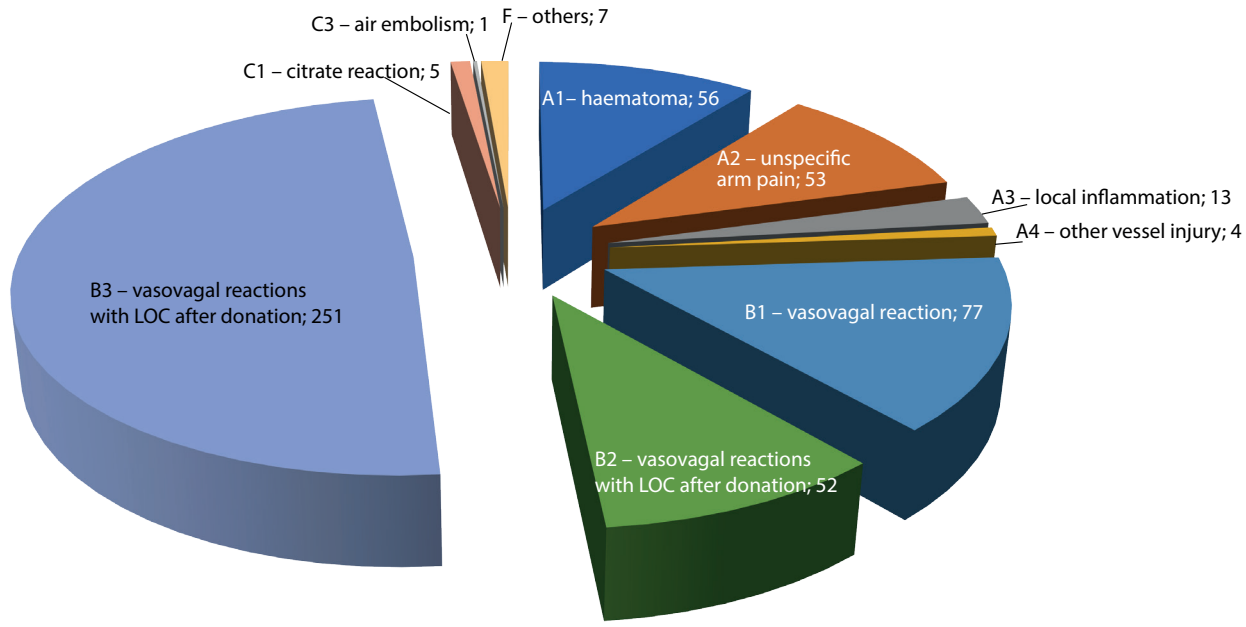


Figure 13 c: Distribution of the donor SAR 2017



Out of the donor SAR reported in 2016 and 2017, 22.6% were local, pin-prick related reactions, 19.1% vasovagal responses without loss of consciousness, and 54.4% vasovagal responses with loss of consciousness. Apheresis-related cardiovascular and other reactions occurred very rarely with 1.9, 1.2 and 1.0%. Altogether, vasovagal responses with and without loss of consciousness are the most frequently occurring donor SAR and concern around 75% of all cases reported. Of note, the vast majority of vasovagal responses with loss of consciousness (80%) only occurred after donation and, in the event of a fall, led to serious injuries in some cases. Here, donation centres should check whether the period of rest following the donation is adequate. No allergic donor reactions were reported in the reporting period. The data collected in 2016 and 2017 confirm the findings of 2015 in that thrombocytapheresis is the type of donation which, referred to the number of donations, most frequently causes donor SAR. Comparable events were also reported for France [21].

// 5. Summary //

- In principle, 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.
- In 2016 and 2017, acute allergic/anaphylactic transfusion reactions were again the most frequent transfusion reactions assessed as confirmed, with rates of around 78 cases for PC, 26 cases of RBC, and 19 cases for plasma, each referring to 106 transfused units.
- Out of a total of 16 transfusion-related deaths in 2016 and 2017, three were caused by anaphylactic reactions (RBC, P-PC, plasma), three by circulatory overload (RBC), three by TTBI (PC), three by HTR (RBC), three by IBCT (RBC), and one by TRALI (RBC).
- The high number of look-back procedures triggered by isolated, specifically positive anti-HBc results [22, 23] remained unchanged in 2016 and 2017. In total, 895 donor look-back procedures were started due to a reasonable suspicion of HBV infection. In 21 out of these 895 donors HBV genome could be detected by means of ID-NAT in the current donation or in a retained sample. All confirmed anti-HBsAg only reactive donations were HBV ID-NAT negative.
- Reports of serious adverse events have continued to increase. In 2016 and 2017, the major share of these events was again due to incidents caused by human error, predominantly by incorrect blood components transfused.
- Reports on serious donor reactions decreased only slightly in 2016 and 2017 as compared to 2015. Of note, the number of reporting facilities decreased significantly in 2017.
- In 2016 and 2017, the highest rate of serious donor reactions referring to the number of donations was again reported for thrombocytapheresis donations.

// 6. References //

1. Funk MB et al. (2015): Haemovigilance Report of the Paul-Ehrlich-Institut 2013/14: Assessment of the Reports of Serious Adverse Transfusion Reactions pursuant to Section 63i AMG (Arzneimittelgesetz, German Medicines Act) (English): www.pei.de/haemovigilance-report
2. www.gesetze-im-internet.de/tfg
3. RICHTLINIE 2005/61/EG DER KOMMISSION vom 30. September 2005 zur Durchführung der Richtlinie 2002/98/EG des Europäischen Parlaments und des Rates in Bezug auf die Anforderungen an die Rückverfolgbarkeit und die Meldung ernster Zwischenfälle und ernster unerwünschter Reaktionen
4. SUMMARY OF THE 2017 ANNUAL REPORTING OF SERIOUS ADVERSE EVENTS AND REACTIONS (SARE) FOR BLOOD AND BLOOD COMPONENTS. http://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/2017_sare_blood_summary_en_0.pdf
5. www.pei.de/tfg-21
6. www.gesetze-im-internet.de/amg_1976
7. www.pei.de/haemovigilanz-formulare
8. Votum 34 AK Blut: Mitteilungen des Arbeitskreises Blut des Bundesministeriums für Gesundheit. Verfahren zur Rückverfolgung (Look Back) (gemäß § 19 Transfusionsgesetz). Bundesgesundheitsbl – Gesundheitsforsch – Gesundheitsschutz. 2006;49:940-957
9. Votum 42 AK Blut: Mitteilung des Arbeitskreises Blut des Bundesministeriums für Gesundheit. Aktualisierung der Voten 34 und 35 „Verfahren zur Rückverfolgung (Look Back) (gemäß §19 Transfusionsgesetz)" vom 14.06.2006 im Hinblick auf Hepatitis-B-Infektionen. Bundesgesundheitsbl – Gesundheitsforsch – Gesundheitsschutz. 2013;56:476-478
10. Funk MB et al.: Recht – Hämovigilanz. Überblick über die gesetzlichen Vorgaben gegenüber der Bundesoberbehörde in Deutschland. Transfusionsmedizin. 2015;5(2):102-107
11. ISBT Working Party on Haemovigilance. Proposed Standard definitions for surveillance of non infectious adverse transfusion reactions. www.isbtweb.org/fileadmin/user_upload/Proposed_definitions_2011_surveillance_non_infectious_adverse_reactions_haemovigilance_incl_TRALI_correction_2013.pdf
12. Ring J, Messmer K: Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet. 1977;26:466-469
13. ISBT Working Party on Granulocyte Immunobiology; Bierling P et al.: Recommendations of the ISBT Working Party on Granulocyte Immunobiology for leucocyte antibody screening in the investigation and prevention of antibody-mediated transfusion-related acute lung injury. Vox Sanguinis. 2009;96:266-269
14. Vlaar APJ, Juffermans NP: Transfusion-related acute lung injury: a clinical review. Lancet 2013; 382:984-994
15. Li G et al.: Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. Transfusion. 2011;51(2):338-343
16. Swiss medic Haemovigilance Annual Report 2015: https://www.swissmedic.ch/swissmedic/de/home.html
17. SHOT reports: www.shotuk.org/shot-reports
18. Nübling CM et al.: Experience of mandatory NAT screening across all blood organizations in Germany: NAT yield versus breakthrough transmissions. Transfusion. 2009;49:1850-1858
19. Fiedler S et al.: Effectiveness of blood donor screening by HIV, HCV, HBV-NAT assays, as well as HBsAg and anti-HBc immunoassays in Germany (2008–2015). Vox Sanguinis. 2019; DOI: 10.1111/vox.12770
20. ISBT Working Party on Haemovigilance. Standard for Surveillance of Complications Related to Blood Donation. www.isbtweb.org/working-parties/haemovigilance/
21. Daurat A et al.: Apheresis platelets are more frequently associated with adverse reactions than pooled platelets both in recipients and in donors: a study from French hemovigilance data. Transfusion. 2016;56:1295-1303
22. Abwehr von Arzneimittelrisiken; Testung auf Antikörper gegen Hepatitis-B-Core-Antigen (anti-HBc) im Blutspendewesen (vom 08. Mai 2006). Bundesanzeiger Nr. 109 vom 13. Juni 2006, S. 4370
23. Bekanntmachung über die Zulassung von Arzneimitteln – Abwehr von Arzneimittelrisiken Stufe II – (Neufassung: Testung auf Antikörper gegen Hepatitis-B-Core-Antigen [anti-HBc] im Blutspendewesen) (vom 07.02.2014). Bundesanzeiger AT 18.03.2014 B6
24. Abwehr von Arzneimittelrisiken – Anordnung von Auflagen zu den Zulassungen von therapeutischem Einzelplasma (in Quarantäne gelagertes oder mit einem Verfahren zur Pathogeninaktivierung behandeltes Plasma) (vom 08. Mai 2009). Bundesanzeiger Nr. 84 vom 10.06.2009, Seite 2064

// 7. Annex with figures and tables //

Figure 1: Number of confirmed SAR per year for the period of 1997–2017

The TRALI graph includes the likely/probable and confirmed cases (new definition); TACO has been recorded systematically since 2009; as from 2009, only ATR of grade III and IV are included.

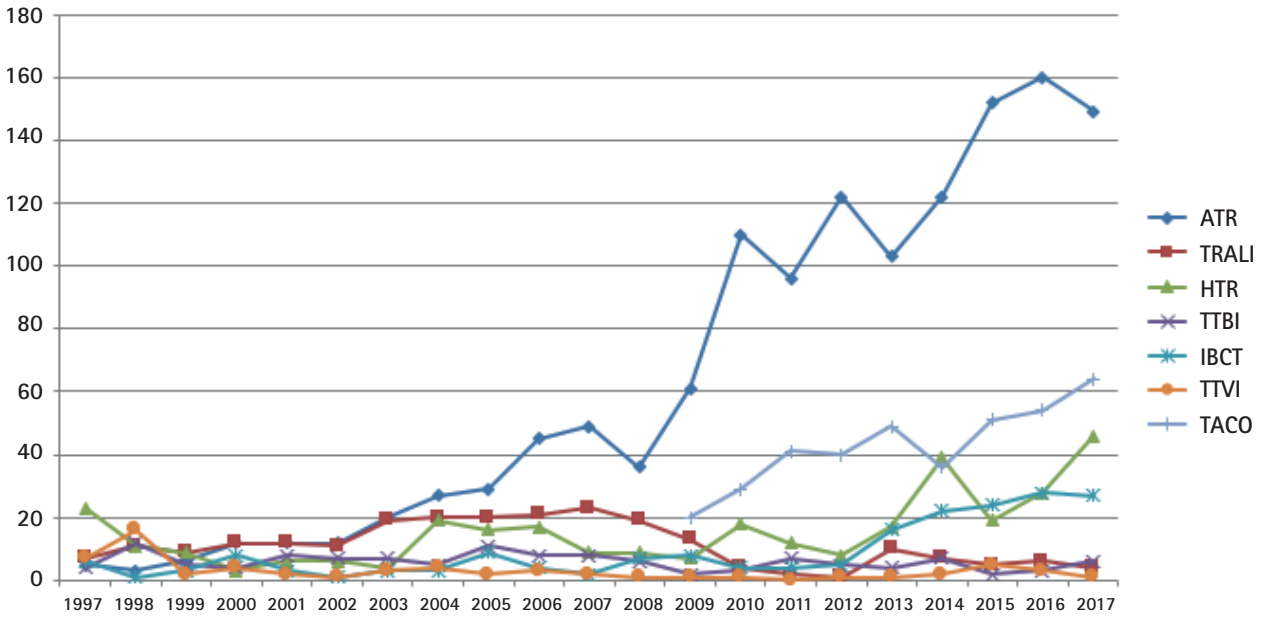


Figure 2: Percentage change in the blood component consumption (2000–2017)

Blood component consumption in 2000 is equivalent to 100 percent. Up to 2017, the consumption of PC increased by 58%. The consumption of RBC, on the other hand, decreased by 11%, and by 34% for plasma.

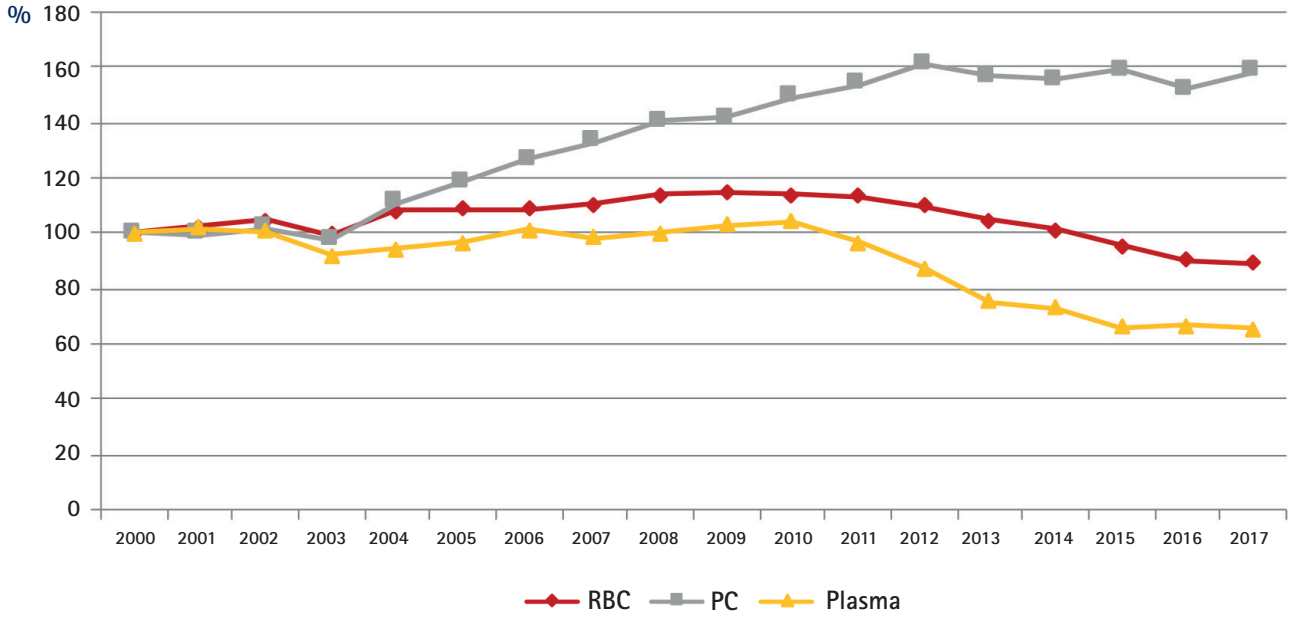


Table 1: Consumption of blood components (2000–2017)

Data calculated from the yearly reports pursuant to Section 21 TFG on the sale and loss at the user (deadline: 15 Jan. 2019). The consumption figures used for the calculation of TACO (systematic data capture since 2009) are listed separately.

	2000–2003	2004–2007	2008–2011	2012–2015	2016	2017	2016–2017	2000–2017
RBC	16,051,470	17,173,130	17,964,825	16,202,065	3,548,124	3,506,417	7,054,541	74,446,032
PC	1,274,659	1,566,873	1,870,911	2,022,453	485,659	506,267	991,926	7,726,822
Plasma	4,515,718	4,469,498	4,616,104	3,453,264	764,399	751,551	1,515,950	18,570,534

TACO	2009-2017
RBC	36,738,765
PC	4,436,151
Plasma	8,441,672

Table 2: Total number of reported transfusion reactions, confirmed transfusion reactions and associated deaths (1997–2017)

Serious adverse transfusion reactions (SAR) 1997–2017	Reported suspected cases	Confirmed cases	Fatal cases therefrom
Acute allergic/anaphylactic transfusion reactions (ATR)*	3,313	1,331	34
Transfusion-related acute lung injury (TRALI)**	1,134	236	22
Haemolytic transfusion reaction (HTR)	626	326	16
Transfusion transmitted bacterial infection (TTBI)	488	124	17
Incorrect blood component transfused (IBCT)	190	188	16
Transfusion transmitted viral infection (TTVI)***	3,567	62	3
Post-transfusional purpura (PTP)	30	18	0
Transfusion-associated Graft versus Host Disease (TA-GVHD)	4	3	1
Transfusions-associated circulatory overload (TACO)****	406	384	15
Other SAR	141	22	0
Total	9,899	2,694	124

* As from 2009 only ATR Grades III and IV were included in the assessment
** As from 2013 only likely/probable and certain TRALI were included as confirmed
*** Includes reports on HCV, HIV, HBV, HAV, and HEV
**** TACO systematically captured only as from 2009

Table 3: Confirmed suspected cases referring to serious allergic and anaphylactic transfusion reactions Grades III and IV (before 2009 including ATR Grades I and II), associated deaths and rate of confirmed reactions referring to 10^6 units transfused (2000–2017)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2017	2000–2017
Confirmed serious allergic/anaphylactic transfusion reactions after administration of						
RBC	27	99	160	277	181	744
PC	12	20	49	108	77	266
Plasma	9	16	54	57	29	165
Combined transfusion	8	15	40	57	22	142
Total	**56**	**150**	**303**	**499**	**309**	**1,317**
Therefrom fatal outcomes after administration of						
RBC	4	2	6	4	1	17
PC	1	1	2	1	1	6
Plasma	1	1	2	0	1	5
Combined transfusion	2	0	1	1	0	4
Total	**8**	**4**	**11**	**6**	**3**	**32**

Rates of confirmed serious allergic/anaphylactic reactions for these periods						
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2017	2000–2017
	ATR per 10^6 units	ATR per 10^6 units	ATR per 10^6 units	ATR per 10^6 units	ATR per 10^6 units	ATR per 10^6 units
RBC	1.68	5.76	8.91	17.10	25.66	9.99
PC	9.41	12.76	26.19	53.40	77.63	34.43
Plasma	1.99	3.58	11.70	16.51	19.13	8.98

Table 4: Confirmed suspected cases referring to TACO, associated deaths and rate of confirmed reactions referring to 10^6 units transfused (2009–2017)

TACO	2009	2010	2011	2012	2013	2014	2015	2016	2017	2009–17
Reported	21	33	42	41	50	42	53	56	68	406
Confirmed	20	29	42	40	49	36	51	54	64	385
RBC	11	18	28	33	36	30	47	47	55	305
PC	1	2	3	3	3	2	0	2	3	19
Plasma	1	2	3	0	4	2	0	1	1	14
Combined administration	7	7	8	4	6	2	4	4	5	47
Deaths	1	2	2	1	1	3	1	1	2	14

Rates of confirmed TACO for the periods								
	2009–2011		2012–2015		2016-2017		2009-2017	
	Consumption units	TACO/ 10^6 units	Consumption units	TACO/ 10^6 units	Consumption units	TACO/ 10^6 units	Consumption units	TACO/ 10^6 units
RBC	13,482,159	4.23	16,202,065	9.01	7,054,541	14.46	36,738,765	8.30
PC	1,421,773	4.22	2,022,453	3.96	991,926	5.04	4,436,151	4.28
Plasma	3,472,458	1.73	3,453,264	1.74	1,515,950	1.32	8,441,672	1.66

Table 5: Confirmed suspected cases referring to serious immunogenic and non-immunogenic TRALI, associated deaths, and rates of immunogenic TRALI, referring to 10^6 transfused units (2000–2017)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2017	2000–2017
TRALI, examination for HLA-/HNA-Ab						
Negative	9	18	12	3	0	42
Donor positive	24	60	26	20	10	140
Not done	21	6	0	0	0	27
Total	**54**	**84**	**38**	**23**	**10**	**209**
TRALI, examination of the donors for HLA-/HNA-Ab positive in						
RBC donors	5	9	5	13	6	38
PC donors	2	3	5	6	2	18
Plasma donors	17	48	18	5	2	90
Total	**24**	**60**	**28**	**24**	**10**	**146**
TRALI with fatal courses						
RBC donors	1	2	0	0	**1**	**4**
PC donors	0	0	1	1	**0**	**2**
Plasma donors	1	10	5	0	**0**	**16**
Total	**2**	**12**	**6**	**1**	**1**	**22**

Rates of confirmed immunogenic TRALI for the periods						
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2017	2000–2017
	TRALI per 10^6 units	TRALI per 10^6 units	TRALI per 10^6 units	TRALI per 10^6 units	TRALI per 10^6 units	TRALI per 10^6 units
RBC	0.31	0.52	0.28	0.80	0.85	0.51
PC	1.57	1.91	2.67	2.97	2.02	2.33
Plasma	3.76	10.74	3.90	1.45	1.32	4.85

A specific donor selection applies as per 1 Sept. 2009 if plasma for transfusion is prepared from the donation.

Table 6: Confirmed suspected cases referring to serious haemolytic transfusion reactions (HTR), associated deaths and rate of HTR, referring to 10^6 transfused units (2000–2017)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2017	2000–2017
Haemolytic transfusion reactions after administration of						
RBC	11	50	41	71	70	**243**
PC	2	4	4	3	0	**13**
Combined transfusion	6	7	1	9	4	**27**
Total	**19**	**61**	**46**	**83**	74	**283**
Therefrom acute and delayed haemolytic transfusion reactions and HTR with evidence of Ab						
Delayed HTR	3	6	21	14	19	**63**
Irregular RBC-Ab	2	4	28	14	42	**90**
Therefrom haemolytic transfusion reactions with fatal courses after administration of						
RBC	0	3	2	0	3	**8**
Combined transfusion	0	1	0	0	0	**1**
Total	**0**	**4**	**2**	**0**	**3**	**9**

Rates of confirmed haemolytic transfusion reactions for the periods						
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2017	200–2017
	HTR per 10^6 units	HTR per 10^6 units	HTR per 10^6 units	HTR per 10^6 units	HTR per 10^6 units	HTR per 10^6 units
RBC	0.69	2.91	2.28	4.38	9.92	3.26
PC	1.57	2.55	2.14	1.48	0.00	1.68

Table 7: Confirmed suspected cases referring to transfusion-transmitted bacterial infections (TTBI), associated deaths and rate of TTBI referring to 10^6 transfused units (2000–2017)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2017	2000–2017
Bacterial infections after administration of						
RBC	7	13	7	8	2	37
Pool-PC	8	9	5	1	3	26
Apheresis-PC	11	9	6	9	4	39
Plasma	0	1	0	0	0	1
Total	**26**	**32**	**18**	**18**	**9**	**103**
Therefrom bacterial infections with fatal courses after administration of						
RBC	0	0	0	0	0	0
Pool-PC	1	1	2	0	2	6
Apheresis-PC	2	2	0	1	1	6
Plasma	0	0	0	0	0	0
Total	**3**	**3**	**2**	**1**	**3**	**12**

Rates of confirmed transfusion-transmitted bacterial infections for the periods of						
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2017	2000–2017
	TTBI per 10^6 units	TTBI per 10^6 units	TTBI per 10^6 units	TTBI per 10^6 units	TTBI per 10^6 units	TTBI per 10^6 units
RBC	0.44	0.76	0.39	0.49	0.28	0.50
PC	14.91	11.49	5.88	4.94	7.06	8.41
Plasma	0.00	0.22	0.00	0.00	0.00	0.05

Table 8: Results of microbiological examinations of confirmed cases of TTBI (1997–2017)

Microorganism	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	FFP	Total	Non-fatal	Fatal	RBC	PC
Pathogens with low (human) pathogenicity								
Staphylococcus *capitis, epidermidis, hominis, saprophyticus, warneri und spp.* *Micrococcus luteus, Corynebacterium spp.* *Propionibacterium acnes*	18	28	2	48	47	1	0	1
Pathogens with medium/high pathogenicity								
Staphylococcus aureus ***Streptococcus*** *pyogenes, dysgalactiae equisimilis, gallolyticus, agalactiae* *Bacillus cereus, Escherichia coli* ***Enterobacter*** *erogenes, amnigenus* ***Klebsiella*** *oxytoca, pneumonia;* *Pantoea agglomerans, Serratia marcescens, Yersinia enterocolitica, Enterococcus spp.* *Acinetobacter Iwoffii, Pseudomonas aeruginosa* *Enterococcus faecalis*	29	44	3	76	60	16	4	12
Total	47	72	5	124	107	17	4	13

Table 9: Confirmed suspected cases referring to transfusion-transmitted virus infections (TTVI) and rate of TTVI referring to 10^6 transfused units (2000–2017)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2017	2000–2017
HIV infections following transfusion of						
RBC	3	1	1	0	**0**	**5**
PC	0	0	0	0	**0**	**0**
Plasma	0	0	0	0	**0**	**0**
Total	3	1	1	0	**0**	**5**
HCV infections following transfusion of						
RBC	0	1	0	0	**0**	**1**
PC	0	0	0	0	**0**	**0**
Plasma	0	0	0	0	**0**	**0**
Total	**0**	**1**	**0**	**0**	**0**	**1**
HBV infections following transfusion of						
RBC	3	8	1	1	**0**	**13**
Pool-PC	0	0	0	0	**0**	**0**
Apheresis-PC	2	0	1	1	**0**	**4**
Plasma	2	1	0	0	**0**	**3**
Total	**7**	**9**	**2**	**2**	**0**	**20**
HEV infections following transfusion of						
RBC				3	**1**	**4**
Pool-PC				1	**1**	**2**
Apheresis-PC				3	**1**	**4**
Plasma				0	**1**	**1**
Total				7	**4**	**11**

Rates of confirmed transfusion-transmitted HBV, HCV and HIV infections for the periods						
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2017	2000–2017
	TTVI per 10^6 units	TTVI per 10^6 units	TTVI per 10^6 units	TTVI per 10^6 units	TTVI per 10^6 units	TTVI per 10^6 units
RBC	0.37	0.58	0.11	0.06	0.00	0.26
PC	1.57	0.00	0.53	0.49	0.00	0.52
Plasma	0.44	0.22	0.00	0.00	0.00	0,16

Rates of confirmed transfusion-transmitted HEV infections for the periods			
	2012–2015	2016–2017	2012–2017
	HEV per 10^6 units	HEV per 10^6 units	HEV per 10^6 units
RBC	0.19	0.14	0.17
PC	1.98	2.02	1.99
Plasma	0.00	0.66	0.20

Table 10: Reports of IBCT with serious adverse reactions (SAR) as well as reports of near-IBCT and/or IBCT without serious adverse reactions (SAE) in the recipient (2000–2017)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2017	2000–2017
SAR RBC	15	18	23	63	51	170
SAR PC			0	1	2	3
SAR plasma			0	3	2	5
SAR total	15	18	23	67	55	178
Therefrom fatal (admin. of RBC)	0	1	4	5	3	13
SAE RBC			6	66	73	145
SAE PC			1	4	11	16
SAE plasma			0	7	12	19
SAE total			7	77	96	180
IBCT (SAE and SAR) total	15	18	30	144	151	358

Notifiable for SAE (near IBCT and/or actual IBCT without SAR) since 2012
Up to 2014, reports of IBCT with serious adverse reactions (SAR) were indicated as ABO incompatibilities.

Rates of confirmed IBCT with serious adverse reactions						
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2017	2000–2017
	IBCT per 10^6 units	IBCT per 10^6 units	IBCT per 10^6 units	IBCT per 10^6 units	IBCT per 10^6 units	IBCT per 10^6 units
RBC	0.93	1.05	1.28	3.89	7.23	2.28
PC	0.00	0.00	0.00	0.49	2.02	0.39
Plasma	0.00	0.00	0.00	0.87	1.32	0.27

Table 11: Rates of serious adverse transfusion reactions for each 10^6 transfused units of RBC, PC, and plasma (2000–2017)

SAR rates per 10^6 transfused units									
	Units transfused 2000–2017	ATR	HTR	TRALI	TTBI	TTVI	IBCT	Units transfused 2009–2017*	TACO*
RBC	74,446,032	9.99	3.26	0.51	0.50	0.31	2.28	36,738,765	8.30
PC	7,726,822	34.43	1.68	2.33	8.41	1.29	0.39	4,436,151	4.28
Plasma	18,570,534	8.89	0.00	4.85	0.05	0.22	0.27	8,441,672	1.66

* TACO cases were only recorded systematically as from 2009. Accordingly, the rates for TACO refer to units consumed between 2009 and 2017.