Federal Institute for Vaccines
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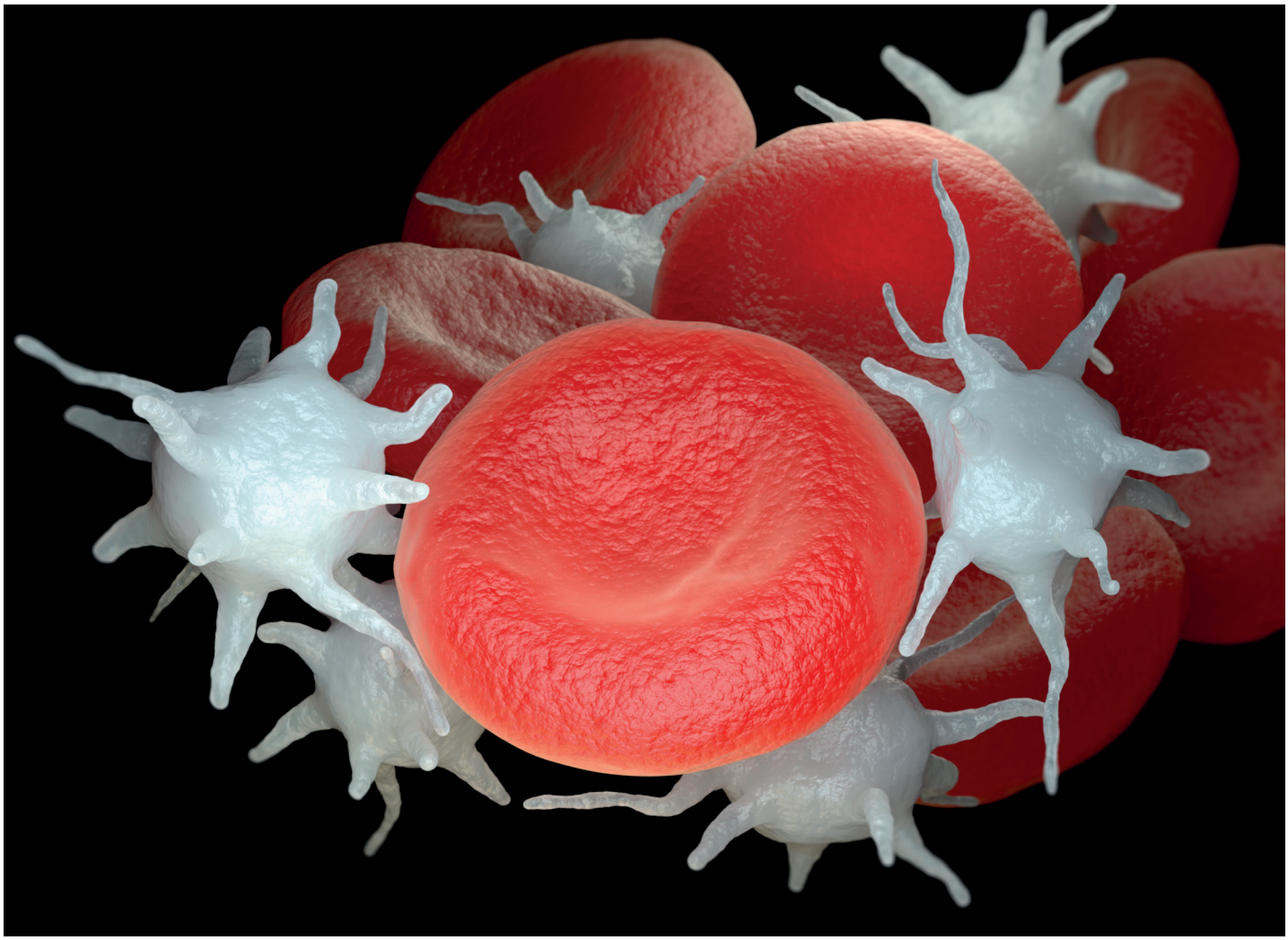
Paul-Ehrlich-Institut

// HAEMOVIGILANCE REPORT OF THE PAUL-EHRLICH-INSTITUT // 2019

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



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Federal Institute for Vaccines
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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

Proof-reading and Layout

Kirsten Külker, Berlin

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

Other co-workers contributing to the haemovigilance report:

Cornelia Witzenhausen[1], Dr Gabriele Ruppert-Seipp[1], Dr Philipp Berg[1], Klaudia Wesp[1], Olaf Henseler[2], Sarah Fiedler[1], Dr Britta Meyer[1], Stefano Orru[1], Dr Brigitte Keller-Stanislawski[1]

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

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// Contents //

// 1. Introduction //

The haemovigilance report 2019 of the Paul-Ehrlich-Institut (PEI) summarises all spontaneous reports from January to December 2019 on serious adverse transfusion reactions (SAR), serious adverse donor reactions (donor SAR), and serious adverse events (SAE) that occurred in the transfusion chain. It continues the analysis and compares the new data to the reports of 2000–2018 [1].

Reports on blood and plasma donor-initiated look-back procedures triggered by confirmed screening test results are summarised and test results of the retain samples from previous donations are presented. Moreover, confirmed cases of suspected HBV infections are broken down by test procedures and vaccination status.

The report contains the available information on bacterial strains involved in the transfusion-transmitted bacterial infections (TTBI) rated as possible or confirmed. It furthermore gives details on confirmed cases of transfusion-related acute lung injury TRALI, and transfusion-transmitted viral infections (TTVI). For the first time, febrile non-haemolytic transfusion reactions (FNHTR) and transfusion-associated dyspnoea (TAD) are included and retrospectively reported starting from 2012.

As noted also in previous reports, many spontaneous case reports received in 2019 were not sufficiently described thus preventing an adequate and conclusive assessment. Therefore, all reporting establishments are again reminded of the importance to submit a detailed documentation (e.g., an anonymised transfer report/epicrisis) in addition to the minimum information explicitly required in Section 14 Transfusion Act (Transfusionsgesetz, TFG) [2]), in particular in the event of transfusion reactions with lethal outcome. This is the only way in which a potential connection of the SAR with the transfusion can be reliably evaluated by the PEI (see Table 14, page 40). The reports pursuant to Section 63i German Medicines Act (Arzneimittelgesetz, AMG) [3] altogether allow for a documentation of the safety standards of blood components in Germany and the assessment of the usefulness of risk-minimising measures.

The haemovigilance data captured relating to the collection, production, and consumption of blood and blood components as well as the suspected cases of SAR and SAE are reported to the European Commission annually by the PEI [4] pursuant to Directive 2005/61/EC [5].

// 2. Abbreviations //

Ab	Antibody(ies)
Ag	Antigen(s)
AK Blut	Arbeitskreis 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 leukemia
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
CMV	Cytomegalovirus
FNHTR	Febrile, non-haemolytic transfusion reaction(s)
HAV	Hepatitis-A virus
HBV	Hepatitis-B virus
HCV	Hepatitis-C virus
HEV	Hepatitis-E virus
HF	Health care facility
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(s) transfused
ID-NAT	Individual Donor-NAT
ISBT	International Society of Blood Transfusion
NAT	Nucleic Acid Amplification Technology
PC	Platelet concentrate(s)
PEI	Paul-Ehrlich-Institut
P-PC	Pooled 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
TAD	Transfusions-associated dyspnoea
TTBI	Transfusion-transmitted bacterial infection(s)
TTVI	Transfusion-transmitted viral infection(s)
TFG	Transfusionsgesetz (German Transfusion Act)
TRALI	Transfusion-related acute lung injury

// 3. Methods //

Each spontaneous report of a suspected SAR in a donor or transfusion recipient is captured at the PEI and completed by means of additional information requests if necessary. Table 14 (page 40) 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 [5]. A SAR is considered as confirmed if it has been categorised as certain or likely/probable, and if the SAR refers to cases of TRALI, TTBI, TTVI or incorrect blood component transfused (IBCT). Since, in particular for allergic and anaphylactic transfusion reactions (ATR), FNHTR, and TAD, partly also for haemolytic transfusion reactions (HTR), and transfusion-associated circulatory overload (TACO), unique clinical parameters are missing, which could unambiguously provide proof for the relationship between a SAR and the transfusion, in these cases 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, if available, point to a certain or likely/probable causal relationship with the blood component transfused.

The confirmed SAR are grouped and their ratio calculated by comparing them with the number of blood components determined as transfused in accordance with Section 21 TFG [6] and presented as share per million transfused units. Donor SAR reported by the blood establishments (BE) due to whole-blood or apheresis donations are grouped by the type of reaction and, in addition, are presented as rate of confirmed SAR per number of the respective donations from all reporting BE. The frequency of SAE, which did not cause a reaction in the donor or the recipient, are listed and presented based on their occurrence in the transfusion chain from the donation up to their use.

The legal basis for SAE and SAR reporting required from the BE is laid down in Section 63i AMG [3], and regarding treating physicians in Sections 14 and 16 TFG [2]. For this type of reporting, the PEI provides standardised forms on its website [7]. Reports can also be submitted via an online submission platform (https://humanweb.pei.de/index_form, available only in German). In the reporting form, the treating physicians record all essential information on the transfusion, such type of the blood component(s) administered and time, course and outcome of the transfusion reaction. Details required on the person receiving the transfusion include date of birth, sex, transfusion trigger, underlying disease(s), and all relevant concomitant diseases and medication. The BE involved in the manufacture of the appropriate blood components shall complete the information by specific data on the respective donors as well as on additional blood products that may have been prepared from these donations. In addition, the BE shall report the results of lab tests performed and the initiation of a look-back procedure, if applicable [2, 8, 9]. In the event of a donor SAR, the type of donation and donor reaction shall be reported, too. Cases in which incorrect blood component(s) were transfused (IBCT) without resulting in a transfusion reaction as well as errors in the transfusion chain that could have led to IBCT must be reported by the pharmaceutical company to the senior federal authority as SAE pursuant to Section 63i AMG [3]. A reporting obligation pursuant to Section 16 (2) TFG [2, 10] also applies to the treating doctor in the event of an IBCT involving an adverse transfusion reaction. As the duty to report exclusively applies to serious adverse reactions and events, the PEI only sporadically receives information on non-serious ones, which are not included in the evaluation. Since 2014, the Drug Commission of the German Medical Association (AkDÄ) has been forwarding all received reports to the PEI; all transfusion reactions therein rated as serious are included in the current haemovigilance report.

For calculating the frequencies of confirmed SAR, the reports pursuant to Section 21 TFG on the sale and loss of red blood cell concentrates (RBC), platelet concentrates (PC) and plasma served as a basis for estimating the number of units transfused (deadline 16 September 2020 [6]).

The first part of the haemovigilance report presents the data captured in the reporting period 2019; tables and figures in the Annex continue the summary collection of the German haemovigilance data since 2000.

// 4. Results //

4.1 Serious adverse transfusion reactions (SAR)

Altogether, 856 suspected cases of serious adverse transfusion reactions were reported in 2019, and a causal connection with the administration of blood components was confirmed in 609 of the cases (for definitions, see table 15, page 40). In 7 cases the transfusion triggered adverse reaction was assessed as causal for a fatal outcome.

For the first time, FNHTR and TAD are included within the reported and confirmed SAR cases in Table 4.1. Data for FNHTR and TAD have been systematically captured since 2012 (see also Tables 6, 8, 13, pages 35, 36, 39).

Table 4.1: Overview of reported cases of suspected serious adverse transfusion reactions (SAR), confirmed SAR, and deaths due to a transfusion reported in 2019

	SAR 2019	Reported	Confirmed	Fatal cases
1	ATR Grade I/II	78	73	0
2	ATR Grade III/IV	185	170	0
3	TACO	63	51	0
4	TRALI	84	3	1
5	TAD	23	21	0
6	HTR	78	50	5
7	FNHTR	191	183	0
8	Other	32	15	0
9	TTBI	44	4	1
10	HCV, HIV, HBV	30	2	0
11	HEV	18	10	0
12	Other TTVI*	4	1	0
13	IBCT	26	26	0
	Total	**856**	**609**	**7**

* Within the category "other TTVI" one transmission of parvovirus B19 was confirmed.

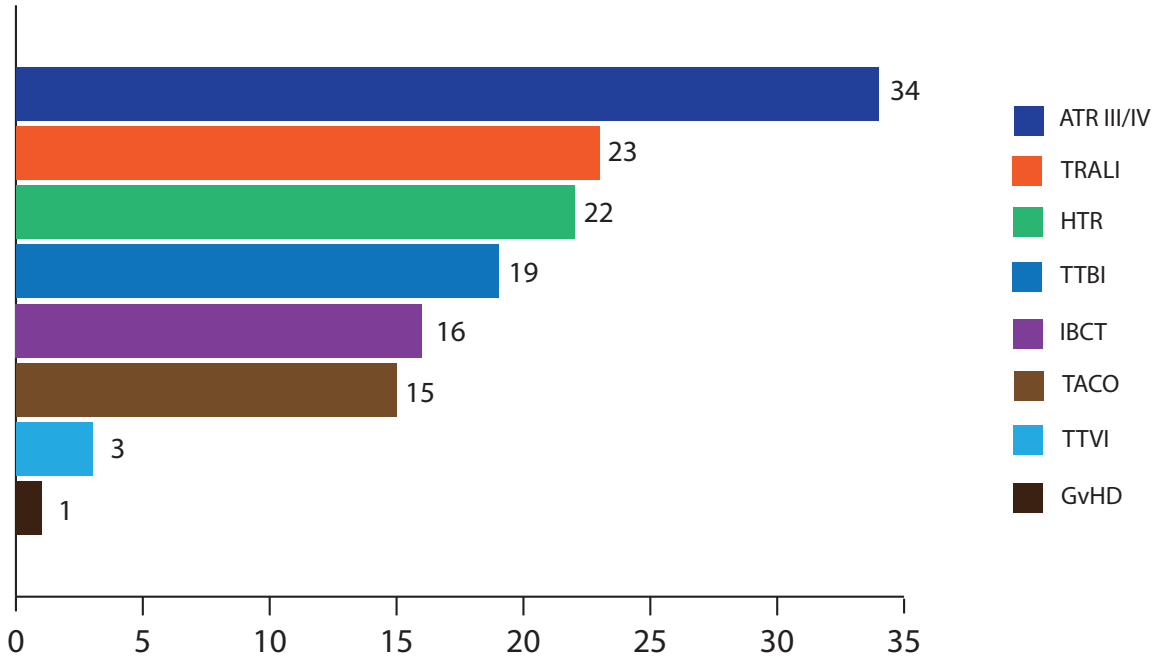
Deaths:

RBC transfusions caused 3 lethal cases of an acute HTR and 2 of a delayed HTR. The lethal outcome in case of a TRALI was associated with the transfusion of a pool-PC (P-PC). Bacterial contamination caused the death of a patient following transfusion of an apheresis-PC (A-PC).

Thus, 133 fatal cases have been attributed to the administration of blood components during the observation period of 23 years (1997–2019). With 34 reported cases, ATR grade III and IV were documented as the most common cause of death so far, followed by TRALI with 20 cases prior to as well as three cases after the introduction of the requirement designed to reduce the risk of TRALI by specific donor selections and/

or donor testing [11]. The lethal cases further include 22 cases due to haemolytic transfusion reactions, 19 caused by transmission of bacterial infections, 16 due to incorrect blood components transfused, and 15 due to circulatory overload. In addition, three lethal cases have been reported after viral infections and one after a graft-versus-host-disease (GvHD) (Figure 4.1, Table 2, page 31).

Figure 4.1: Number of serious adverse transfusion reactions with lethal outcome (1997–2019)



4.2 Acute allergic/anaphylactic transfusion reactions (ATR)

ATR are defined by a set of clinical symptoms rather than specific laboratory parameters. Many symptoms can be unspecific – apart from the development of urticaria or itching – and can overlap with features 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 has exclusively been assessed as "likely/probable" or "possible".

In line with previous reports, serious allergic/anaphylactic transfusion reactions have again been reported more frequently following the administration of PC than following the administration of other blood components (see Tables 3 and 13, pages 33, 39).

Table 4.2: Number of suspected cases of ATR Grades I/II and III/IV, confirmed cases after administration of RBC, PC, plasma or combined administration, as applicable as well as the SAR rates per 10^6 units transfused (2019)

ATR 2019	ATR I and II	ATR III and IV	Rate ATR III and IV per 10^6 units
Reported cases	78	185	
Confirmed cases following administration of			
RBC	45	90	26.93
PC	23	43	89.15
Plasma	3	24	32.64
Combined products	2	13	
Total confirmed cases	73	170	

Distinction ATR Grades I and II from ATR Grades III and IV according to Ring and Messmer [12]

Deaths:

No cases of lethal ATR were reported in 2019.

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 [13], and the differentiation from non-immunogenic or possible TRALI or Acute Respiratory Distress Syndrome (ARDS) is complex inasmuch as the differences in the symptoms may be blurred. The findings of newly developed pulmonary oedema in a thorax x-ray, and rapid recovery after the administration of diuretics are diagnostic criteria pointing to circulatory overload. The diagnostic biomarkers brain natriuretic peptide (BNP) and the N-terminal pro-hormone of BNP (NT-proBNP) can be used, especially for a distinction from non-immunogenic TRALI. A strong increase in NT-proBNP levels during the course of the observation can support while low levels of BNP can exclude the TACO diagnosis. However, the validity of these markers is limited in critical ill patients [14].

Table 4.3: Number of suspected cases reported for transfusion-associated circulatory overload (TACO), confirmed cases after the administration of RBC, PC, plasma, or combined administration as well as the SAR rates per 10^6 units transfused (2019)

TACO	2019	Rate of TACO per 10^6 units
Reported cases	63	
Confirmed cases following administration of		
RBC	43	12.87
PC	2	4.15
Plasma	3	4.08
Combined administration	3	
Combined administration	51	

Deaths:

No cases of TACO with lethal outcome were reported in 2019.

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 pulmonary insufficiency (e.g., cardiologic diseases, etc.) should be ruled out. Unlike in TACO, radiological signs of lung oedema are less commonly observed in TRALI but rather bilateral acute perihilar lung infiltrates (definition, see also Table 15, page 40). Immunogenic TRALI is confirmed by evidence of specific antibodies (Ab) in the donor and the corresponding antigen (Ag) in the recipient.

The algorithm introduced in the haemovigilance report 2013–2014 [15] was maintained for the current assessment of the suspected cases of TRALI, thus permitting a comparison of the data published ever since. First, clinical symptoms are reviewed and possible other causes ruled out. Second, the donors are tested for relevant HLA-Ab or HNA-Ab and recipients are tested for corresponding Ag. Depending on the result, the reaction is then categorized as immunogenic or non-immunogenic TRALI [16]. In 2019, an international group (CA, US, NL, DE) of medical professionals in the fields of transfusion, intensive care, and laboratory research published a suggestion of a redefinition not focussed on the immunological aspect but the clinical picture and pre-existing risk factors of the transfusion recipients [17].

For a conclusive distinction of TRALI from closely related symptoms, however, further findings from well-described cases from the field of haemovigilance are required. Likewise, in 2019, the Haemovigilance Working Party of the ISBT published a redefinition of TACO as an adaption of the last revision in 2013 [18]. Especially in those cases that, due to missing evidence of corresponding Ab, cannot easily be distinguished from TACO, and 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 course of BNP and NT-proBNP levels can be used as a diagnostic decision criterion.

In 2019, the PEI received altogether 84 suspected cases of TRALI of which two could be confirmed as immunological TRALI and one case as non-immunological TRALI (see Tables 4.4 a and 4.4 b). Furthermore, 23 suspected TRALI cases were assessed as possible and 58 as unlikely. The blood components involved in confirmed TRALI derived from three whole blood donations and the cases are briefly described below:

(i) A patient suffering from multiple myeloma required transfusion of three RBC and 8 plasma units due to intraoperative blood loss during reconstitution of a femur fracture. Immediately following transfusion of plasma, deriving from a male donor with unknown immunisation history, the patient reacted with typical signs of TRALI. TACO could be excluded by transoesophageal echocardiography. Analysis of the plasma donor revealed strong pan-reactive, pseudo-specific granulocyte auto-Ab. Because of pan-reactivity of the donor Ab an Ag typing of patients´ cells was omitted. Even showing all clinical and laboratory signs of TRALI the case was not assessed as certain but as probable/likely because a bone cement caused fat embolism could not been excluded.

(ii) An adipose patient with papillary carcinoma, MALT lymphoma, arterial hypertension, bilateral lung embolism and deep vein thrombosis obtained four P-PC during a laparotomy. She developed clinical signs of TRALI within 3 hours and did not recover. Analysis revealed broad reactive HLA-Class II Ab in a female donor with pregnancies in the history whose platelets were a part of one P-PC. Corresponding Class II

Ag were found on the patient's cells. However, an aqueous but not a foamy lung exudate was observed. An autopsy to clarify the cause of death was denied. Thus, the causality of the reaction was not assessed as certain but as probable/likely.

(iii) A patient with relapse of an advanced ovarian carcinoma and a pronounced thrombocytopenia received two P-PC. She developed typical clinical signs of TRALI 7 hours later, starting with foamy exudate and bilateral lung infiltration. TACO could be excluded. Because of the late onset, missing Ab-Ag correlation and relatively mild course it was classified as a non-immunologic TRALI case with probable/likely causality. Particulars on donors, i.e., sex or immunisation history were not provided by the reporting BE.

Table 4.4 a: Number of suspected cases of transfusion-related acute lung injury (TRALI), confirmed cases following the administration of plasma and PC as well as the SAR rates per 10^6 units transfused (2019)

TRALI	2019	Rate of TRALI per 10^6 units
Number of reported cases	84	
Confirmed cases following administration of		
RBC	0	0.00
PC	2	4.15
Plasma	1	1.36
Total of confirmed cases	**3**	

Table 4.4 b: Listing of confirmed cases of TRALI in 2019

TRALI	Donor			Recipient	
Evaluation	**Ab**	**Blood-component**	**Sex**	**Corresponding Ag**	**Underlying disease**
Likely/probable	Male WB donor, pan reactive granulocyte Auto-Ab (CD16, CD11, HLA)	Plasma	Male, immunisation history not known	not determined because of wide pan reactive donor Ab	Multiple myeloma, autologous stem cell transplantation, bleeding during femur fracture reconstitution
Likely/probable	Female WB donor HLA-Ab Class II positive (i.a. DR 11, 12, 13, DQ 7, 8, 9)	P-PC	Female, positive history of pregnancy	HLA-DR 13	Papillary carcinoma, MALT lymphoma
Likely/probable	WB donor	P-PC	immunisation history not known	not determined	Ovarian carcinoma

MALT = mucosa-associated lymphoid tissue

Deaths:

In 2019 one deaths due to confirmed immunological TRALI after transfusion of a P-PC occurred.

4.5 Transfusion-associated dyspnoea (TAD)

For 2019, 23 suspected cases of TAD were reported as serious adverse transfusion reactions; in 21 cases, a connection with the transfusion was confirmed.

Table 4.5: Number of suspected cases of TAD, of confirmed cases after administration of RBC, PC, plasma, or combined administration as well as the SAR rates per 10^6 units transfused (2019)

TAD	2019	Rate of TAD per 10^6 units
Reported cases	23	
Confirmed cases following administration of		
RBC	16	4.79
PC	3	6.22
Plasma	1	1.36
Combined administration	1	
Total of confirmed cases	**21**	

Deaths:

No lethal 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 the typical clinical symptoms are supported by laboratory findings. The causality is considered as certain if the antiglobulin test or the cross-matching is positive.

Despite some fluctuations, the number of confirmed HTR show an increasing tendency over the last 5 years (see Figure 1, page 31). In 2019, of 78 reported cases 50 HTR could be confirmed, 45 of these due to RBC transfusion (Table 4.6 a). No ABO-Ab caused HTR was reported. Of 35 Ab-triggered HTR, 29 were due to irregular allo-Ab and 6 due to auto-Ab. Cases of mixed occurrence of allo- and auto-Ab were categorised as allo-Ab caused HTR. In immunological HTR most often allo-Ab against Rh-Ag, Jk(b), Jk(a), and Fy(a) as well as auto-Ab of cold or warm type were observed.

No underlying immunological reaction was observed in 12 cases, and in three cases details are missing (Table 4.6. b).

Acute reactions were reported in 27 and delayed reactions in 22 of all HTR cases.

The numbers of acute and delayed HTR are more or less balanced as also reported from other countries [19].

Table 4.6 a: Number of reports of suspected cases of haemolytic transfusion reactions (HTR), confirmed cases after administration of RBC and plasma, deaths after administration of RBC as well as the SAR rates per 10^6 units transfused (2019)

HTR	2019	Rate of HTR per 10^6 units
Reported cases	78	
Confirmed cases following administration of		
RBC	45	13.47
Plasma	1	1.36
Combined administration	4	
Fatal cases (RBC)	5	
Total of confirmed cases	**50**	

Table 4.6 b: Confirmed HTR by type of reaction and Ab detection (2019)

HTR 2019	Acute HTR	Delayed HTR	Unknown*	Total
ABO Ab	0	0	0	0
Other Allo Ab	10 RBC	18 RBC, 1 comb. adm.	0	29
Auto Ab	5 RBC	1 RBC	0	6
Non-immunological	7 RBC, 1 Plasma, 1 comb. adm.	1 RBC, 1 comb. adm.	1 comb. adm.	12
Not specified	3 RBC	0	0	3
Total HTR	**27**	**22**	**1**	**50**

* Data from the time point of transfusion are missing.
comb. adm. = combined administration

Deaths:

In 2019, a total of 5 HTR with a fatal outcome following RBC transfusion were confirmed.

(i) One patient suffering from oxygen ventilation requiring silicosis, coronary heart disease, progressed heart insufficiency, recurrent bladder cancer, and acute bronchopulmonary infection with pan-reactive allo-Ab and possibly drug induced autoimmune haemolytic Ab of warm type developed following RBC transfusion a delayed HTR. The fatal course of the delayed HTR was aggravated by the poor general condition of the patient who died 3 days after the transfusion.

(ii) A second patient died in the course of a delayed HTR triggered by allo-Jk(a) Ab. As underlying diseases progressed peripheral arterial disease, chronic kidney insufficiency, obesity, diabetes mellitus, and cerebral ischemia were known. The poor general conditions added to the lethal outcome.

(iii-v) Acute HTR following RBC transfusion provoked three further cases of death. Allo-Jk(a) Ab caused the reaction in one patient with atrial fibrillation, heart insufficiency and condition after gastro-intestinal and leg variceal bleeding as well as in a second patient suffering from kidney and liver failure, aspiration pneumonia, and bronchial bleeding. A third patient with chronic lymphocytic leukemia and peripheral arterial disease developed autoimmune haemolytic Ab of warm type which caused the lethal HTR.

4.7 Febrile non-haemolytic transfusion reactions (FNHTR)

FNHTR, systematically recorded since 2012, are included in the haemovigilance report for the first time. It is currently unclear, if the observed steep increase since than (Figure 1, page 31) is due to a changed focus by reporting BE or to a real increase of FNHTR.

Table 4.7: Number of reports of suspected cases of febrile non-haemolytic transfusion reactions (FNHTR) and confirmed cases after administration of RBC, PC and combined administration as well as the SAR rates per 10^6 units transfused (2019)

FNHTR	2019	Rate of FNHTR per 10^6 units
Reported cases	191	
Confirmed cases following administration of		
RBC	151	45.19
PC	23	47.68
Combined administration	9	
Total of confirmed cases	**183**	

Deaths:

No death due to FNHTR has been reported since its systematic recording starting from 2012.

4.8 Other transfusion reactions

In 2019, the PEI received further 32 suspected cases of transfusion reactions, which were predominantly caused by the underlying disease(s). However, in 15 of them the transfusion possibly contributed to the observed reactions in the patients.

4.9 Transfusion-transmitted bacterial infections (TTBI)

The number of confirmed bacterial infections due to a transfusion of PC declined by roughly 50% after shortening the PC shelf life in 2008 [20]. However, fatal cases are still observed. In 2019, 44 suspected cases of TTBI had been reported. None of the confirmed TTBI could be classified as "certain" because a proof of the homology of the pathogens, e.g. by an identical antibiogram, was missing. Three cases following PC transfusion and one case following RBC transfusion could be confirmed as "likely/probable" because the responsible bacterial strains were detected in patients' blood as well as in the residual volumes of the transfused blood components (Tables 4.9 a and 4.9 c). Due to incomplete case clarification in 6 reports the correlation of a septic reaction in the patients following transfusion could not be confirmed as the pathogen was detected either only in the blood component or only in the recipient. In one case the antibiotic treatment gave a negative test result in the patients' blood sample (Table 4.9 b).

Reports of suspected TTBI were rated as cases without sufficient causality (unlikely) if no evidence of pathogen was provided, the time interval was exceeded, or the clinical picture was unclear. This applied to 31 reports of suspected TTBI. Due to missing data, in two cases of RBC transfusion and in one case of a combined administration an assessment was not possible.

Table 4.9 a: Number of suspected cases of transfusion-transmitted infections (TTBI), and confirmed cases after the administration of RBC and PC as well as the SAR rates per 10^6 units transfused (2019)

TTBI	2019	Rate of TTBI per 10^6 units
Reported cases	44	
Confirmed following administration of		
RBC	1	0.29
PC	3	6.22
Fatal cases (PC)	1	
Total of confirmed cases	**4**	

Table 4.9 b: Transfusion-transmitted bacterial infections with possible causality (2019)

Pathogen	Product	Evidence of pathogen recipient/ product	Outcome
Staphylococcus aureus	RBC	Positive/1 RBC negative, 1 RBC not done	Restored
Staphylococcus epidermidis and *Staphylococcus warneri*	RBC	Not done/plasma from identical WB donation positive	Restored
Enterococcus faecium	RBC	Not done/RBC positive	Restored
Staphylococcus epidermidis	RBC	Negative (antibiosis)/RBC positive	Restored
Staphylococcus epidermidis	RBC	Not done/RBC positive	Restored
Citrobacter koseri	A-PC	Positive/no data	Restored
Staphylococcus capitis	RBC	Not done/RBC positive	Restored

Table 4.9 c: Transfusion-transmitted bacterial infections with confirmed causality (2019)

Pathogen	Product	Evidence of pathogen recipient/product	Outcome	Assessment
Streptococcus dysgalactiae ssp. equisimilis	A-PC	Both	Restored	Likely/probable
Streptococcus dysgalactiae ssp. equisimilis	A-PC	Both	Lethal	Likely/probable
Klebsiella pneumoniae	P-PC	Both	Restored	Likely/probable
Escherichia coli, recipient negative before transfusion	RBC	Both	Restored	Likely/probable

Deaths:

The fatal case in 2019 was due to transfusion of an A-PC contaminated with *Streptococcus dysgalactiae ssp. equisimilis*. The recipient was a critically ill CML patient following a second allogeneic stem cell transplantation who needed artificial ventilation and antifungal therapy. Immediately following transfusion, the patient reacted with a fulminant septic shock and cardio circulatory insufficiency and died 34 hours later despite three resuscitation attempts. A second A-PC deriving from the identical apheresis procedure and transfused some hours later at the same day caused a life-threatening septicaemia in a Ewing sarcoma patient after stem cell transplantation under broad antibiotic therapy. Both A-PC had been transfused on the same day, i.e., at day 3 after collection. An earlier transfused third A-PC out of the same apheresis procedure did not cause a septic reaction.

4.10 Transfusion-transmitted viral infections (TTVI)

Viral transmission is confirmed by means of the criteria conforming to Opinions 42 and 47 of the AK Blood for Hepatitis B (HBV), Hepatitis C (HCV), Hepatitis E (HEV) and human immune deficiency virus (HIV) [8, 9] or using comparable criteria for other viruses.

In 2019, two transmissions of HCV and 10 transmissions of HEV were confirmed (Table 4.10) while the causality of 14 suspected cases of HBV and 2 HIV transmissions were rated as "unlikely".

HCV

The two HCV transmissions were due to one RBC and one P-PC deriving from the identical WB donation that tested negative in a very early phase of donor infection by HCV. Testing of retain sample by ID-NAT did not consistently yield positive results, depending on the respective limit of detection. The donor was HCV-NAT positive, although still seronegative, in the donation screening two month later, which triggered the look-back procedure [21].

(i) Genome identity by sequencing was shown in case of the P-PC recipient, who was transfused due to blood loss following acute myocardial infarction and operation under heart-lung machine. The P-PC was prepared from the buffy-coats of 4 WB donations. One of them and the plasma portion, altogether about 40-60ml, derived from the low titer index donation.

(ii) A thalassemia major patient who received the RBC from the concerned index donation (calculated plasma portion 25-39ml) was tested HCV-NAT highly positive 3 months later. Since sequencing was not done to demonstrate genome identity, the causality of the HVC transmission by the RBC was rated as "probable/likely".

The both cases of a HCV transmission by blood components, containing a relatively low plasma portion from an infected donor with a very low virus titer, illustrate the high infectivity of the Hepatitis C virus.

The last time a transfusion-transmitted HCV infection was confirmed was in 2004. Similar to the transmission in 2019, the HCV-contaminated donation in 2004 was harvested in a very early phase of donor infection and was not even detected by the HCV-ID-NAT used for screening of cell apheresis donations.

HEV

(i) One of the 4 PC-associated TTVI was due to two HEV-contaminated A-PC originating from one and the same donor but from two different apheresis procedures. The affected patient with AML was transfused in course of a stem cell transplantation with 86 RBC, and 54 PC. He was negative before treatment and became HEV-NAT positive one month following transfusion of the first of the two contaminated A-PC. All other retain samples tested negative; a sequencing for proof of viral genome identity was not performed.

(ii) Another patient with AML, obtained 25 RBC and 26 P-PC in course of preparation of stem cell transplantation and was tested positive in HEV-NAT about 2 month following initial transfusion. Only one of the retain samples out of the corresponding 57 donations was tested positive in HEV-NAT, sequencing for proof of viral genome identity was not performed. The BE started screening for HEV-NAT shortly after.

(iii) A third patient with AML became HEV positive for the first time two month following transfusion of two A-PC deriving from one donation. The HEV transmission was proven by sequence homology. The recipient of another contaminated A-PC from the same donor was deceased.

(iv) A patient with a complex thoracic trauma and pleural emphysema tested positive 12 days following transfusion of 8 RBC. One of the RBC derived from a donor infected by HEV. No genome sequencing was performed.

(v) A patient suffering from ovarian cancer tested positive for the first time after transfusion of two RBC. The retain sample of one of the donations was also HEV-NAT positive; genome sequencing was not performed.

(vi) Similar, a further patient obtained two RBC of which one derived from a HEV-NAT positive donor; genome sequencing was not performed.

(vii) A donor's infection triggered a look-back procedure that revealed two HEV transmissions due to one P-PC and one RBC prepared from the same WB donation. The P-PC recipient was a patient suffering from ALL and pancytopenia who obtained 26 RBC, 13 P-PC, and 4 A-PC. The first positive HEV-NAT test result was obtained about one month after transfusion of the P-PC in question. All other retain samples gave negative HEV-NAT results. Genome sequencing could not be performed as the patient later on became NAT negative again.

(viii) The transmission of HEV to the RBC recipient, who for the first time became HEV positive 10 weeks post transfusion, was conclusively proven by genome sequencing.

(ix) The transfusion-transmitted HEV infection after combined administration was observed in a patient with pleura mesothelioma, who received 8 RBC and 42 plasma units during therapeutic plasmapheresis. The RBC from one WB donor and 4 plasma units from one apheresis donor were contaminated by HEV. Genome sequencing was not performed. Altogether 70 retain samples had been tested during the recipient triggered look-back procedure and further 4 were positive in HEV-NAT. The concerned clinics were informed; no further data were obtained.

(x) In course of a spleen transplantation a patient obtained 13 RBC and 9 plasma units. He tested HEV positive about two month later. Testing of retain samples revealed a HEV-NAT positive plasma donation. The transmission was proven by genome sequencing.

Table 4.10 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 as well as the SAR rates per 10^6 units transfused (2019)

TTVI (HIV, HCV, HBV, HEV)	2019	Rate of TTVI per 10^6 units
Reported cases	48	
Cases following administration of		
RBC	5	1.50
PC	5	10.37
Plasma	1	1.36
Combined administration	1	
Total	**12**	

Deaths:

In 2019 no deaths due to TTVI have been reported.

Other transfusion-transmitted infections

In 2019, three reports on suspected cases of transfusion-transmitted infections could not be confirmed while one suspected transmission of parvovirus-B19 by transfusion of one A-PC was confirmed.

Since the PEI started recording transfusion reactions in 1997 up to and including 2019, no suspected transmissions of viral pathogens such as West Nile virus (WNV), chikungunya virus (CHIKV), dengue virus (DENV), Zika virus (ZIKV), or other arthropod-borne viruses have been reported. During this period, a total of six HIV, 22 HCV, 25 HBV, two HAV, 23 HEV, and one malaria transmission due to transfusions have been confirmed.

4.11 Look-back procedures based on a donor-infection (donor look-back)

In the reporting year 2019, altogether 1,692 confirmed screening results in donors were received that resulted in donor look-back procedures. Compared to the preceding year with 867 confirmed positive screening results the number nearly doubled. This is connected with a considerable increase of HEV cases likely caused by the early introduction of HEV-NAT into donor screening following PEI's announcement of mandatory testing as of 2020 [22]. The overview in Table 4.11 shows that in 58 cases final data are still missing, mainly in cases of HEV infections.

Table 4.11 a: Donor look-back procedures in 2019 triggered by confirmed or undetermined results analogue with Opinions 42 and 47 of the AK Blut [8, 9]

2019	Confirmed positive index donations	Retain sample				
Pathogen	Reported	Negative	Not tested[1]	Positive[2]	Positive[3]	Missing data
HEV	947	692	184	36	3	32
HBV	511	439	61	1	0	10
HCV	95	61	31	0	1	2
HIV	38	29	9	0	0	0
HAV	2	2	0	0	0	0
CMV	37	36	1	0	0	0
Parvovirus B19	6	3	0	3	0	0
WNV[4]	1	0	1	0	0	0
Syphilis	55	10	30	1	0	14
Total	**1,692**	**1,272**	**317**	**41**	**4**	**58**

[1] previous donation outside the look-back period/collection of plasma for fractionation/products not released/RBC stored for more than 5 days (syphilis)/NUP missing/confirmed HBV vaccination

[2] recipient negative or deceased (HEV), products not released (HBV, Syphilis)/recipient informed (Parvovirus B19)

[3] possible/confirmed TTVI: cases described in section 4.10 Transfusion-transmitted viral infections (TTVI)

[4] Case identified as Usutu virus

Table 4.11 b: Look-back procedures (2019) starting from donors suspected to be infected with HBV or having a first-time specifically positive anti-HBc result analogue with Opinions 42 and 47 of the AK Blut [8, 9]

HBV look-back procedures 2019	Index donation			Retain sample			
	Reported	Of them vaccinated[1]	Of them ID-NAT positive	Retain sample negative	Not tested[2]	Retain sample positive: no product release	Missing data
NAT isolated positive	3	0	3	3	0	0	0
NAT, HBsAg positiv	1	0	1	1	0	0	0
NAT, Anti-HBc positive	1	0	1	1	0	0	0
NAT, HBsAg, Anti-HBc positive	2	0	2	2	0	0	0
HBsAg isolated positive	49	21	1	36	13	0	0
HBsAg, Anti-HBc positive	3	0	0	3	0	0	0
Anti-HBc isolated positive	450	0	1	391	48	1	10
Not specified	2	0	0	2	0	0	0
Total	**511**	**21**	**9**	**439**	**61**	**1**	**10**

[1] Positive information only in case of isolated HBsAg positive donations

[2] Previous donations outside the look-back period/collection of plasma for fractionation/products not released/confirmed vaccination/NUP missing

HBV look-back procedures due to a confirmed screening result revealed in only 9 cases a confirmation by a positive HBV ID-NAT. Besides 7 screening-NAT positive donations only one of 45 HBsAg isolated positive donations and one of the 450 Anti-HBc isolated positive donations were confirmed by a positive ID-NAT result. It is worth to mention that vaccination could be proven in 21 donors with isolated positive HBsAg. Only one retain sample of all donations within the HBV look-back period tested positive. It derived from the Anti-HBc isolated positive donation which HBV infection was confirmed by a positive HBV ID-NAT. Interestingly, in 28 of the 450 Anti-HBc isolated positive donations an Anti-HBs-Titer of ≥1,000 IU/l was reported.

4.12 Incorrect blood component transfused (IBCT)

The term IBCT refers to transfusions in which a blood component was issued 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.

In the reporting year 2019, 22 suspected cases of transfusion reactions due to IBCT of RBC, one due to PC, and 3 due to plasma were reported. IBCT were confirmed in all 26 cases.

Table 4.11 a summarises the IBCT 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 transfusion-related health impairment in the recipient and were reported as SAE (see also Section 4.13).

Table 4.12: IBCT with (IBCT-SAR) and IBCT without serious transfusion reactions (IBCT-SAE) in the recipient (2012–2019)

	2012	2013	2014	2015	2016	2017	2018	2019
IBCT-SAR	5	16	22	24	28	27	31	26
IBCT-SAE	2	12	29	34	41	55	40	40
Total	**7**	**28**	**51**	**58**	**69**	**82**	**71**	**66**

The reports on IBCT-SAR and the reports on IBCT-SAE, for which reporting is obligatory since 2012 with the 16 amendment of the AMG [3], have remained constant since 2016.

Deaths:

No deaths caused by IBCT were reported in 2019.

4.13 Serious adverse events (SAE)

Serious adverse events pursuant to Section 63i (6) AMG [3] include, above all, (i) recurrent adverse events, which give rise to the assumption of a faulty processing procedure or defective materials; (ii) critical events, also without the products being supplied; and (iii) IBCT without any serious reactions in the recipient [10].

The number of SAE reports has increased nearly six-fold, from 29 to 169 cases, since the 16th amendment of the AMG came into force in 2012 up to the reporting year 2019. During the same period, the total number of blood components transfused has decreased by 16% (see Table 1, page 32, and Figure 2, page 31). The SAE reports in 2019 originated from 14 establishments of medical care without associated BE, 7 reports from the AkdÄ, 4 from the Arzneimittelkommission der Deutschen Apotheker, and two reports from competent federal authorities; the remaining reports originated from BE.

Pursuant to Directive 2005/61/EC [5], adapted by the competent secretariat-general at the European Commission (DG Sante) in 2018, serious adverse events are categorised by the occurrence in the transfusion chain (collection, donor testing, processing, storage, distribution, and use) and by the cause of the adverse event (defective product, material, or equipment, or human error). With the amendment in 2018, the distinction was introduced as to whether an incorrect product selection or an incorrect issuing of blood

components to the patient, respectively, or whether an incorrect compatibility testing by cross-match occurred in the BE or in the health care facility (HF). If data were available in a sufficiently differentiated manner, the adverse events were recorded and presented accordingly. In 2019, no events were reported that were due to issuing or cross matching errors in the BE.

Table 4.13 a: Distribution of serious adverse events (SAE) by occurrence in the transfusion chain and by cause of the SAE (2019)

	Product defect	Equipment failure	Material defect	Human error	Other	Total
Donor selection	0	0	0	10	46[1]	56
Whole blood collection	0	1	0	0	1	2
Apheresis collection	0	10	0	0	0	10
Testing of donations	0	2	0	2	0	4
Processing	13	2	1	4	0	20
Storage	0	1	0	2	0	3
Distribution	0	2	0	8	0	10
Other	1	1	1	17	4	24
Component selection BE	0	0	0	1	0	1
Component selection HF	0	0	0	21[2]	0	21
Issue to patient BE	0	0	0	0	0	0
Issue to patient HF	0	0	0	17[2]	1	18
Cross match BE	0	0	0	0	0	0
Cross match HF	0	1[2]	0	0	1[2]	2
Total	**14**	**20**	**2**	**82**	**53**	**171**

[1] This refers to exclusion criteria that became known in retrospect (PDI = Post Donation Information)

[2] Events leading to IBCT without a serious transfusion reaction (IBCT-SAE)

Altogether 87 transfusions were recorded, for which a serious adverse event became known in retrospect without any serious adverse reaction in the recipient. These were mainly IBCT due to human error or due to donor exclusion criteria that became known in retrospect (see Table 4.13 b). The documented SAE with an incorrect blood component transfused were caused by 29 RBC, 6 PC, and 5 plasma transfusions.

Table 4.13 b: Transfusion of blood components that did not cause SAR in the recipient but for which a serious adverse event became known in retrospect (2019)

Components transfused, SAE known in retrospect Source of error in the transfusion chain	BE	HF	Causes
Apheresis collection (clot formation)	1	0	equipment failure
Testing of donations (test or documentation failure)	2	0	equipment failure, human error
Donor selection (infections, travel risks, diseases etc. known by PDI or follow up donation)	28	0	25 x other, 3 x human error
Processing (bacterial contamination)	9	0	product defect
Storage (storage of expired product)	0	1	human error
Distribution (documentation failure)	2	1	human error
Component selection BE (labelling error)	1	0	human error
Component selection HF (mix-up, documentation failure)	0	21	human error
Issue HF (mix-up, documentation failure)	0	14	13 x human error, 1 x other
Compatibility testing cross match (1 x missing control in emergency transfusion)	0	2	equipment failure, other
Other	1	4	1 x equipment failure, 4 x other
Total (87)	**44**	**43**	

BE: Occurrence of the SAE in the blood establishment
KE: Occurrence of the SAE in the health care facility

A detailed analysis of the error sources for SAE can only be performed in the institutions themselves. However, the presented data can be used for further training and error analysis in BE and HF performing blood transfusions.

4.14 Serious adverse donor reactions (donor SAR)

Since 2015, the number of annual reports of donor SAR have been in an approximately comparable range. In the reporting year 2019, the total number of reporting BE doubled after a reminder to report donor SAR: reports on donor SAR were available from 32 BE; 28 BE reported that they had not observed any donor SAR, and reports are missing from 9 BE. The numbers refer to parent companies and not to single donation centres.

Table 4.14 a: Development of the reporting figures for donor SAR from 2011 to 2019

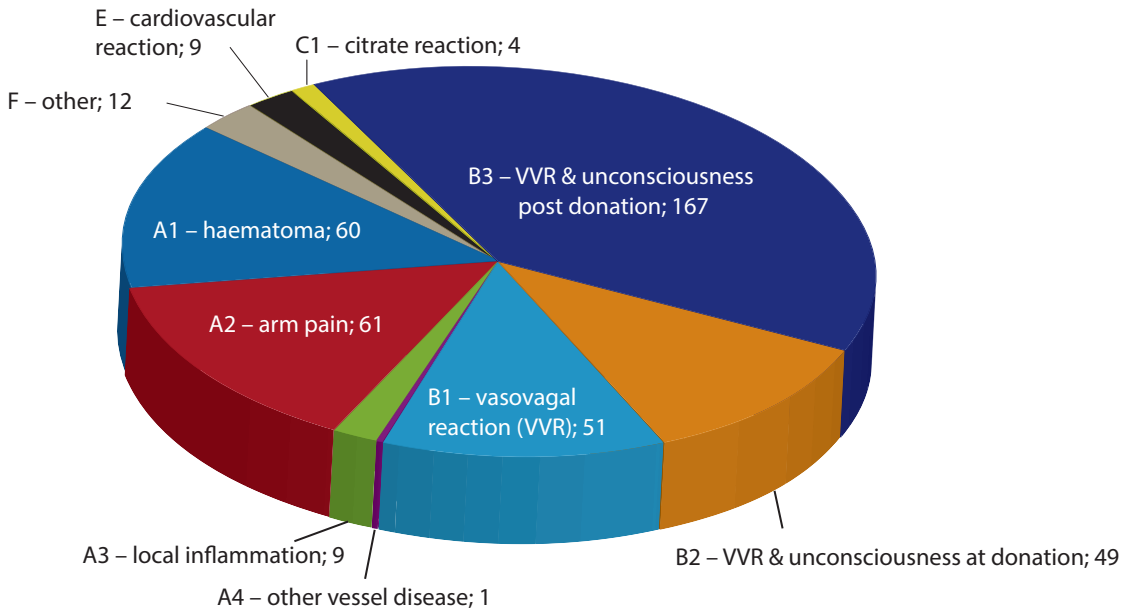
	2011	2012	2013	2014	2015	2016	2017	2018	2019
Number of confirmed donor SAR	1	3	13	24	531	459	527	444	423
Number of reporting BE	1	1	3	5	35	40	26	30	60

The table presents reports from 55 BE licenced for blood components for transfusion as well as 4 direct reports and 1 report via a competent federal authority from BE, exclusively collecting plasma for fractionation. To calculate the rate of donor SAR per type of donation, only the number of donations from the 60 reporting establishments was used. Platelet apheresis and multiple component apheresis were grouped together into cell apheresis for the evaluation. In 2019, there were no reports on donor SAR due to granulocyte apheresis or red blood cell apheresis. Of the 425 donor SAR reported, a causal connection could be established in 423 cases, 23 of them with possible connection to the donation. Trauma injuries due to 5 cases of vasovagal reactions (VVR) and one cardiovascular reaction prior to a WB donation are assigned to WB donation-caused donor SAR as they were assessed as psychologically related to the anticipated donation.

Similar to the definition by the ISBT [23], donor SAR were subdivided into A) local symptoms, related to the insertion of the needle, B) generalised symptoms, C) apheresis-specific complications, D) allergic reactions, E) cardio-vascular events, and F) other events. Figure 4.14a illustrates the shares of the respective type of reaction referred to all donor SAR in the reporting year. As in the previous years, VVR with and without loss of consciousness were the most frequently occurring donor SAR and concerned 63 percent of all the cases reported. Of the donor SAR reported in 2019, 31 percent accounted for local, phlebotomy related reactions, roughly 12 percent for VVR without, and 51 percent for VVR with loss of consciousness. Apheresis-specific, cardiovascular, and other reactions occurred very rarely with 1, 2, and 3 percent. Cardiovascular reactions with possible relation to the donation included 2 acute myocardial infarctions, of whom one donor died the day after a WB donation, and 6 cases of arrhythmia. Reactions indicated as "other" were 2 suspected stroke cases, 2 epileptic reactions, one pulmonary embolism, one D-dimer increase, one incontrollable circulatory collapse and unspecific pain reports, one due to prior drug consume. In these cases, SAR onset were most likely triggered by the donation while the basic causes were the donors' underlying physiological conditions. Only the D-Dimer increase obviously was due to an insufficient citrate administration during a plasmapheresis procedure.

As in the previous reports, allergic donor SAR were not reported.

Figure 4.14a: Distribution of the donor SAR in 2019



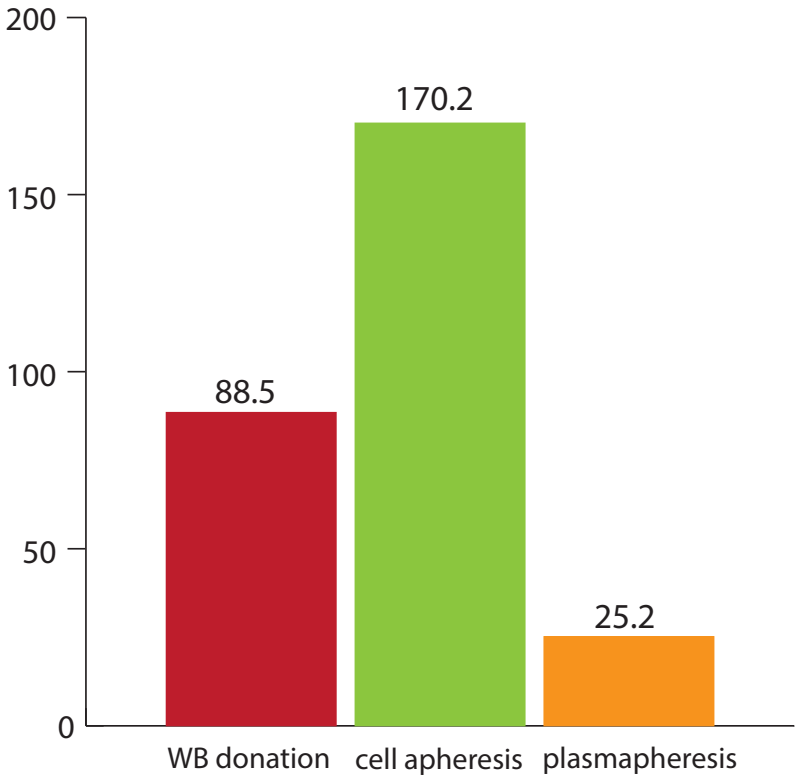
With regard to the type of donation, there were differences in the SAR distribution. While for whole blood collections and plasmapheresis, the portion of vasovagal reactions with loss of consciousness after the donation was predominant, vasovagal reactions without loss of consciousness accounted for the major part of reactions related to cell apheresis (Table 4.14 b).

Table 4.14 b: Assignment of serious donor reactions to types of donations (2019)

Donor SAR 2019	WB donation	Plasma-pheresis	Cell apheresis	w/o donation	Total
A1 – haematoma	49	6	5	0	**60**
A2 – arm pain	55	5	1	0	**61**
A3 – local inflammation	7	2	0	0	**9**
A4 – other vessel damage	0	0	1	0	**1**
B1 – vasovagal reaction (VVR)	27	7	12	5	**51**
B2 – VVR & faint during donation	32	15	2	0	**49**
B3 – VVR & faint after donation	147	17	3	0	**167**
C1 – citrate reaction	0	1	3	0	**4**
E – cardiovascular reaction	5	4	0	0	**9**
F – other	2	9	0	1	**12**
Total	**324**	**66**	**27**	**6**	**423**

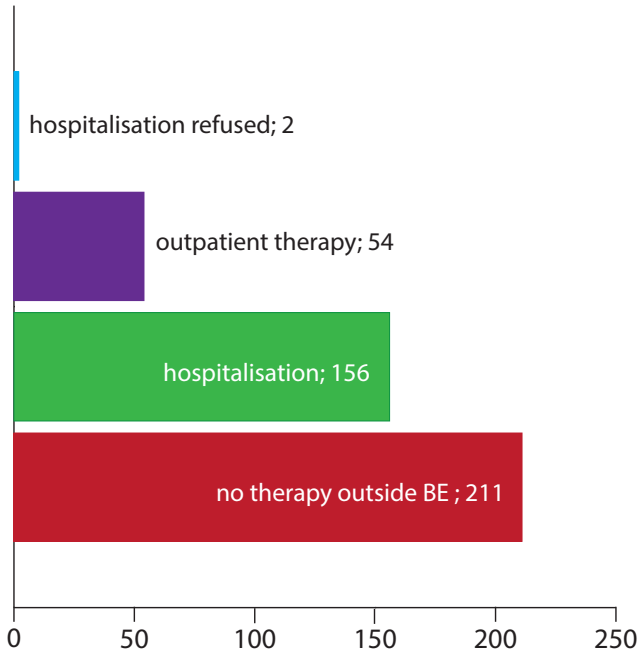
In accordance with earlier reports, the reporting rates of SAR referred to 10^6 donations differ between donation types (Figure 4.14b). The observation that donor SAR occur most frequently with cell apheresis, in line with reports from other countries [24, 25], was confirmed in 2019. For the first time, the major part of BE reported donor SAR or the absence of such, and calculations are therefore considered more representative than in previous years with lower overall donor SAR rates per donations collected.

Figure 4.14 b: Rates of confirmed donor SAR per million donations based on reports from 60 establishments. Cell apheresis comprise platelet apheresis and multicomponent apheresis



In-patient treatment was required in 156 out of 423 confirmed cases of donor SAR; 32 of these SAR occurred outside the BE. Out-patient treatment was required in 54 cases, 29 of them occurred outside the BE. In two cases, a recommended treatment was rejected. Of the 211 cases without medical treatment 14 SAR occurred outside the BE (Figure 4.14 c). Altogether, 75 SAR occurred after donors had already left the establishment and the majority (61) required medical treatment.

Figure 4.14 c: Donor SAR, share requiring medical treatment (2019)



Altogether, 37 repeat and 10 first-time donors suffered from injuries due to VVR caused falling (Table 4.14c). In 9 cases more than one injury was reported, e.g., twofold mandibular fracture and loss of 3 teeth.

Table 4.14 c: Injuries due to vasovagal reaction caused fallings (2019)

Type of reaction	Number of injuries in 47 cases of VVR caused falls
Lacerations requiring surgical dressing	22
Bruises to the head, contusion	21
Sprain, strain trauma, contusion	5
Bone fracture	11
Damage/loss of teeth	8
Total	**67**

// 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 actual incidence of serious adverse transfusion reactions.
- In 2019, SAR based on 10^6 transfused units were again most frequently reported for platelet concentrates.
- In the reporting year 2019, a total of 7 fatal cases with a confirmed causal relationship were reported. These included 5 haemolytic reactions following RBC transfusion, one bacterial infection after the transfusion of an apheresis derived platelet concentrate, and one TRALI caused by a pooled platelet concentrate.
- For the first time since 2004, transmissions of HCV were reported due to transfusion of contaminated blood components from a donor in a very early phase of infection. Nevertheless, with 3 reported HCV transmissions and about 110 million blood components transfused since 2000, blood transfusions in Germany can be considered very safe with respect to HCV, a fact underlined by findings of Fiedler et al. [26].
- With 1692 reports, the number of look-back procedures nearly doubled compared to the previous year, which mainly was due to a prominent increase of HEV cases.
- The reports of serious events (SAE) have been in a similar range for four years. The major share of these events was again due to incidents caused by human error, out of which nearly a third relate to incorrect blood components transfused (IBCT).
- In 2019, the highest rate of serious donor SAR, referred to the number of donations, was again reported for cell apheresis donations. For the first time reports from nearly all BE have been obtained. In one case of an acute myocardial infarction the donor died one day following donation; the exact cause of death could not be determined due to lack of information.

// 6. References //

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// 7. Annex with figures and tables //

Figure 1: Serious adverse transfusion reactions (SAR) confirmed annually (1997–2019)

TACO has been recorded systematically since 2009; as from 2009, only ATR of grade III and IV are included; FNHTR and TAD are newly included starting from 2012.

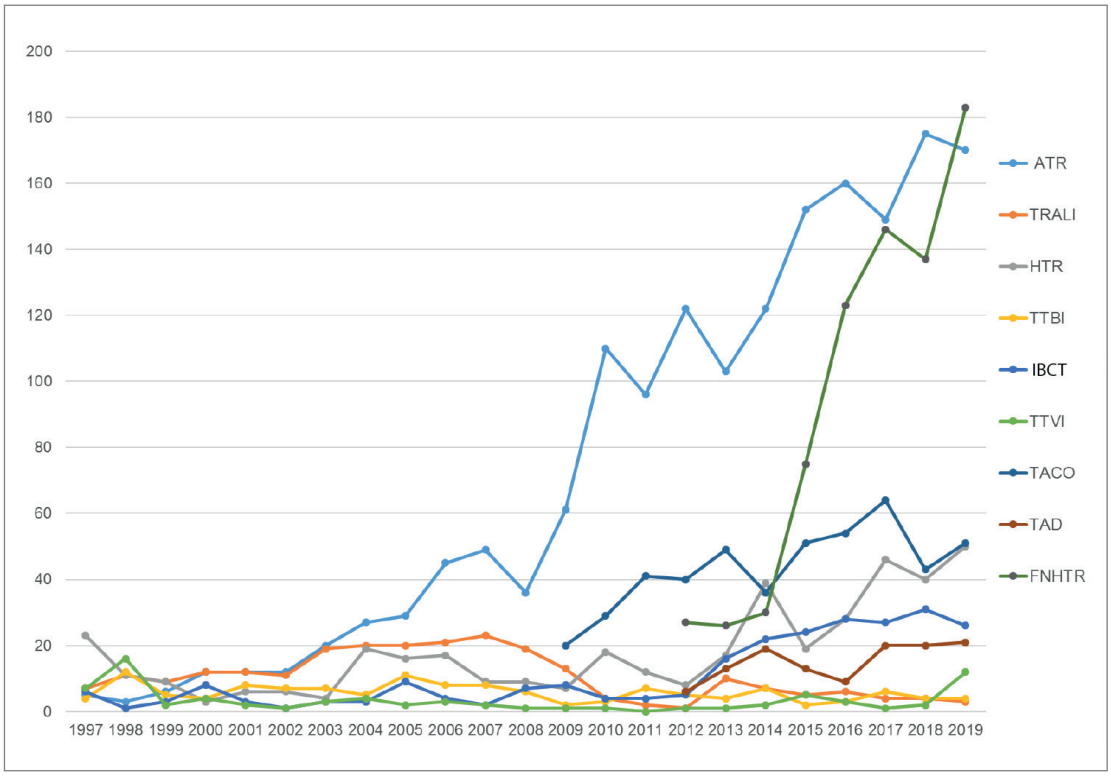

Figure 2: Percentage change in the consumption of blood components (2000–2019)

Blood component consumption in 2000 is equivalent to 100 percent. The consumption of PC increased steadily and reached 161% in 2011. Since then, PC consumption stagnates at this level with minor changes. On the other hand, RBC consumption decreased by 15%, and plasma consumption by 36%.

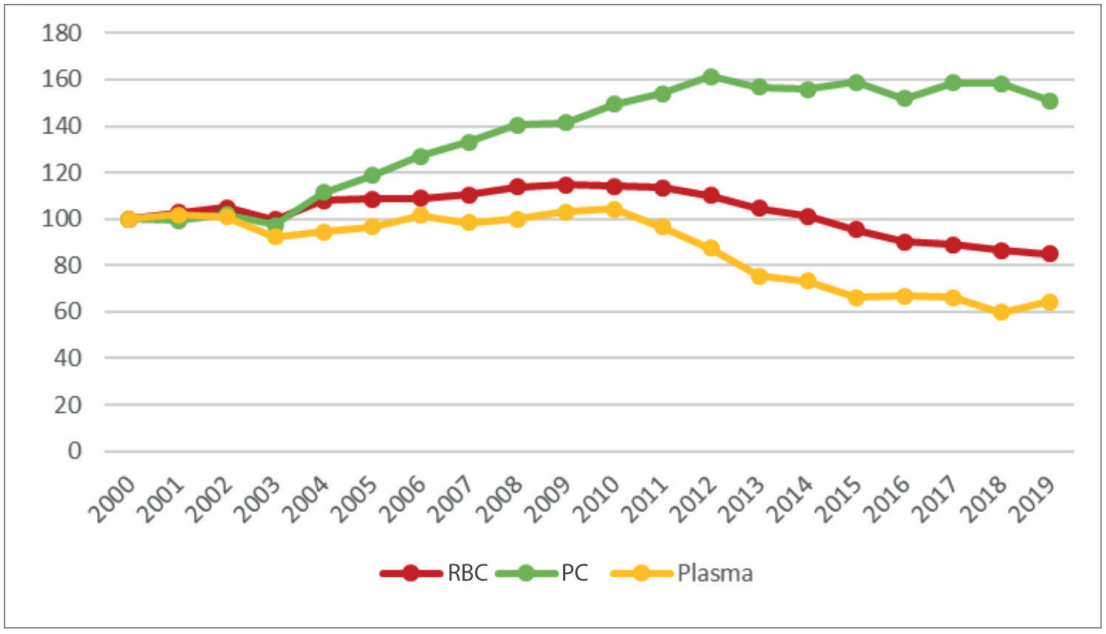

Table 1: Consumption of blood components in Germany (2000–2019)

Calculated from the data reported on the sale and loss at the user pursuant to Section 21 TFG (deadline 16th Sept. 2020, [6]). The consumption figures used for the calculation of TACO (data capture since 2009) and of FNHTR and TAD (data capture since 2009) are listed separately.

	2000–2003	2004–2007	2008–2011	2012–2015	2016	2017	2018	2019	2000–2019
RBC	16,051,470	17,173,130	17,964,825	16,202,065	3,548,124	3,506,417	3,410,524	3,341,592	81,197,695
PC	1,274,659	1,566,873	1,870,911	2,022,453	485,659	506,267	505,312	482,360	8,713,624
Plasma	4,515,718	4,469,498	4,616,104	3,453,264	764,399	751,551	683,303	735,310	19,998,488

TACO	2009-2019	TAD, FNHTR	2012-2019
RBC	43,491,106	RBC	30,008,962
PC	5,423,812	PC	4,002,081
Plasma	9,869,626	Plasma	6,397,168

Table 2: Total number of suspected adverse transfusion reactions reported, confirmed reactions and portion of associated deaths (1997–2019)

Serious adverse transfusion reactions (SAR) 1997–2019	Reported suspected cases	Confirmed cases	Fatal cases
Acute allergic/anaphylactic transfusion reactions (ATR)[1]	3,689	1,676	34
Transfusion-related acute lung injury (TRALI)[2]	1,273	243	23
Haemolytic transfusion reaction (HTR)	767	416	22
Transfusion transmitted bacterial infection (TTBI)	573	132	19
Incorrect blood component transfused (IBCT)	247	245	16
Transfusion transmitted viral infection (TTVI)[3]	3,665	76	3
Post-transfusional purpura (PTP)	30	18	0
Transfusion-associated Graft versus Host Disease (TA-GvHD)	4	3	1
Transfusion-associated circulatory overload (TACO)[4]	521	478	15
Transfusion acssociated dyspnoe (TAD)[5]	157	124	0
Febrile non-hemolytic transfusion reactions (FNHTR)[5]	807	733	0
Other SAR	205	43	0
Total	**11,938**	**4,187**	**133**

[1] As from 2009, only ATR Grades III and IV were included in the assessment

[2] As from 2013, only likely/probable and certain TRALI were included as confirmed

[3] Includes reports on HCV, HIV, HBV, HAV, HEV

[4] TACO systematically captured as from 2009

[5] TAD and FNHTR systematically captured only as from 2012

Table 3: Confirmed reports of suspected serious allergic/anaphylactic transfusion reactions Grades III and IV, associated deaths, and rates of confirmed reactions referring to 10^6 units transfused (2000–2019)

Since 2009, only confirmed ATR Grades III and IV are used as the basis for calculating the rates of ATR per million units transfused.

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2000–2019
Confirmed serious allergic/anaphylactic transfusion reactions after administration of						
RBC	27	99	160	277	368	931
PC	12	20	49	108	167	356
Plasma	9	16	54	57	70	206
Combined	8	15	40	57	49	169
Total	**56**	**150**	**303**	**499**	**654**	**1,662**
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	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	2016–2019	2000–2019
	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	26.56	11.47
PC	9.41	12.76	26.19	53.40	84.36	40.86
Plasma	1.99	3.58	11.70	16.51	23.79	10.30

Table 4: Confirmed reports of suspected serious TACO, associated deaths, and rates of confirmed reactions referring to 10^6 units transfused (2009–2019)

	2009–2011	2012–2015	2016–2019	2009–2019
RBC	57	146	179	382
PC	6	8	9	23
Plasma	6	6	7	19
Combined	22	16	17	55
Total	**91**	**176**	**212**	**479**
Therefrom fatal outcomes				
Total	5	6	3	14

Rates of confirmed TACO for these periods				
	2009–2011	2012–2015	2016–2019	2009–2019
	TACO per 10^6 units	TACO per 10^6 units	TACO per 10^6 units	TACO per 10^6 units
RBC	4.23	9.01	12.96	8.78
PC	4.22	3.96	4.55	4.24
Plasma	1.73	1.74	2.38	1.93

Table 5: Confirmed reports of suspected serious TRALI, associated deaths, and rates of TRALI referring to 10^6 units transfused (2000–2019)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2000–2019
TRALI, donor examination for HLA-/HNA-Ab positive in the case of						
RBC donors	5	9	5	13	7	39
PC donors	2	3	5	6	7*	23*
Plasma donors	17	48	18	5	3	91
Total	**24**	**60**	**28**	**24**	**17***	**153***
TRALI with fatal courses following transfusion of						
RBC	1	2	0	0	**1**	**4**
PC	0	0	1	1	**1**	**3**
Plasma	1	10	5	0	**0**	**16**
Total	**2**	**12**	**6**	**1**	**2**	**23**

Rates of confirmed TRALI for the periods						
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2000–2019
	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	0.51	0.48
PC	1.57	1.91	2.67	2.97	3.54	2.64
Plasma	3.76	10.74	3.90	1.45	0.68	4.50

* Summarizing number includes one P-PC induced non-immunogenic TRALI case.

Specific donor selection and donor screening, respectively applies as per 1 Sept. 2009 [11], if plasma for transfusion is prepared from a blood or plasma donation.

Table 6: Confirmed reports of suspected cases of transfusion associated dyspnoea (TAD) and rates of TAD, referring to 10^6 units transfused (2012–2019)

TAD	2012	2013	2014	2015	2016	2017	2018	2019	2012–2019
TAD after administration of									
RBC	3	9	17	9	9	16	13	16	92
PC	1	2	0	2	1	3	6	3	18
Plasma	0	1	0	1	1	1	0	1	5
Combined transfusion	2	1	2	1	1	0	1	1	9
Total	**6**	**13**	**19**	**13**	**12**	**20**	**20**	**21**	**124**
Rates of confirmed TAD per 10^6 units									
RBC	0.69	2.18	4.27	2.40	2.54	4.56	3.81	4.79	**3.07**
PC	1.94	3.99	0.00	3.94	2.06	5.93	11.87	6.22	**4.50**
Plasma	0.00	1.16	0.00	1.32	1.31	1.32	0.00	1.36	**0.78**

Table 7: Confirmed reports of suspected serious haemolytic transfusion reactions (HTR), associated deaths and rates of HTR, referring to 10^6 units transfused (2000–2019)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2000–2019
Haemolytic transfusion reactions after administration of						
RBC	11	50	41	71	152	**325**
PC	2	4	4	3	1	**14**
Combined transfusion	6	7	1	9	10	**33**
Plasma	0	0	0	0	1	**1**
Total	**19**	**61**	**46**	**83**	**164**	**373**
Therefrom delayed haemolytic transfusion reactions and HTR with evidence of Ab						
Delayed HTR	3	6	21	14	55	**99**
Irregular RBC-Ab	2	4	28	14	97	**145**
Therefrom haemolytic transfusion reactions with fatal courses after administration of						
RBC	0	3	2	0	9	**14**
Combined transfusion	0	1	0	0	0	**1**
Total	**0**	**4**	**2**	**0**	**9**	**15**

Rates of confirmed haemolytic transfusion reactions for the periods						
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2000–2019
	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	11.01	4.00
PC	1.57	2.55	2.14	1.48	0.51	1.61
Plasma					0.34	0.05

Table 8: Confirmed reports of suspected serious febrile-non-haemolytic transfusion reactions (FNHTR) and rates of FNHTR, referring to 10^6 units transfused (2012–2019)

FNHTR	2012	2013	2014	2015	2016	2017	2018	2019	2012-2019
FNHTR after administration of									
RBC	11	19	22	61	108	125	121	151	618
PC	1	4	5	7	14	14	12	23	80
Plasma	0	0	0	2	1	0	0	0	3
Combined transfusion	1	3	3	5	0	7	4	0	32
Total	**13**	**26**	**30**	**75**	**123**	**146**	**137**	**183**	**733**
Rates of confirmed FNHTR per 10^6 units									
RBC	2.53	4.61	5.52	16.25	30.44	35.64	35.48	45.19	20.59
PC	1.94	7.99	10.04	13.78	28.83	27.65	23.75	47.68	19.99
Plasma	0.00	0.00	0.00	2.64	1.31	0.00	0.00	0.00	0.47

Table 9: Confirmed reports of suspected transfusion-transmitted bacterial infections (TTBI), associated deaths, and rates of TTBI referring to 10^6 units transfused (2000–2019)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2000–2019
Bacterial infections after administration of						
RBC	7	13	7	8	4	39
Pool-PC	8	9	5	1	6	29
Apheresis PC	11	9	6	9	7	42
Plasma	0	1	0	0	0	1
Total	**26**	**32**	**18**	**18**	**17**	**111**
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	3	8
Plasma	0	0	0	0	0	0
Total	**3**	**3**	**2**	**1**	**5**	**14**

Rates of confirmed transfusion-transmitted bacterial infections for the periods of						
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2000–2019
	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	0.29	0.48
PC	14.91	11.49	5.88	4.94	6.57	8.15
Plasma	0.00	0.22	0.00	0.00	0.00	0.05

Table 10: Results of microbiological examinations of confirmed cases of TTBI (1997–2019)

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	Plamsa	Total	Non-fatal	Fatal	RBC	PC
Pathogens with low (human) pathogenicity								
Staphylococcus *capitis, epidermidis, hominis, saprophyticus, warneri and 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 lwoffii, Pseudomonas aeruginosa* *Enterococcus faecalis*	31	50	3	84	66	18	4	14
Total	**49**	**78**	**5**	**132**	**113**	**19**	**4**	**15**

Table 11: Confirmed reports of suspected transfusion-transmitted viral infections (TTVI) and rates of TTVI referring to 10^6 units transfused (2000–2019)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2000–2019
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	**1**	**2**
PC	0	0	0	0	**1**	**1**
Plasma	0	0	0	0	**0**	**0**
Total	**0**	**1**	**0**	**0**	**2**	**3**
HBV infectins 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	**5**	**8**
Pool-PC				1	**4**	**5**
Apheresis PC				3	**4**	**7**
Plasma				0	**3**	**3**
Total				7	**16**	**23**

Rates of confirmed transfusion-transmitted HBV, HCV and HIV infections for the periods						
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2000–2019
	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	0.07	0.25
PC	1.57	0.00	0.53	0.49	0.51	0.57
Plasma	0.44	0.22	0.00	0.00	0.00	0.00

Rates of confirmed transfusion-transmitted HEV infections for the periods				
		2012–2015	2016–2019	2012–2019
		HEV per 10^6 units	HEV per 10^6 units	HEV per 10^6 units
RBC		0.19	0.36	0.27
PC		1.98	4.04	3.00
Plasma		0.00	1.52	0.31

Table 12: Reports of incorrect blood components transfused (IBCT) involving serious adverse transfusion reactions (IBCT-SAR), as well as reports of IBCT prevented or IBCT without any serious adverse reactions (IBCT-SAE) in the recipient (2000–2019)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2000–2019
SAR RBC	15	18	23	63	101	220
SAR PC			0	1	3	4
SAR Plasma			0	3	8	11
SAR Total	**15**	**18**	**23**	**67**	**112**	**235**
Therefrom fatal (administration of RBC)	0	1	4	5	3	13
SAE RBC			6	66	130	202
SAE PC			1	4	24	29
SAE Plasma			0	7	23	30
SAE Total			**7**	**77**	**177**	**261**
IBCT (SAE and SAR) Total	**15**	**18**	**30**	**144**	**289**	**496**

Notifiable for SAE (near IBCT and/or actual IBCT without SAR) since 2012.

Up to 2014, reports of IBCT with serious reactions (SAR) were indicated as ABO incompatibilities.

Rates of confirmed IBCT with serious adverse reactions						
	2000–2003	2004–2007	2008–2011	2012–2015	2016-2019	2000-2019
	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	7.31	2.71
PC	0.00	0.00	0.00	0.49	1.52	0.46
Plasma	0.00	0.00	0.00	0.87	2.72	0.55

Table 13: Rates of confirmed serious adverse transfusion reactions reported summarised for the period of 2000–2019, each referring to 10^6 transfused units of RBC, PC, and plasma, respectively

SAR rates per 10^6 transfused units												
	units transfused 2000-2019	ATR	HTR	TRALI	TTBI	TTVI[1]	IBCT	units transfused 2009-2019[2]	TACO[2]	units transfused 2012-2019[3]	FNHTR[3]	TAD[3]
RBC	81,197,695	11.47	4.00	0.48	0.48	0.34	2.71	43,491,106	8.78	30,008,962	20.59	3.07
PC	8,713,624	40.86	1.61	2.64	8.15	1.95	0.46	5,423,812	4.24	4,002,081	19.99	4.50
Plasma	19,998,488	10.30	0.05	4.50	0.05	0.25	0.55	9,869,626	1.93	6,397,168	0.47	0.78

[1] TTVI: HIV, HBV, HCV, HEV

TACO[2] is recorded systematically only as from 2009, thus, the rates refer to TACO as a share of the consumption of transfused units from 2009–2019.

FNHTR[3] and TAD[3] were recorded systematically only as from 2012, thus, the rates refer to TAD and FNHTR as a share of the consumption of transfused units from 2012–2019.

Table 14: Imputability levels to assess serious adverse transfusion reactions [5]

Connection with transfusions	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	The 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 of the relationship.

Table 15: Definition of adverse transfusion reactions according to the Haemovigilance Working Party of the International Society of Blood Transfusion (ISBT) [27]

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-related acute lung injury (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).

Heamolytic 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 >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, 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; evidence of the bacterium and the same bacterial strain in the transfused blood product and/or the recipient.

Transfusion-transmitted viral infection (TTVI):

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

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, 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, which must be performed by the pharmaceutical company (Section 63i [6] AMG).

Transfusion-associated dyspnoea (TAD):

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.

Serious febrile non-haemolytic transfusion reaction:

Fever ≥39°C and a change of ≥2°C from pre-transfusion value, accompanied by chills, rigors, possibly also by headache and nausea and which occurs during or within 4 hours following transfusion. Exclusion of other causes such as HTR, TBBI or underlying disease.