Federal Institute for Vaccines
and Biomedicines

Paul-Ehrlich-Institut

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

2018

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

// Publication details //

Published by

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Please quote this report as follows:
Funk MB, Heiden M, Müller S, et al. 2020. Haemovigilance Report of the Paul-Ehrlich-Institut 2018: Assessment of the Reports of Serious Adverse Transfusion Reactions and Events pursuant to Section 63i AMG (German Medicines Act).
Available from: www.pei.de/haemovigilance-report

You can subscribe to presse@pei.de if you wish to receive this report as a pdf version.

ISSN (Internet) 2192-2314

Title image: www.shutterstock.com, Stock vector graphics No.: 349890737

// Contents //

// 1. Introduction //

The haemovigilance report 2018 of the Paul-Ehrlich-Institut (PEI) summarises all spontaneous reports from January to December 2018 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 2000–2017 [1]. The assessment algorithm introduced in the haemovigilance report 2013–2014 [2] for transfusion-related acute lung injury (TRALI) was maintained, thus permitting a comparison of the data published ever since.

For donor-initiated look-back procedures that did not lead to transfusion-transmitted viral infections (TTVI), the shares of confirmed infections and the test results of the retain samples from previous donations are presented. The confirmed cases of suspected HBV infection reports are broken down by test procedures. A note on the respective vaccination status is provided.

The report contains the available information on the respective bacterial strains involved for all the transfusion-transmitted bacterial infections (TTBI) rated as possible or confirmed.

As has been common practice since 2015, reports received in 2018 on donor-related SAR and SAE that occurred in the transfusion chain are presented in detail. Furthermore, a distinction is made between incorrect blood components transfused (IBCT) with SAR (IBCT-SAR) and those without transfusion reactions (IBCT-SAE).

In the case of spontaneous reports received in 2018, it has become clear that again many SAR are not sufficiently described, as has already been emphasised in previous reports. This again made it difficult or even impossible to accurately evaluate and assign the data reported in many cases. The submission of a detailed documentation (e.g. an anonymised transfer report/epicrisis) is therefore requested in addition to the minimum information explicitly required in Section 14 Transfusion Act (Transfusionsgesetz [3]), 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 12). The reports pursuant to Section 63i AMG [4] 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 pursuant to Directive 2005/61/EC [5] [6].

// 2. Abbreviations //

Ab	Antibody
Ag	Antigen
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)
Anti-HBc	Antibodies against hepatitis B-core antigen
A-PC	Apheresis platelet concentrate(s)
ATR	Acute allergic/anaphylactic transfusion reaction(s)
BE	Blood establishment(s)
BNP	Brain natriuretic peptide or B-type 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
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 12 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 a TRALI, a transfusion-transmitted bacterial infection (TTBI), a transfusion-transmitted viral infection (TTVI), or an incorrect blood component transfused (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 (TACO), 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, 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 Transfusion Act (Transfusionsgesetz, TFG) [7] and presented as share per million transfused units. Donor SAR reported by the blood establishments (BE) as 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 reports of SAE and SAR required from the blood establishments (BE) is laid down in Section 63i, German Medicines Act (Arzneimittelgesetz, AMG) [4], and the legal basis for those required from treating physicians is laid down in Sections 14 and 16, Transfusion Act (TFG) [3]. For this type of reporting, the PEI provides standardised forms on its website [8]. 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 records all essential information on the transfusion, such as time and type of the blood component(s) administered and course of the transfusion reaction. Data required on the person receiving the transfusion include data of birth, gender, 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 the donations. In addition, the BE shall report the results of lab tests performed and the initiation of a look-back procedure, if applicable [3, 9-11]. In the event of a donor SAR, the type of donation and donor reaction shall be reported, too. Incorrect blood components transfused (IBCT) without a transfusion reaction and 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 [4] (16th amendment of the AMG). A reporting obligation pursuant to Section 16 (2) TFG [3, 8, 11] 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 ad events, the PEI only sporadically receives information on non-serious incidents. These are, therefore, 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 were 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 15 January 2019) [7].

The first part of the haemavigilance report presents the data captured in the reporting period 2018; 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)

Out of the 612 suspected cases of serious adverse transfusion reactions reported in 2018, a causal connection with the administration of blood components was confirmed in 395 of the cases (for definitions, see table 13). Thus, the number of the spontaneous reports on transfusion reactions captured since 2012 as well as the cases assessed as confirmed has increased notably compared with the previous year (cf. Table 4.1a). On a positive note, the number of cases with a lethal outcome due to a transfusion has at the same time decreased to the lowest level since 2012.

Table 4.1 a: Reports of suspected, confirmed and fatal cases due to a transfusion (2012–2018)

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
2018	612	395	2

Table 4.1 b: Overview of reported cases of suspected serious adverse transfusion reactions (SAR), confirmed SAR, and deaths due to a transfusion reported in 2018

	SAR	Reported	Confirmed	Fatal cases thereof
1	ATR Grade I/II	95	90	0
2	ATR Grade III/IV	191	175	0
3	TRALI	55	4	0
4	HTR	63	40	1
5	TTBI	41	4	1
6	IBCT	31	31	0
7	HCV, HIV, HBV	41	0	0
8	HEV	8	2	0
9	Other TTVI	3	0	0
10	TACO	52	43	0
11	Other	32	6	0
	Total	**612**	**395**	**2**

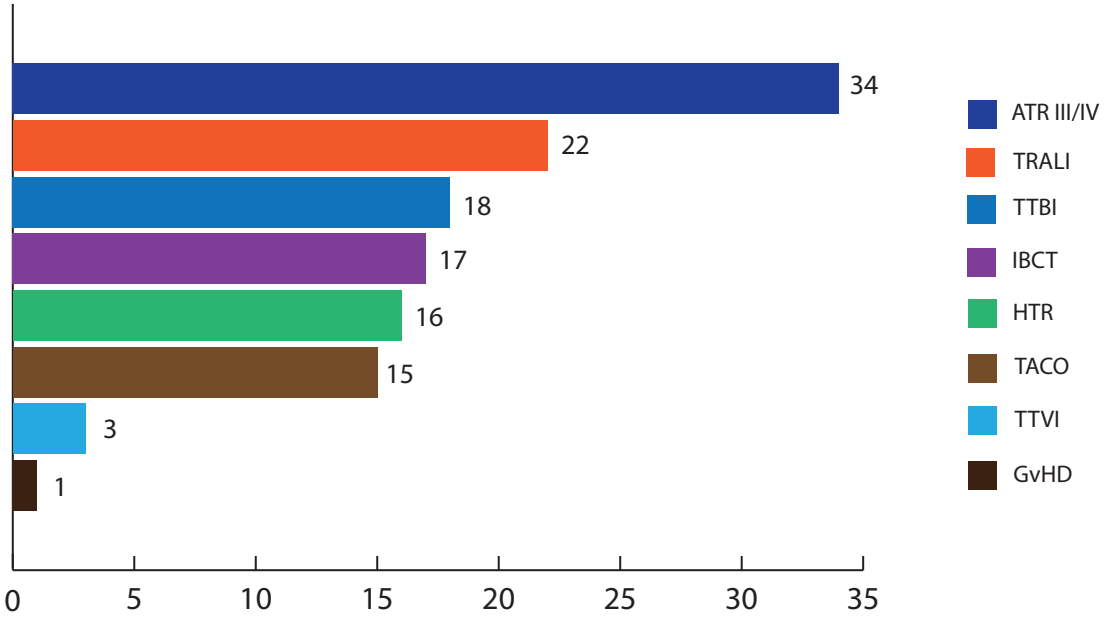
As in previous haemovigilance reports, transfusion-associated dyspnoea (TAD) and febrile non-haemolytic transfusion reactions (FNHTR) were not included in the table for reasons of consistency. In the next haemovigilance report for 2019, these two reactions will be included in the overview table. In 2018, 26 suspected cases of TAD and 143 cases of FHNTR were reported, out of which 20 and 137, respectively, were assessed as confirmed. The category "other TTVI" groups reports of suspected cases of one transmission of each hepatitis A virus (HAV), human cytomegalovirus (CMV), and parvovirus B19.

Deaths:

The causes of the two transfusion-associated fatal cases reported in 2018 were one confirmed bacterial contamination of a PC and one HTR assessed as likely/probable. The post-mortem report required to conclusively assess the HTR case was denied by the concerned prosecutor.

Thus, 126 fatal cases have been attributed to the administration of blood components during the observation period of 22 years (1997–2018). 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 2 cases after the introduction of the requirement designed to reduce the risk of TRALI by specific donor selections and/or donor testing [12]. The total fatal cases further include 18 caused by transmission of bacterial infections, 17 due to haemolytic transfusion reactions, 16 due to incorrect blood components transfused, and 15 due to circulatory overload. In addition, three fatal cases have been reported after viral infections and one fatal case after a graft-versus-host-disease (GvHD) (see Figure 4.1, Annex, Table 2).

Figure 4.1: Number of serious adverse transfusion reactions with fatal outcome (1997–2018)



4.2 Acute allergic/anaphylactic transfusion reactions (ATR)

Since 2009, only confirmed ATR Grades III and IV are used as the basis for calculating the SAR rates out of the total number of serious acute allergic/anaphylactic reactions reported. The distinction between allergic transfusion reactions Grades I and II from serious anaphylactic transfusion reactions Grades III and IV is made according to Ring and Messmer [13].

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 Grades III or IV, classified as confirmed, the causality assessment 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 Annex, Tables 3 and 11).

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 (2018) as well as the SAR rates per 10^6 transfusion units

ATR	ATR I and II	ATR III and IV	Rates ATR III and IV per 10^6 units
Reported cases	95	191	
Confirmed cases following administration of			
RBC	62	97	28,44
PC	19	47	93,01
Plasma	5	17	24,88
Combined products	4	14	
Total confirmed cases	**90**	**175**	

Deaths:

No cases of ATR with fatal course were reported in 2018.

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 [14], 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. Another diagnostic parameter, which has been established for some time, is the brain natriuretic peptide (BNP) value, especially for a distinction from

non-immunogenic TRALI. A strong increase in BNP levels during the course of the observation can support the TACO diagnosis.

Table 4.3: Number of suspected cases reported for transfusion-associated circulatory overload (TACO) as well as confirmed cases after the administration of RBC, PC, plasma, or combined administration (2018)

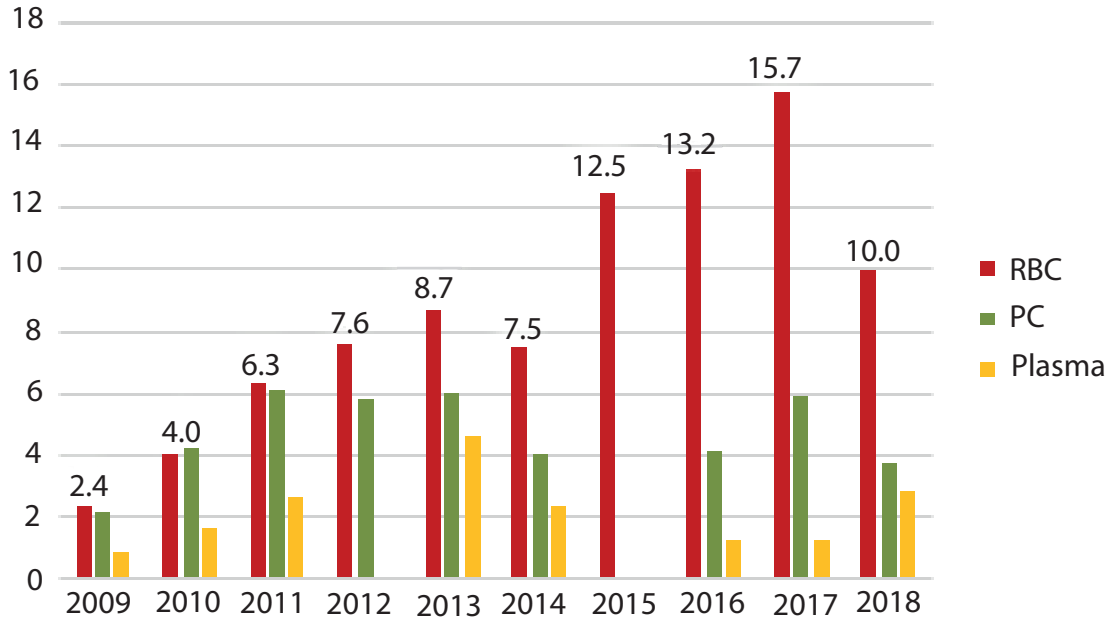
TACO	2018	Rate of TACO per 10^6 units
Reported cases	52	
Confirmed cases following administration of		
RBC	34	9,97
PC	2	3,69
Plasma	2	2,93
Combined administration	5	
Total of confirmed cases	**43**	

Since the systematic capture of TACO has been started in 2009, the number of suspected cases as well as of confirmed cases rose steadily up to 2017. In 2018, the rates of confirmed cases were at the level of 2013 (Fig. 4.3).

Deaths:

No cases of TACO with fatal outcome were reported in 2018.

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) up to 2018



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 13). Immunogenic TRALI is confirmed by evidence of specific antibodies (Ab) in the donor and the corresponding antigen (Ag) in the recipient.

The algorithm already described [2] 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, this algorithm is currently reassessed, in particular with regard to a distinction between immunogenic and non-immunogenic TRALI [15]. Unfortunately, testing of the recipients for corresponding antigens is performed very rarely in practice, and is almost 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 based on a revised algorithm. 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 [16]. For a conclusive distinction of TRALI from closely related symptoms, however, further findings from medical research and 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 [17].

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 BNP levels can be used as a diagnostic decision criterion.

In 2018, the PEI received altogether 55 suspected cases of TRALI of which four could be confirmed as immunogenic TRALI (see Tables 4.4 a and b). The blood components affected derived in all cases from whole blood donations, out of which three originated from donors with pregnancies in their history. HLA Classes I, II or HNA-Ab could be detected in the donations, and in three of the recipients also the corresponding antigens.

BNP values were not available in any of the cases. In one case with evidence of HNA-3a antibodies and the corresponding antigen, the female patient died about 1 hour following the transfusion of the PC. Because of the severity of the pre-existing diseases, the patient's poor general state and a pre-existing pneumonia prior to the transfusion, the development of TRALI was not considered as the cause of death.

The cases confirmed exclusively for the administration of RBC and PC on the one hand show the effectiveness of a restriction from 2009 preventing TRALI caused by plasma from women with pregnancies in their history. On the other hand, it became apparent that immunogenic TRALI can also be triggered by PC with a relatively low ratio of plasma. This suggests that only donations from women without pregnancies in their history or a negative test result for TRALI-inducing antibodies should be used for the preparation of PC.

Table 4.4 a: Number of suspected cases of transfusion-related acute lung injury (TRALI) and confirmed cases following the administration of RBC and PC (2018)

TRALI	2018	Rate of TRALI per 10^6 units
Number of reported cases	55	
Confirmed cases following administration of		
RBC	1	0.29
PC	3	5.94
Plasma	0	0
Combined administration	0	
Total of confirmed cases	**4**	

Table 4.4 b: Listing of confirmed cases of TRALI in 2018

TRALI	Donor			Recipient	
Evaluation	**Antibody (Ab)**	**Blood component**	**Sex**	**Corresponding antigen**	**Underlying disease**
Certain	WB donor HLA-Ab class II positive	RBC	Male, without immunisation in the history	HLA-II DPB1 positive	Anaemia with HUS and acute kidney failure postpartum, stress-related cardiomyopathy
Likely/ probable	WB donor HLA-Ab class II positive	PC	Female, positive history of pregnancy	No data	Stomach cancer, pleural and bone metastasis
Certain	WB donor HLA-Ab class I positive, various specificities	PC	Female, positive history of pregnancy	Yes, HLA-A24, A68, -B49	AML, condition after stroke, kidney insufficiency, bladder cancer, stent implant, infected gout topos
Certain	WB donor HNA-3a-Ab positive	PC	Female, positive history of pregnancy	HNA-3a positive	AML relapse, acute kidney failure, pneumonia

AML=Acute myeloid leukaemia

Deaths:

No confirmed deaths due to TRALI occurred in 2018.

4.5 Transfusion-associated dyspnoea (TAD)

For 2018, 26 suspected cases of transfusion-associated dyspnoea were reported as serious adverse transfusion reactions; in 20 cases, a connection with the transfusion was confirmed.

Cases of dyspnoea have not been assigned to the serious adverse transfusion reactions in PEI haemovigilance reports up to now. Documenting the frequency of reports will be continued.

Table 4.5: Number of suspected cases of dyspnoea and of confirmed cases after administration of RBC, PC, plasma, or combined administration (2018)

Dyspnoea	2018	Rate dyspnoea per 10^6 units
Reported cases	26	
Confirmed cases following administration of		
RBC	13	3.81
PC	6	11.87
Plasma	0	0
Combined administration	1	
Total of confirmed cases	**20**	

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 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.

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 2018, the largely thoroughly performed documentation of HTR provided evidence of irregular red blood cell Ab in 21 (53%) of the total of 40 confirmed cases, out of which two thirds were due to rhesus antigen, as well as Jk (b) and Fy (a) incompatibilities. Apart from 3 cases (1 PC administration, 2 combined administrations), all confirmed HTR were caused by the administration of RBC. Just above one third of all confirmed cases (15) were delayed haemolytic reactions. For 6 reports (15%), information on the time point of the transfusion or the beginning of the reaction were missing, so that the cases could not be assessed. Thus, the data on delayed HTR are again of the same order of magnitude as described in other countries [18].

Table 4.6 a: Number of reports of suspected cases of haemolytic transfusion reactions (HTR), confirmed cases, and deaths after administration of RBC and PC (2018)

HTR	2018	Rate of HTR per 10^6 units
Reported cases	63	
Confirmed cases following administration of		
RBC	37	10.85
PC	1	1.98
Plasma	0	0
Combined administration	2	
Fatal cases (RBC)	1	
Total of confirmed cases	**40**	

Table 4.6 b: Confirmed HTR by type of reaction and antibody detection

HTR 2018	Acute HTR	Delayed HTR	Unknown*	Totals
ABO Ab (A1)	0	0	1	1
Other Allo Ab	9	11 (10 RBC, 1 combined administration)	1	21
Auto Ab/non-specific Ab	5	1	1	7
Non-immunological	4	3	0	7
Not specified	1	0	3 (2 RBC, 1 combined administration)	4
All HTR	**19 (18 RBC, 1 PC)**	**15 (14 EK, 1 combined administration)**	**6**	**40**

* Data from the timepoint of transfusion are missing.

Deaths:

In the case of an acute HTR with AnWj antibodies and a fatal outcome, a complex serological situation was presented. Because the autopsy result was not available, the connection between the reaction and the transfusion could only be assessed as likely/probable. There are only few described cases of an AnWj-associated HTR in the literature [19]. AnWj is one of the highly prevalent red blood cell antigens. HTR caused by anti-AnWj antibodies are thus very rare, but usually severe.

4.7 Other transfusion reactions

In the reporting period, the PEI received 32 suspected cases of transfusion reactions the cause of which was predominantly due to the underlying disease. In 6 cases, the connection with the transfusion was assessed as possible. These referred to cases of lung artery embolism with atrial thrombus, lung embolism with atrial thrombosis, hypertensive crisis, cardio-vascular failure, coronary heart disease with exertional dyspnoea, and D1 stenosis.

4.8 Transfusion-transmitted bacterial infections (TTBI)

The order of magnitude for the number of confirmed bacterial infections due to a transfusion with RBC or PC has been more or less constant for about 10 years. Based on the reporting data available, the connection with the transfusion could be assessed as likely/probable or certain, and thus as confirmed in the case of 4 out of the 41 suspected cases reported. In 2018, one RBC and three PC (see Table 4.8 a) were the source of contamination of the transmissions confirmed. TTBI are observed most frequently in the case of transfusions with PC due to its storage temperatures, which favour bacterial growth. Since 2000, only one case of bacterial transmission occurred that was caused by transfusion of plasma.

Table 4.8 a: Number of suspected cases of transfusion-transmitted infections (TTBI), and confirmed cases after the administration of RBC and PC (2018)

TTBI	2018	Rate of TTBI per 10^6 units
Reported cases	41	
Therefrom: cases confirmed following administration of		
RBC	1	0.29
PC	3	5.94
Fatal cases therefrom (PC)	1	
Total of confirmed cases	**4**	

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. In five cases, an assessment was not possible:

Case 1: No data on the microbiological examination of the patient's blood were available from a patient who developed signs of septic shock during the transfusion of 650 ml cell saver blood and one unit RBC; in the absence of residual material to be tested the transfused RBC could not be examined either.

Case 2: No pathogen was detected in the patient's blood, and since no material was available for testing, the RBCs could not be examined.

Case 3: Only the residual material of the RBC was tested and found to be negative in a combined administration; the pool-PC (P-PC) was not examined; findings regarding the patient were not available.

Case 4: For a comparable case, the findings on the patient, the time of the transfusion, and the time of the reaction onset were missing. No microbiological growth occurred in the residual volume of the transfused RBC; a residual volume of the apheresis-PC (A-PC) was not provided for examination.

Case 5: In the case of a new-born with sepsis following a PC transfusion, an examination of the PC was not possible because no residual material was available for testing; no other information was available on the patient.

Where the pathogen could be detected either only in the blood component or only in the recipient, the 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, in this report the transfused blood product was considered as the possible cause of the septic reaction in two reported cases without pathogen detection, since the clinical courses were strongly in favour of this assumption. As in previous reports, Table 4.8 b lists all cases of transfusion-transmitted bacterial infections that fall into the category "possible". Table 4.8 c only lists the confirmed cases of the categories "likely/probable" and "certain".

Table 4.8 b: Transfusion-transmitted bacterial infections with possible causality (2018)

Pathogen	Product	Evidence of pathogen recipient/product	Outcome
Grampositive bacteria, possibly propioni bacteria	RBC	n.d./RBC primary culture positive	Restored
Staphylococcus epidermidis	P-PC	n.d./P-PC primary culture positive	Restored
Propionibacterium acnes	RBC	negative (antibiosis) / RBC positive	Restored
Staphylococcus saprophyticus	RBC	negative/RBC positive	Restored
Escherichia coli	RBC	positive/pipe segment negative	Restored
Staphylococcus aureus (without resistence)	RBC	positive/RBC negative, 1 RBC not tested	Restored
Diagnosis based on clinical symptoms	RBC	n.d./RBC completely transfused	Restored

n.d. = no data

Table 4.8 c: Transfusion-transmitted bacterial infections with confirmed causality (2018)

Pathogen	Product	Evidence of pathogen recipient/product	Outcome	Assessment
Escherichia coli, pathogen identification in 2 A-PC, donor stool, patient blood	A-PC	Both	Fatal case	Certain
Bacillus cereus	PC	Both	Restored	Likely/probable
Escherichia coli	RBC	Both	Restored	Likely/probable
Streptococcus agalactiae	P-PC	Both (corresponding RBC negative)	Restored	Likely/probable

Deaths:

One fatal case in 2018 was due to a transfusion of an A-PC contaminated with *E. coli*, which was transfused on the second day following collection. The causality was confirmed by pathogen identification during the examination of the patient blood, of the two A-PC, and a stool sample from the donor.

4.9 Transfusion-transmitted viral infections (TTVI)

Viral transmission was confirmed by means of the criteria conforming to Opinion 34, 35, and 42 of the AK Blood for Hepatitis (HBV), Hepatitis C (HCV) and human immune deficiency virus (HIV) [9, 10] 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

TTVI (HIV, HCV, HBV, HEV)	2018		Rate of TTVI per 10^6 units
Cases following administration of	Reports	Confirmed	
RBC	29	0	0
PC	3	2	3.96
Plasma	2	0	0
Combined administration	15	0	
Total	**49**	**2**	

Transfusion-transmitted HIV, HCV and HBV infections

In 2018, none of the suspected cases reported on a transfusion-related transmission of HIV (4), HCV (21), or HBV (16) were rated as likely/probable or certain.

Since the introduction of the HCV and HIV-1 donor screening by means of nucleic acid-technology (NAT), two cases of HIV transmission (2007 and 2010) and one case of HCV transmission (2004) have been documented. In both cases, the transmission was caused by RBC from whole-blood donors, in whom the infections could not be detected in the NAT pool testing [20]. Since the introduction of the donor screening for HBV core Ag (anti-HBc) [21], 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, and one A-PC each in 2009, and 2012). A favourable effect on product safety with regard to HBV was reached by the voluntary introduction of a pool-NAT for HBV-DNA into the donor screening, which was established by the majority of the BE more or less simultaneously with the anti-HBc screening [22].

Deaths:

No cases of confirmed transfusion-related transmissions of HIV, HCV, or HBV occurred in 2018 and, thus, no deaths have been reported for these periods.

Transfusion-related HEV infections

The two confirmed virus transmissions for 2018 were caused by HEV.

Altogether eight suspected cases of a transfusion-related HEV transmission were reported in 2018, out of which four were ruled out as unlikely. In a suspected case following plasma exchange transfusion (32 plasma units) with a negative HEV-NAT result before and a positive result following transfusion, the connection with the transfusion could not be assessed, because the retain samples were not tested for HEV genome. Likewise, a suspected case with seroconversion and an increase in transaminases following RBC transfusion

was not assessable (51 RBC units over a period of 8 months) as no test results were available for the retain samples. In one suspected case of HEV transmission, which was rated as "likely/probable", seroconversion and a corresponding course of liver transaminase levels were found in the recipient as well as a plausible temporal connection with the transfusion of a HEV-NAT positive P-PC. The recipient's blood was not examined by NAT.

In another case, the transfusion of three HEV-NAT positive A-PC from one donor was confirmed as the cause of an HEV infection in the recipient by comparative sequence analysis.

Altogether, the data available on the suspected cases of transfusion-related HEV infection reported in 2018 are difficult to assess, since either the retain samples of the suspected donations were not examined or the examination of the patients was limited to the clinical chemistry (transaminases) and the infection serology (anti-HEV-IgG and anti-HEV-IgM). It can be assumed that the data quality will improve significantly when the new look-back opinion comes into force and donor testing by means of HEV-NAT becomes mandatory as from 1 January 2020 [23].

Thus, altogether 30 suspected cases of transfusion-related HEV transmission have been reported since the first report in 2013 up to and including 2018. In 8 cases, the causality was assessed as unlikely, in 4 cases as possible, and in 13 as confirmed. The confirmed cases were due to 5 RBC, 1 plasma, and 7 PC transfusions; the latter with 3 pool and 10 apheresis PC, i.e. some patients received mor than one contaminated PC. Because the data available were inadequate, the connection of the recipients' infection with the transfusion could not be assessed in 5 cases.

Deaths:

In 2018, no fatal case was reported in connection with a transmission of HEV.

Other transfusion-transmitted infections

In 2018, the PEI received reports on suspected cases of one transfusion-related CMV, one HAV, and one parvovirus-B19 infection. None of the cases could be confirmed.

Since the PEI started recording transfusion reactions in 1997 up to and including 2018, 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, 20 HCV, 25 HBV, two HAV, 13 HEV, and one malaria transmission due to transfusions have been confirmed.

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

In the reporting year 2018, altogether 867 suspected infections in the donor were received that resulted in donor look-back procedures. Both the number of suspected cases and the portion of confirmed donor infections were in the order of magnitude of the previous years. Four reports concerned first-time donors; in one case, the donor status was unknown. Similar to the previous years, the number of repeatedly undetermined results that induced a donor look-back procedure was highest for suspected cases of an HCV infection. No final reports are currently available from 10 look-back procedures.

Table 4.10 a: Donor look-back procedures in 2018 triggered by confirmed infections, first-time specifically positive Anti-HBc findings and/or undetermined results in laboratory diagnostics analogue with Annexes B2, A2, and C2, as applicable according to AK Blut Opinions 34 and 42 (or an analogue method, as applicable)

2018	Index donation				Look-back procedure: retain sample			
Pathogen	Reported	Not confirmed	Confirmed	Undetermined	Retain sample negative	Look-back not done[1]	Retain sample positive: recipient negative or dead	Cases still pending
HEV	154	0	154	0	141	6	6	1
HBV	425	46*	372**	7	339	31	2	7
HCV	122	7	44	71	89	20	4	2
HIV	53	15	30	8	21	15	2	0
HAV	2	0	2	0	1	1	0	0
CMV	25	0	25	0	24	0	1	0
Parvovirus B19	13	0	13	0	5	8	0	0
WNV	4	4***	0	0	0	0	0	0
Syphilis	69	4	57	8	19	46	0	0
Total	**867**	**76**	**697**	**94**	**639**	**127**	**15**	**10**

[1] Previous donations outside the look-back period/collection of plasma for fractionation/products not transfused/RBC stored for more than 5 days in the case of lues/first-time donor.

* Therefrom 23 donors vaccinated. ** Therefrom 11 donors ID-NAT positive. ***Cases were identified as Usutu virus.

Table 4.10 b: Look-back procedures (2018) starting from donors suspected to be infected with HBV or having a first-time specifically positive anti-HBc result analogue with Opinions 35 and 42 of the AK Blut

Look-back procedures 2018 for HBV	Index donation				Look-back procedure: retain sample			
	Reported	Not confirmed (vaccinated)	Confirmed (ID-NAT positive)	Undetermined	Retain sampel negative	Look-back procedure not done[1]	Retain sample positive: recipient negative or dead	Cases still pending
NAT isolated positiv	5	0	5 (5)	0	3	1	1	0
NAT, HBsAg positive	4	0	4 (4)	0	3	1	0	0
NAT, HBsAg, Anti-HBc positive	2	0	2 (2)	0	2	0	0	0
HBsAg isolated positive	57	33 (20)	21 (0)	3	21	3	0	0
HBsAg, Anti-HBc positive	3	2 (1)	1 (0)	0	1	0	0	0
Anti-HBc isolated positive	354	11 (2)	339 (0)	4	309	26	1	7
Total	425	46 (23)	372 (11)	7	339	31	2	7

[1] Previous donations outside the period of the look-back procedure/collection of plasma for fractionation/products not transfused.

As shown in Table 4.10 b, both the 44 confirmed isolated HBsAg-reactive donations and the donations with isolated specifically positive anti-HBc result were negative in the HBV-ID NAT. In 11 donors an HBV infection could be identified by means of NAT in the current donation. In addition, the retain sample of an isolated anti-HBc positive and ID-NAT negative donation was tested positive for HBV-NAT, and, at the same time, an anti-HBs-titre of 395 IU/L was detected. In the case of the recipient of the RBC from this donation, an HBV infection could be ruled out. The second recipient (donation and retain sample were HBV-NAT positive), died from the underlying disease. Altogether, an HBV infection could be detected by means of ID-NAT in only eleven of the 372 donations stated as confirmed according to the Opinions of the AK Blut. This corresponds to the order of magnitude of look-back procedures triggered by suspected HBV cases of the previous years.

For 235 of the 354 donations with isolated positive anti-HBc, information on anti-HBs was available: An anti-HBs titre of more than 10 IU/l was detected in a total of 123 donations. 79 of these donations had an anti-HBs titre of more than 100 IU/l and 44 had a titre of more than 1000 IU/l. A history of vaccination was known in only one of the 44 donors with very high titres.

4.11 Incorrect blood component transfused (IBCT)

The term IBCT refers to transfusions in which the blood component to be transfused 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 2018, 28 suspected cases of transfusion reactions due to IBCT of RBC and 3 suspected cases due to IBCT of plasma were reported. The suspected IBCT were confirmed in all 31 cases.

Table 4.11 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 4.12).

Table 4.11: IBCT with (IBCT-SAR) and IBCT without serious transfusion reactions (IBCT-SAE) in the recipient (2012–2018)

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

The reports on IBCT-SAR and the reports on IBCT-SAE have been at a comparable level since 2016. However, since 2012 a significant increase in reports has been recorded over time, which is probably due to the reporting obligation applying also to IBCT without a reaction as introduced with the 16 amendment of the German Medicines Act (Arzneimittelgesetz, AMG).

Deaths:

No deaths caused by IBCT were reported in 2018.

4.12 Serious adverse events (SAE)

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

The number of SAE reports has nearly increased fourfold, from 29 to 114 cases, since the 16th amendment of the AMG came into force in 2012 up to the reporting year 2018. During the same period, the total number of blood components transfused has decreased by 15 % (see Annex Table 1 and Figure 2). The SAE reports in 2018 originated from 16 establishments of medical care without associated BE, one report from the AkdÄ, and two reports from the competent federal authorities; the remaining reports originated from BE.

Pursuant to Directive 2005/61/EC [5], 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). In 2018 the assignment was adapted to the modified questions in the survey by the competent secretariat-general at the European Commission (DG Sante) (Table 4.12 a). A distinction is made for the first time 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. If the data were available in a sufficiently differentiated manner, the adverse events were recorded and presented accordingly. In 2018, no events were reported that were due to errors in the storage phase of the transfusion chain.

Table 4.12 a: Distribution of serious adverse events (SAE) by occurrence in the transfusion chain and by cause of the SAE (2018)

	Product defect	Equipment failure	Material defect	Human error	Other	Total
Donor selection	0	0	0	0	31*	31
Collection of whole blood	0	0	0	0	0	0
Collection by apheresis	3	4	0	1	0	8
Donor testing	0	2	0	6	2	10
Processing	0	2	2	3	0	7
Storage	0	0	0	0	0	0
Distribution	0	0	0	1	0	1
Other	3	0	0	9	0	12
Product selection BE	0	0	0	1	0	1
Product selection HF	0	0	0	41**	0	41
Issue to patient BE	0	0	0	1	0	1
Issue to patient HF	0	0	0	0	0	0
Cross match BE	0	0	0	0	0	0
Cross match HF	0	0	0	1	0	1
Total	**6**	**8**	**2**	**64**	**33**	**113**

HF = Health care facility

* This refers to exclusion criteria that predominantly became known in retrospect (PDI = Post Donation Information).

** This refers to predominantly IBCT prevented or IBCT without SAR.

Altogether 62 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 exclusion criteria that became known in retrospect (see Table 4.12 b). The documented SAE with an incorrect blood component transfused were caused by 28 RBC, 7 PC, and 6 FFP transfusions.

Table 4.12 b: Transfusion of blood components that did not cause SAR in the recipient but for which a serious adverse event became known in retrospect (2018)

Source of error in the transfusion chain	BE	HF	Causes
Apheresis (coupled preparation contaminated)	1		Product defect
Donor testing (irregular anti-M Ab not recognised, incorrect Rh declaration due to missing comparison with previous result)	2	0	Human error
Donor testing (altered Rh formula by further developed test reagents)	1	0	Other
Donor testing (requirement D weak – determination not transmitted in the data processing system "LIMS")	1	0	Equipment failure
Processing (incorrect stabiliser declaration, incorrect irradiation not recognised, banned product dispensed)	3	0	Human error
Component selection (confusion of blood components, confusion of patients, transfusion not indicated)	1	40	Human error
Other (donor documents lost)	1	0	Human error
Other (retrospective information on HEV contamination)	2	0	Product defect
Other (donor exclusion criteria became known in retrospect such as underlying diseases, infections, injuries caused by needle insertions, intake of medicines, periods of stay in the UK)	10	0	Other
Total	**22**	**40**	

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

A detailed analysis of the error sources for SAE in the BE or the health care facilities can only be performed in the facilities themselves. However, the data can already be used for further training and error analysis in blood donation establishments and health care facilities performing blood transfusions.

4.13 Serious adverse donor reactions (donor SAR)

Since the separate survey conducted by the PEI in 2015, the number of annual reports of donor SAR are approximately in a comparable range. In the reporting year 2018, reports on donor SAR were available from 26 BE; four BE reported that they had not observed any donor SAR.

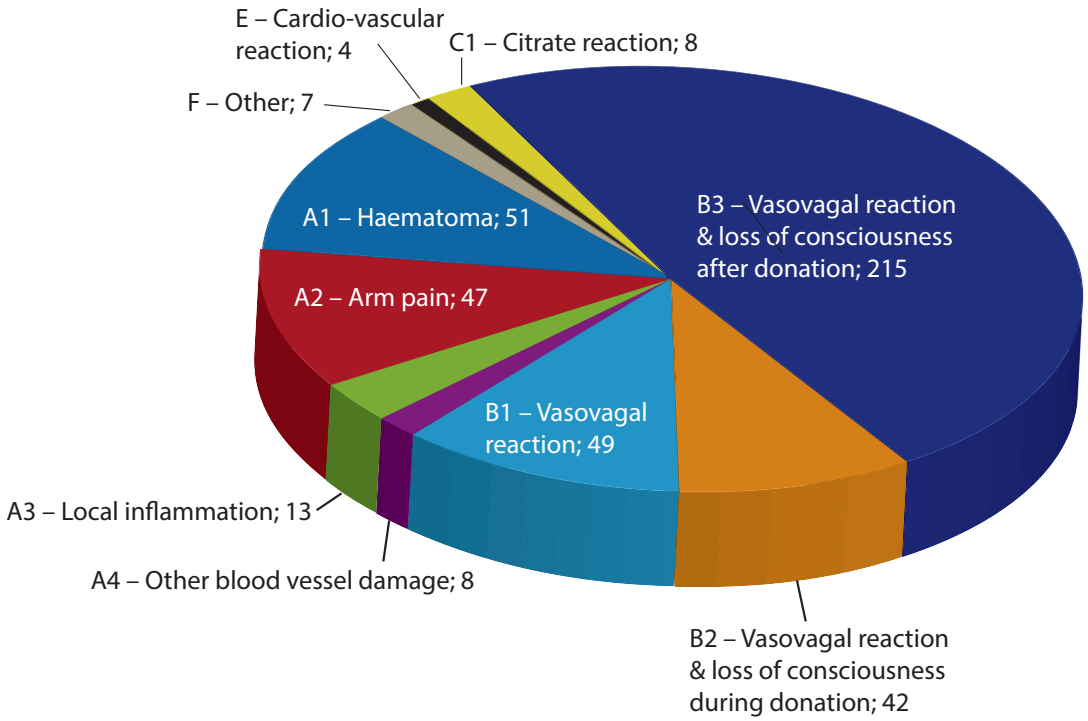
Table 4.13 a: Development of the reporting figures for donor SAR from 2011 to 2018

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

The table presents direct reports from BE as well as reports from competent federal authorities on establishments that exclusively collect plasma for fractionation. For calculating the rate of donor SAR per type of donation, only the number of donations from the 30 establishments was used, which had submitted a report on the occurrence of a donor SAR. Platelet aphereses and multiple component aphereses were grouped together into cytaphereses for the evaluation. In 2018, there were no reports on donor SAR for granulocyte aphereses or red blood cell aphereses. Of the 445 donor SAR reported, a causal connection could be established in 444 cases. In one case, the fall of a female donor and the trauma caused by this, was in a temporal, however, not in a causal relationship with the donation.

Similar to the definition by the Haemovigilance Working Party of the International Society of Blood Transfusion (ISBT) [24], the SAR that occurred during a donation 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 13 illustrates the shares of the respective type of reaction referred to all donor SAR in the reporting year. As in the previous years, vasovagal reactions with and without loss of consciousness were the most frequently occurring donor SAR and concerned 68 percent of all the cases reported. Of the donor SAR reported in 2018, 27 percent accounted for local, phlebotomy related reactions, roughly 11 percent for vasovagal reactions without, and 57 percent for vasovagal reactions with loss of consciousness. Apheresis-specific, cardiovascular, and other reactions occurred very rarely with 2, 1, and 2 percent. Allergic donor SAR were not reported.

Figure 4.13 a: Distribution of the donor SAR in 2018



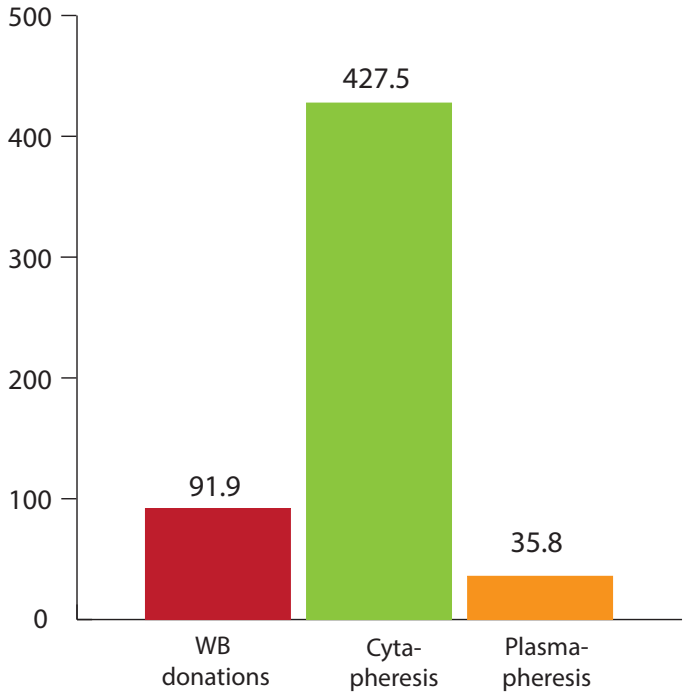
With regard to the type of donation, there are differences in the distribution. While for whole blood collections and plasmaphereses, the portion of vasovagal reactions with loss of consciousness is the highest after the donation, vasovagal reactions without loss of consciousness account for the major part of the cytaphereses (Table 4.13 b).

Table 4.13 b: Assignment of serious donor reactions to types of donations (2018)

Donor SAR 2018	WB donation	Plasma pheresis	Cytapheresis	Total
A1 – Haematoma	37	5	9	51
A2 – Arm pain	38	6	3	47
A3 – Local inflammation	10	3	0	13
A4 – Other vessel damage	7	1	0	8
B1 – Vasovagal reaction	23	5	21	49
B2 – Vasovagal reaction & post-donation unconsiousness	21	18	3	42
B3 – Vasovagal reaction & post-donation unconsiousness	183	30	2	215
C1 – Citrate reaction	0	2	6	8
E – Cardiovascular reaction	1	3	0	4
F – Other	4	3	0	7
Total	**324**	**76**	**44**	**444**

Also the reporting rates of SAR referred to 10^6 donations differ between donation types (Figure 4.13 b). Thus, the data collected for 2018 too, confirm the observation that donor SAR occur most frequently with cell apheresis. [25]. However, a final assessment can only be performed once reports on the occurrence of donor SAR are available from all BE.

Figure 4.13 b: Rates of confirmed donor SAR per million donations based on reports from 30 establishments. Cytaphereses comprise platelet apheresis and multicomponent aphereses.



In 161 out of the 444 confirmed donor SAR in-patient treatment and in 65 cases, out-patient treatment was required. In 3 cases, a recommended treatment was rejected (Figure 13.4 c). In the case of 162 donors requiring treatment, symptoms already occurred in the blood establishment, in 64 of the cases, they occurred after donors had left the establishment.

In particular vasovagal reactions resulted in serious traumata caused by collapses in 61 of 257 cases (Table 4.13 c).

Figure 4.13 c: Donor SAR, share requiring medical treatment (2018)

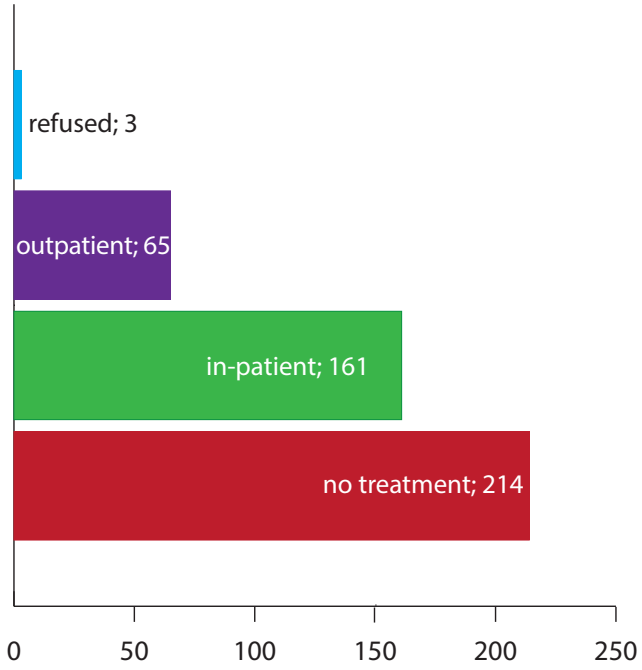


Table 4.13 c: Traumata caused by collapses resulting from vasovagal reactions following a donation (2018)

Type of reaction	Number
Bone fractures/injuries	12
Dental trauma	6
Contusions, swellings, lacerations	30
Haematoma in the head area	9
Traumatic brain injuries, therefrom three with degree of severity 2	4
Total	**61**

// 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 2018, acute allergic/anaphylactic transfusion reactions were again the most frequent type of confirmed serious adverse transfusion reactions based on 10^6 transfused units of RBC, PC, and plasma, respectively.
- In the reporting year 2018 two fatal cases were reported, of which the relationship with the transfusion was confirmed. One was an acute haemolytic transfusion reaction after administration of RBC and one was a bacterial infection after the transfusion of a PC.
- With 867 reports, the number of look-back procedures was in the order of magnitude of previous years. This also applied to look-back procedures triggered by isolated, specifically positive anti-HBc findings [21, 26]. In 11 out of 383 donors in which the look-back procedures were initiated because of a justified suspicion of an HBV infection, HBV genome could be confirmed by means of ID-NAT in the current donation, and in one case, in a retain sample. All isolated confirmed HBsAg and all isolated specifically anti-HBc positive donations were HBV-ID-NAT negative.
- The reports of serious events have been in a similar range for 3 years. The major share of these events was again due to incidents caused by human error, out of which nearly a third were incorrect blood components transfused (IBCT).
- In 2018, the highest rate of serious donor SAR, referred to the number of donations, was again reported for cell apheresis donations. However, this ratio could change if all blood establishments will submit a report on the occurrence of donor SAR.
- In 2018, with almost 70 % of all cases reported, vasovagal reactions with and without loss of consciousness were again the most frequently occurring donor SAR.

// 6. References //

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// 7. Annex with figures and tables //

Figure 1: Serious adverse transfusion reactions (SAR) confirmed annually (1997–2018)

The TRALI graph includes only 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.

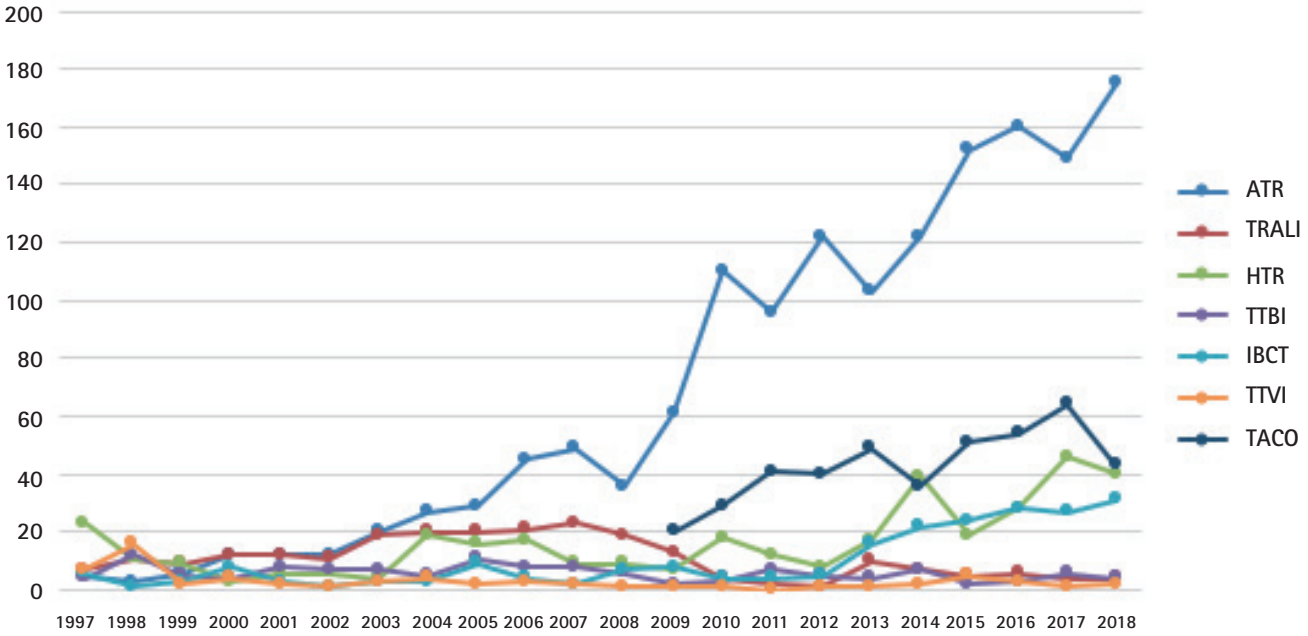

Figure 2: Percentage change in the consumption of blood components (2000–2018)

Blood component consumption in 2000 is equivalent to 100 percent. Up to 2018, the consumption of PC increased by 58 percent. The consumption of RBC, on the other hand, decreased by almost 14 percent, and by 40 percent for plasma.

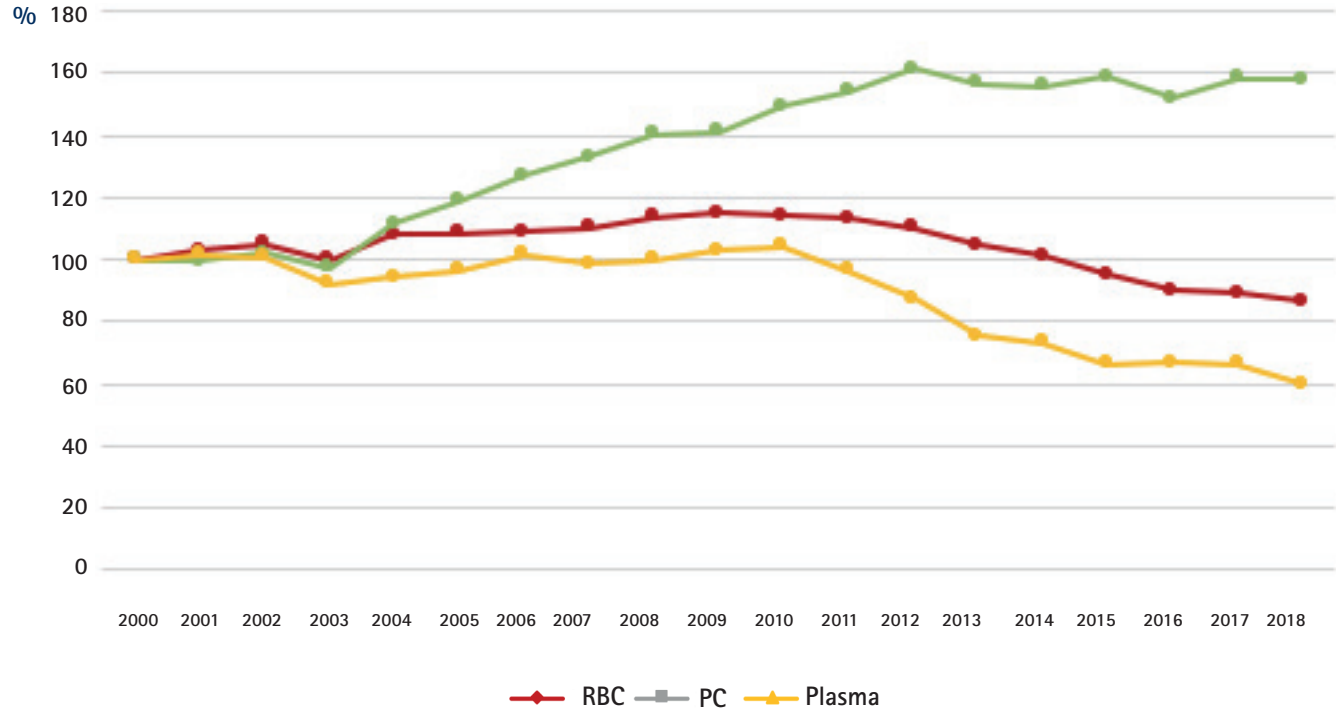

Table 1: Consumption of blood components (2000–2018)

Data calculated from the data reported on the sale and loss at the user pursuant to Section 21 TFG (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	2018	2000–2018
RBC	16,051,470	17,173,130	17,964,825	16,202,065	3,548,124	3,506,417	3,410,524	77,856,954
PC	1,274,659	1,566,873	1,870,911	2,022,453	485,659	506,267	505,312	8,232,161
Plasma	4,515,718	4,469,498	4,616,104	3,453,264	764,399	751,551	683,303	19,260,616

TACO	2009-2018
RB	40,149,219
PC	4,941,527
Plasma	9,133,737

Table 2: Total number of suspected adverse transfusion reactions reported, confirmed reactions and portion of associated deaths (1997–2018)

Serious adverse transfusion reactions (SAR) 1997–2017	Reported suspected cases	Confirmed cases	Fatal cases therefrom
Acute allergic/anaphylactic transfusion reactions (ATR)*	3,504	1,506	34
Transfusion-related acute lung injury (TRALI)**	1,189	240	22
Haemolytic transfusion reaction (HTR)	689	366	17
Transfusion transmitted bacterial infection (TTBI)	529	128	18
Incorrect blood component transfused (IBCT)	221	219	16
Transfusion transmitted viral infection (TTVI)***	3,617	64	3
Post-transfusional purpura (PTP)	30	18	0
Transfusion-associated Graft versus Host Disease (TA-GvHD)	4	3	1
Transfusion-associated circulatory overload (TACO)****	458	427	15
Other SAR	173	28	0
Total	**10,414**	**2,999**	**126**

* 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, HEV

**** TACO systematically captured only as from 2009

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 (2000–2018).

The distinction between allergic transfusion reactions Grades I and II from serious allergic or anaphylactic transfusion reactions, Grades III and IV, was performed according to Ring and Messmer [13]. As has been common practice since 2009, only serious acute allergic/anaphylactic transfusion reactions Grades III and IV were included into the full evaluation.

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2018	2000–2018
Confirmed serious allergic/anaphylactic transfusion reactions after administration of						
RBC	27	99	160	277	278	841
PC	12	20	49	108	124	313
Plasma	9	16	54	57	46	182
Combined	8	15	40	57	36	156
Total	**56**	**150**	**303**	**499**	**484**	**1,492**
Therefrom fatal coutomes 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	2016–2018	2000–2018
	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	25.56	10.80
PC	9.41	12.76	26.19	53.40	82.82	38.02
Plasma	1.99	3.58	11.70	16.51	20.85	9.45

Table 4: Confirmed reports of suspected serious TACO, associated deaths, and rates of confirmed reactions referring to 10^6 units transfused (2009–2018)

TACO	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2000–2018
Reported	21	33	42	41	50	42	53	56	68	52	458
Confirmed	**20**	**29**	**42**	**40**	**49**	**36**	**51**	**54**	**64**	**43**	**428**
RBC	11	18	28	33	36	30	47	47	55	34	339
PC	1	2	3	3	3	2	0	2	3	2	21
Plasma	1	2	3	0	4	2	0	1	1	2	16
Combined administration	7	7	8	4	6	2	4	4	5	5	52
Deaths	1	2	2	1	1	3	1	1	2	0	14

Rates confirmed TACO for the periods				
	2009–2011	2012–2015	2016–2018	2009–2018
	TACO / 10^6 units	TACO / 10^6 units	TACO / 10^6 units	TACO / 10^6 units
RBC	4.23	9.01	13.00	8.44
PC	4.22	3.96	4.68	4.25
Plasma	1.73	1.74	1.81	1.75

Table 5: Confirmed reports of suspected serious TRALI, associated deaths, and rates of immunogenic TRALI referring to 10^6 units transfused (2000–2018)

Confirmed suspected cases of TRALI were subdivided into immunogenic and non-immunogenic TRALI [15, 27].

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2018	2000–2018
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	5	21
Plasma donors	17	48	18	5	2	90
Total	**24**	**60**	**28**	**24**	**14**	**150**
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	2016–2018	2000–2018
	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	0.67	0.50
PC	1.57	1.91	2.67	2.97	3.34	2.55
Plasma	3.76	10.74	3.90	1.45	0.91	4.67

Specific donor selection and donor screening, respectively applies as per 1 Sept. 2009 [12], if plasma for transfusion is prepared from donation.

Table 6: Confirmed reports of suspected serious haemolytic transfusion reactions (HTR), associated deaths and rates of HTR, referring to 10^6 units transfused (2000–2018)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2018	2000–2018
Haemolytic transfusion reactions after administration of						
RBC	11	50	41	71	107	**280**
PC	2	4	4	3	1	**14**
Combined transfusion	6	7	1	9	6	**29**
Total	**19**	**61**	**46**	**83**	114	**323**
Therefrom delayed haemolytic transfusion reactions and HTR with evidence of Ab						
Delayed HTR	3	6	21	14	34	**78**
Irregular RBC-Ab	2	4	28	14	63	**111**
Therefrom haemolytic transfusion reactions with fatal courses after administration of						
RBC	0	3	2	0	4	**9**
Combined transfusion	0	1	0	0	0	**1**
Total	**0**	**4**	**2**	**0**	**4**	**10**

Rates of confirmed haemolytic transfusion reactions for the periods						
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2018	2000–2018
	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	10.22	3.60
PC	1.57	2.55	2.14	1.48	0.67	1.70

Table 7: Confirmed reports of suspected transfusion-transmitted bacterial infections (TTBI), associated deaths, and rates of TTBI referring to 10^6 units transfused (2000–2018)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2018	2000–2018
Bacterial infections after administration of						
RBC	7	13	7	8	3	38
Pool-PC	8	9	5	1	5	28
Apheresis PC	11	9	6	9	5	40
Plasma	0	1	0	0	0	1
Total	**26**	**32**	**18**	**18**	**13**	**107**
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	2	7
Plasma	0	0	0	0	0	0
Total	**3**	**3**	**2**	**1**	**4**	**13**

Rates of confirmed transfusion-transmitted bacterial infections for the periods of						
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2018	2000–2018
	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	0.49
PC	14.91	11.49	5.88	4.94	6.68	8.26
Plasma	0.00	0.22	0.00	0.00	0.00	0.05

Table 8: Results of microbiological examinations of confirmed cases of TTBI (2000–2018)

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	Plasma	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 lwoffii, Pseudomonas aeruginosa Enterococcus faecalis*	30	47	3	80	63	17	4	13
Total	48	75	5	128	110	18	4	14

Table 9: Confirmed reports of suspected transfusion-transmitted viral infections (TTVI) and rates of TTVI referring to 10^6 units transfused (2000–2018)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2018	2000–2018
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	**2**	**3**
Apheresis PC				3	**2**	**5**
Plasma				0	**1**	**1**
Total				7	**6**	**13**

Rates of confirmed transfusion-transmitted HBV, HCV and HIV infections for the periods						
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2018	2000–2018
	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	0.24
PC	1.57	0.00	0.53	0.49	0.00	0.49
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	2016–2018	2012–2018
	HEV per 10^6 units	HEV per 10^6 units	HEV per 10^6 units
RBC	0.19	0.10	0.15
PC	1.98	2.67	2.27
Plasma	0.00	0.45	0.18

Table 10: 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 (2000–2018)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2018	2000–2018
SAR RBC	15	18	23	63	79	198
SAR PC			0	1	2	3
SAR Plasma			0	3	5	8
SAR total	**15**	**18**	**23**	**67**	**86**	**209**
Therefrom fatal (administration of RBC)	0	1	4	5	3	13
SAE RBC			6	66	101	173
SAE PC			1	4	18	23
SAE Plasma			0	7	18	25
SAE total			7	77	137	221
IBCT (SAE and SAR) total	15	18	30	144	223	430

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	2016-2018	2000-2018
	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	7.55	2.54
PC	0.00	0.00	0.00	0.49	1.34	0.36
Plasma	0.00	0.00	0.00	0.87	2.27	0.42

Table 11: Rates of confirmed serious adverse transfusion reactions reported summarised for the period of 2000–2018, each referring to 10^6 transfused units of RBC, PC, and plasma, respectively

SAR rates per 10^6 transfused units									
	Units transfused 2000-2018	ATR	HTR	TRALI	TTBI	TTVI	IBCT	Units transfused 2009-2018*	TACO**
RBC	77,856,954	10.8	3.60	0.50	0.49	0.30	2.54	40,149,219	8.44
PC	8,232,161	38.02	1.70	2.55	8.26	1.21	0.36	4,941,527	4.25
Plasma	19,260,616	9.45	0.00	4.67	0.05	0.21	0.42	9,133,737	1.75

* TTVI: HIV, HBV, HCV, HEV
** TACO were recorded systematically only as from 2009, thus, the rates refer to TACO as a share of the consumption of transfused units from 2009–2018.

Table 12: Imputability levels to assess serious adverse transfusion reactions

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 13: Definition of 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-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 63 i [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.

Definition of serious transfusion reactions according to the Haemovigilance Working Party of the International Society of Blood Transfusion (ISBT) [28]