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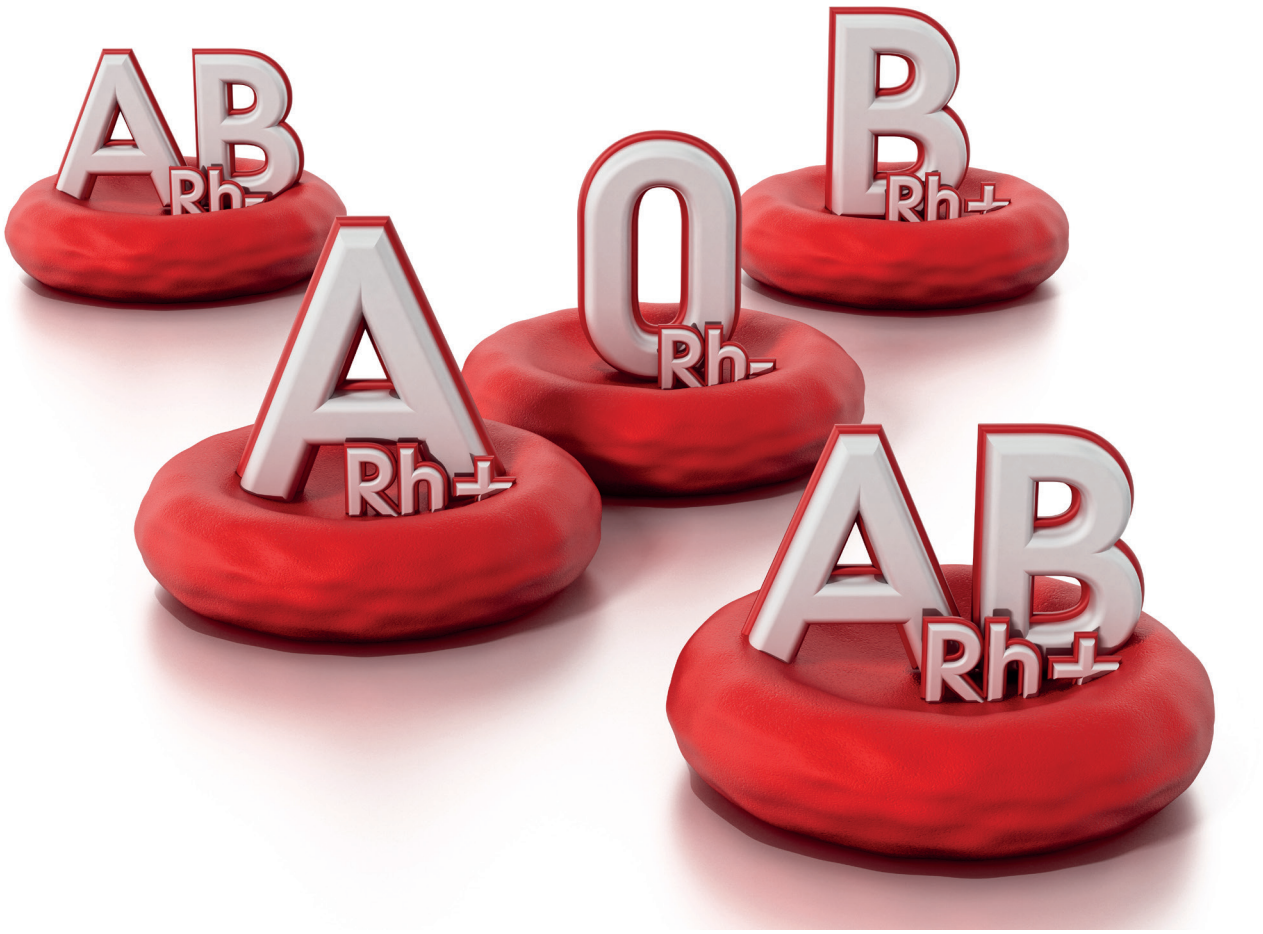
Paul-Ehrlich-Institut

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

2021

Assessment of Reports of Serious Adverse Reactions and Events in Accordance with Section 63i of the AMG (German Medicinal Products Act)



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// 1. Introduction //

The 2021 Haemovigilance Report reflects another year of intense debate regarding the significance of SARS-CoV-2 to blood safety and the blood supply.

Since no viral RNA could be detected in the blood of asymptomatic SARS-CoV-2 patients (lack of viremia), there is still no evidence of a risk of transmission of SARS-CoV-2 via transfusion [1, 2]. The Paul-Ehrlich-Institut refers in this context to the unchanged valid donor requirements as described in the Haemotherapy Guideline [3]. These requirements do not require a deferral of blood donors after a SARS-CoV-2 vaccination [4].

Proactive measures taken by blood establishments and their cooperation with the authorities and national bodies, such as the German National Advisory Committee Blood, has largely prevented an undersupply of blood components in Germany.

With regard to the safety of blood products, measures to reduce the risk of transmission of pathogens have rightly been a priority in recent decades. However, many other factors influence the safety of blood products. These factors include avoiding mix-ups during the collection of blood for cross-testing, making appropriate selections for patient-compatible blood products, and assigning the correct finished product to the intended recipient at the ward or in the doctor‘s office. The obligations to document and report adverse events related to the use of blood products primarily serve to ensure and continuously improve the high safety standard of transfusions. Given this context, this year‘s haemovigilance report focuses on the topic of ABO-incompatible transfusion errors.

As in past reports, the 2021 haemovigilance report also includes a summary of all spontaneous reports from 2021 of serious adverse transfusion reactions (SAR), serious unexpected reactions in donors (donor SAR), and serious adverse events (SAE) in the transfusion chain and continues the comparative analysis with the reports from previous years [5].

Like in previous years, the partially insufficient data quality limits the correct classification and, consequently, the causality assessment. The information types most frequently missing were the blood group of the transfused preparations; the performance and results of the bedside test; or the results of the immunohaematological, laboratory, or microbiological evaluation. A factor that is of particular importance for increasing data quality is that reporting forms are filled out as completely as possible, including the associated additional forms. The reporting forms were updated in 2022 and are available on the Paul-Ehrlich-Institut‘s website, as are the updated definitions based on IHN criteria [6]. Despite these limitations, the reports submitted in accordance with section 63i of the AMG [7] collectively allow the safety standard of blood components in Germany to be documented and evaluated and the benefits of risk-minimising measures to be assessed.

// 2. Abbreviations //

Ag	Antigen
Ak	Antibody
AK Blood	Arbeitskreis Blut (German National Advisory Committee Blood)
AkdÄ	Arzneimittelkommission der deutschen Ärzteschaft (Drug Commission of the German Medical Association)
AMG	Arzneimittelgesetz (Medicinal Products Act)
A-TK	Apheresis platelet concentrate
ARDS	Acute respiratory distress syndrome
ATR	Acute allergic/anaphylactic transfusion reaction
BE	Blood establishment
BNP	Brain natriuretic peptides
CMV	Cytomegalovirus
EBV	Eppstein-Barr virus
FNHTR	Febrile non-haemolytic transfusion reaction
FUS	Follow-up sample
GIFT	Granulocyte immunofluorescence test
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HNA	Human neutrophil antigen
HPA	Human platelet antigen
HTR	Haemolytic transfusion reaction
ISBT	International Society of Blood Transfusion
IBCT	Incorrect blood component transfused
LBP	Look-back procedure
NAT	Nucleic acid amplification technology
PC	Platelet concentrate
P-PC	Pooled platelet concentrate
PEI	Paul-Ehrlich-Institut
PTP	Post-transfusion purpura
RBC	Red blood cell concentrate
SAE	Serious adverse event
SAR	Serious adverse reaction
TACO	Transfusion-associated circulatory overload
TAD	Transfusion-associated dyspnoea
TTBI	Transfusion-transmitted bacterial infection
TTVI	Transfusion-transmitted viral infection
TFG	Transfusionsgesetz (German Transfusion Act)
TRALI	Transfusion-related acute lung injury
WNV	West Nile Virus

// 3. Methods //

Each spontaneous report of a suspected SAR occurring during donation or transfusion is recorded at the PEI and initial reports are supplemented by targeted enquiries, if necessary. Table 14 (Annex) provides an overview of how the relationship between a SAR and a transfusion is evaluated in accordance with the criteria set out in Annex II, Part B of Directive 2005/61/EC, "Imputability levels to assess serious adverse reactions" [8]. An SAR is considered to be confirmed if the causal relationship has been assessed as "certain" or "likely", provided that the SAR relates to a TRALI, HTR, TTBI, TTVI, or IBCT. As in some SARs there are no clear, clinically measurable parameters that can unequivocally prove the connection of a SAR with the transfusion, in particular for allergic and anaphylactic transfusion reactions (ATR); febrile non-haemolytic transfusion reactions (FNHTR); transfusion-associated dyspnoea (TAD); and sometimes for transfusion-associated circulatory overload (TACO), events with a possible connection involving these SARs are also classified as confirmed serious transfusion reactions. Reported deaths are only considered to be a confirmed attributed transfusion reaction if the clinical course of the SAR and any additional recorded laboratory parameters or autopsy findings indicate a confirmed or probable causal relationship with the transfusion of the blood component.

The confirmed SARs are summarised and compared with the number of blood components determined to have been transfused in accordance with section 21 of the Transfusion Act (TFG) [9] and presented as a share per million transfused units. For SARs in which it is difficult to determine the product responsible for the event due to multiple transfusions or in which patient-specific factors contribute to the reaction, the confirmed cases are included in the calculation of the reporting rate. This leads to a change in the reporting rate calculation for TTBI and TTVI cases. The 2021 rate for these cases was based on the number of affected products per 10^6 transfused products for each product type. Since some patients received more than one affected product, this calculation allows for a more accurate representation of the transmission risk for each product group.

Donor SARs reported by the blood establishments (BEs) to be the result of whole blood or apheresis donations are grouped by the type of reaction and are also shown as a share of confirmed SARs per number of donations from all reporting BEs.

The legal basis for reports of SAEs and SARs on the part of BEs is laid down in section 63i of the Medicinal Products Act (AMG) [7] and for treating physicians in sections 14 and 16 of the TFG [10]. Standardised forms are offered on the PEI website for these reports [6]. The reporting physician forms document information relating to the transfusion, such as the time of the transfusion, type of blood component(s) administered, and the course of the transfusion reaction. Required information on the transfused patient includes date of birth, gender, transfusion trigger, underlying condition(s), and relevant comorbidities and medication. The BEs involved in the production of the blood components in question supplement the information with specific data on each donor and on any other blood products that may have been produced from the donations. In addition, the BEs report the results of laboratory tests carried out and, if necessary, the initiation of an LBP [10, 11, 12]. In the case of donor SARs, the type of donation and donor SAR must also be specified. Incorrect blood components transfused (IBCT) that did not result in transfusion reactions, as well as errors in the transfusion chain that could have led to an IBCT, are to be reported as SAEs to the higher federal authority in accordance with section 63i of the AMG [7] by the pharmaceutical companies (16th AMG amendment). In the case

of IBCTs with a transfusion reaction, the treating physician is also obliged to report in accordance with section 16 subsection 2 of the TFG [10, 12]. As treating physicians mostly report serious reactions and serious adverse events, the PEI only receives sporadic information on non-serious events. Therefore, only IBCTs with (potentially) serious reactions are presented in the haemovigilance report.

The frequency of confirmed SARs is based on a calculation of the number of transfused units using reports on the sale and expiry of red blood cell concentrates (RBC), platelet concentrates (PC) and plasma (reports submitted by 8 Sept 2022 in accordance with section 21 of the TFG [9]).

The first part of the haemovigilance report presents the data collected in the 2021 reporting period; the tables and figures in the annex continue with the summary haemovigilance data presentation.

// 4. Results //

4.1 General Overview of Serious Adverse Transfusion Reactions (SARs)

Past observations have shown that there is often uncertainty among reporters regarding the distinction between serious and non-serious transfusion reactions. The uncertainty mainly involves ATR and FNHTR cases. Definitions of these terms based on the updated definitions of the Haemovigilance Working Party at the International Society for Blood Transfusion and the International Haemovigilance Network have been available on the PEI website since August 2022 in the Haemovigilance section under "Reporting forms" [6, 13]. When assessing the severity of a reaction, it is important to emphasise that the severity is determined by the symptoms and not the duration of the symptoms.

Of the 908 total suspected cases reported in 2021 of a serious adverse transfusion reaction (see Annex Table 15 for definition), a causal relationship with the administration of blood components was confirmed in 619 cases. In seven cases, the transfusion reaction was classified as being partially causal for the fatality.

Table 4.1: Overview of the suspected cases of serious adverse transfusion reactions (SARs), confirmed SARs and deaths as a result of a transfusion reported in 2021

	SARs 2021	reported	confirmed	number of deaths
1	IBCT	30	29	3
2	incompatibility*	1	1	0
3	ATR Grades I/II	118	101	0
4	ATR Grades III/IV	202	175	0
5	TACO	78	67	1
6	TRALI	55	9	2
7	TAD	24	20	0
8	HTR	77	20	0
9	FNHTR	200	181	0
10	TTBI	31	5	1
11	HCV, HIV, HBV	12	0	0
12	HEV	4	1**	0
13	other TTVI***	2	0	0
14	PTP	3	2	0
15	other	71	8	0
	total	**908**	**619**	**7**

* The "incompatibility" category contains a case of a subsequently detected anti-E alloantibody after emergency transfusion of two E-positive red blood cell concentrates that were not cross-tested. Haemolysis was not detected with any level of certainty.

** The HEV transmission case occurred in 2020 and was subsequently reported in 2021. Two HEV-positive plasma donations that were donated in 2019 were received by the donor during the period in question.

*** The "other TTVI" category contains one unconfirmed suspicion of CMV transmission and one of EBV transmission.

4.1.1 Overview of deaths

In 2021, a total of seven deaths were reported where the link to the transfusion was assessed to be certain or probable. Three of the seven cases are due to ABO-incompatible IBCTs. In two other cases, in one case the transfusion of an apheresis PC and in the second case the combined administration of components as a trigger for a TRALI were at least partly responsible for the lethal course of the underlying condition. One patient died of sepsis caused by *Serratia marcescens* following transfusion of a contaminated pooled PC preparation. Furthermore, there was one death related to a TACO after transfusion of an RBC.

Thus, during the 25-year observation period (1997–2021), a total of 146 deaths can be attributed to the administration of blood components. Grade III and IV ATRs have been documented as the most common cause of death, with 34 cases, followed by HTRs (25 cases), TRALIs (25 cases), TTBIs (21 cases), IBCTs (21 cases), TACOs (16 cases), TTVIs (three cases), and one death from GVHD in 2001. The GVHD death was related to a massive transfusion of 17 RBCs, 20 FFPs and 13 PCs (see Figure 4.1 and Annex Table 2). 20 of the deaths resulting from TRALI occurred before the introduction of the requirement to reduce the risk of TRALI through targeted donor selection and/or testing, and five occurred after [14] (see Annex Table 5).

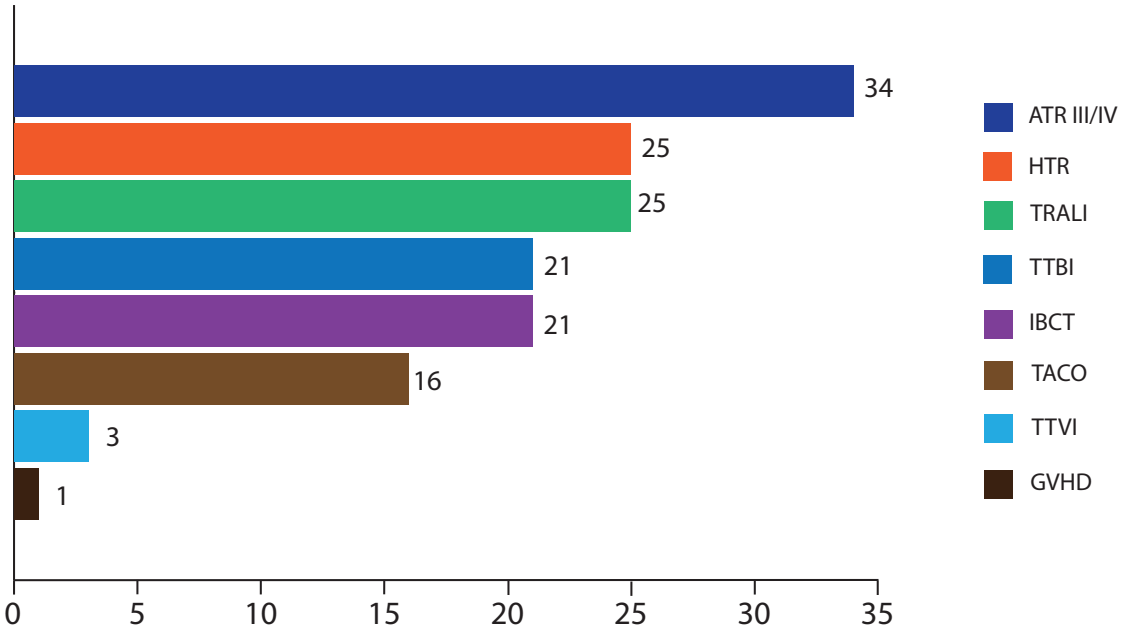

Figure 4.1.1: Number of fatal serious adverse transfusion reactions (1997–2021)

4.2 Acute Allergic/Anaphylactic Transfusion Reactions (ATRs)

ATRs are defined by a set of clinical symptoms rather than by specific laboratory parameters. Apart from the development of urticaria and itchiness, ATR symptoms are nonspecific and can overlap with symptoms of other transfusion reactions such as dyspnoea or febrile reactions Therefore, it is almost impossible to evaluate ATR cases as certain. As a result, the grade III and IV ATRs recorded as confirmed in 2021 are mostly cases with probable or possible causality.

It can again be seen that serious allergic/anaphylactic transfusion reactions occur more frequently after PC administration than after administration of other blood components (see also Annex, Tables 3 and 13).

Table 4.2: Number of suspected reports of grade I/II and III/IV ATRs, confirmed cases after administration of RBCs, PCs, plasma or a combination of these and SAR rates per 10^6 transfused units (2021)

2021	ATRs I and II	ATRs III and IV	Rate of ATRs III and IV per 10^6 units
Number of reports	118	202	
Confirmed cases after administration of			
RBCs	56	107	33,02
PCs	26	43	86,05
Plasma	12	13	20,31
Combination	7	12	
Total confirmed cases	**101**	**175**	

Distinction of ATR grades I and II from ATR grades III and IV according Ring et al. [15]

Deaths:

No fatal ATRs with a confirmed or probable link to the transfusion were reported in 2021.

4.3 Transfusion-Associated Circulatory Overload (TACO)

Similar to ATRs, clinical parameters are decisive when assessing a suspected TACO case [16]. Differentiation from non-immunogenic or potential TRALIs or from acute respiratory distress syndrome (ARDS) is often difficult, as the differences in symptoms are somewhat fluid. Finding newly developed pulmonary oedema in a chest x-ray and rapid recovery after the administration of diuretics are diagnostic criteria that indicate circulatory overload. The brain natriuretic peptide (BNP) and the N-terminal prohormone of BNP (NT-proBNP) can serve as diagnostic parameters, in particular to distinguish a TACO from a non-immunogenic TRALI. A sharp increase in NT-proBNP levels of more than one and a half times over the course of the reaction may corroborate a TACO diagnosis. Normal BNP values exclude a TACO diagnosis. Ideally, NT-proBNP or BNP values should be assessed over time, since an increased single value is not very meaningful in relation to the reaction to be evaluated. Due to the possible influences of conditions such as impaired kidney function, the informative value of these parameters is also limited in critically ill persons [17].

Table 4.3: Number of reported suspected cases of transfusion-associated circulatory overload (TACO), confirmed cases following the administration of RBC, PC, plasma, or a combination of these and SAR rates per 10^6 transfused units (2021)

TACO	2021	TACO rate per 10^6 units
Number of reports	78	
Confirmed cases after administration of		
RBCs	59	18.20
PCs	2	4.00
Plasma	2	3.12
Combination	4	
Total confirmed cases	**67**	

Deaths:

In 2021, there was one death related to a confirmed TACO diagnosis. The case involved a patient with a history of severe COPD and small cell lung cancer. Two hours before the transfusion, the patient had increased NT-proBNP levels. She then died in close temporal relation to the transfusion (unfortunately, no levels were taken after the transfusion). Taking into account the close temporal relation and the anamnesis, it can be assumed that the transfusion was decisive for the final circulatory overload, and as a result the patient died.

4.4 Transfusion-Related Acute Lung Injury (TRALI)

A TRALI is characterised by a rapid occurrence of respiratory distress within a maximum of six hours after the end of the transfusion along with the simultaneous exclusion of other diseases that can cause pulmonary insufficiency (e.g. cardiological diseases). In contrast to TACO, a TRALI rarely shows radiological signs of pulmonary oedema, but acute bilateral perihilar pulmonary infiltrates (for definition, see also Table 15, Annex). Immunogenic TRALIs are confirmed by the detection of specific antibodies (Ab) in the donor and the corresponding antigen (Ag) in the recipient. In the case of a reverse TRALI, the symptoms are caused by the Ag in the donor and the corresponding Ak in the recipient [18].

The algorithm first introduced in the 2013–2014 haemovigilance report was retained for the assessment of suspected cases of TRALI [19]. The symptoms are reviewed first and any possible other causes are excluded. This is followed by the examination of the donors for relevant HLA-Ab or HNA-Ab. If HLA-Ab is detected in the donor, the recipient is also earmarked for corresponding Ag testing, however, in practice the testing often does not occur. Depending on the result, the reaction is classified as an immunogenic or non-immunogenic TRALI [20]. An international group of physicians (CA, US, NL, DE) with expertise in transfusion, intensive care and laboratory medicine published a recommendation in 2019 to redefine TRALIs. This definition no longer focuses on the immunological aspect, but on the clinical picture and pre-existing risk factors in the transfusion recipient [21]. The new definition has not been used in the present evaluation, as it has not yet been included in the ISBT/IHM criteria.

Further insights from the haemovigilance field using well-described cases could help to distinguish TRALIs more reliably from closely related reactions in the future. A contribution was made to this

effort with the redefinition of TACOs published in 2019 by the Haemovigilance Working Party of the International Society of Blood Transfusion (ISBT) [22]. If there is no detection of Ab but with the interval to first symptoms matches a TRALI, the course of the BNP and NT-proBNP values can be used as an additional diagnostic decision criterion to secure a TACO diagnosis in the context of TACO-predisposing factors.

In 2021, the PEI received a total of 55 suspected TRALI reports, nine of which were confirmed as immunogenic TRALIs (see Tables 4.4 a and b). An additional five suspected TRALI cases were classified as possible and 38 as unlikely. In three cases, no causality assessment could be carried out due to a lack of information.

When looking at the HLA testing results of the confirmed cases, it can be noted that in all cases at least one donor with a pregnancy in their medical history was involved (see Table 4.4 b).

(1) A 31-year-old patient received RBCs and an apheresis PC after allogeneic stem cell transplantation for post-ET myelofibrosis. About two hours after the end of the transfusion, there was an increase in heart rate, dyspnoea, bronchospasm and an O_2 saturation drop below 90 percent. The patient required resuscitation and had to be intubated and transferred to the intensive care unit. This was followed by the diagnosis of new-onset pulmonary oedema and the detection of new-onset bilateral infiltrates in the chest x-ray, leading to a tentative TRALI diagnosis. The immunological evaluation was negative for the RBC donor. In contrast, evaluation of the apheresis PC donor detected multiple HLA-Ab (anti-HLA A66, B7, B13, B27, B47, B48, B57, B60, B61, B62, B63, B73, B75, B76, B77, B81). Six pregnancies were found in the immunisation history of the donor in question. Since examination of the recipient revealed the corresponding Ag HLA-B7, the diagnosis of an immunogenic TRALI as the cause of the transfusion reaction could be confirmed in this case.

(2) A 38-year-old patient received two preoperative RBCs during excision of a haemangioma in the cavernous sinus. About one and a half hours later, the patient experienced a circulatory reaction, a drop in oxygen saturation below 90 percent and ventilation difficulties during the operation. Bilateral infiltrates in the post-op chest X-ray showed no evidence of infection or pulmonary oedema. Her symptoms improved spontaneously over time, but extubation was only possible three days post-op. One of the donors involved tested positive for HLA-Ab (anti-HLA A11, A25, B5, B13, B18, B22, B39, B40, B42). The immunisation history of the donor in question was positive for post pregnancy status. A corresponding antigen was detected in the recipient and the diagnosis of an immunogenic TRALI was confirmed. Furthermore, leukocyte antibodies were also found in the recipient (anti-HLA A1, A11, A23, A24, A36; B8, B44, B45, B76, B82; Cw7), so the possibility that a reverse TRALI could have additionally contributed to the symptoms cannot be ruled out. This cannot be confirmed, however, as the HLA antigen status of the donors is missing.

(3) A 79-year-old patient reacted with pulmonary oedema and hypoxia after transfusion of two pooled PC preparations before scheduled bypass surgery. In the evaluation of the eight donors involved, one donor was identified who had corresponding Ab for the HLA-AG typing of the patient (anti-HLA DR13 and DQ6). An immunogenic TRALI was thus confirmed. In this case, the donor in question also had a history of pregnancy.

(4) An 83-year-old patient received three pooled PCs, two RBCs and two FFPs as part of the surgical removal of a spinal mass. About two and a half hours after starting the transfusion series, the patient developed symptoms of a TRALI. Fourteen of the sixteen donors involved were screened for HLA-Ab. Four donors tested positive. HLA-Ag or HNA-Ag corresponding to three donors were de-

tected in the patient, which led to confirmation of an immunogenic TRALI. The donors were two men with an unknown immunisation history and two women with a history of pregnancy. One of the donors of a pooled PC had a conspicuously high anti-HNA-3a titre, which can be considered the most likely cause of the TRALI.

(5) A 67-year-old patient with a right cerebral ischemia received two RBCs due to anaemia with Hb 4.6 g/dL. About one and a half hours after transfusion, pulmonary oedema occurred with a drop in oxygen saturation to 74 percent. New bilateral infiltrates could be detected in the chest x-ray. An immunological evaluation focussed primarily on the suspicion of a TRALI revealed a positive result for HLA class I and II Ab in one of the two donors involved. The possibility of an immunological TRALI is thus given to secure the diagnosis, but there was no HLA typing of the recipient to detect corresponding Ag. As a trigger of the symptoms, a bilateral pulmonary embolism detected in the chest CT two days after the onset of symptoms could also be considered as a differential diagnosis for the suspected TRALI diagnosis.

(6) A 75-year-old patient with metastatic adenocarcinoma of the lung and aortic valve endocarditis received an apheresis PC due to thrombocytopoenia and developed chills, fever, dyspnoea and an O_2 saturation drop to 70 percent one hour after the start of the transfusion. Immediate anti-allergic and bronchodilator therapy did not significantly improve the symptoms. Three hours later, there was another drastic drop in oxygen saturation to 30 percent. Using an echocardiogram, a diagnosis of a suspected fulminant pulmonary embolism was made due to a dilated right ventricle. The patient required resuscitation and died three and a half hours after the onset of symptoms. A TRALI evaluation was carried out using differential diagnostics. The donor of the apheresis PC had HLA class I and II antibodies, including anti-HLA DQA1*05. Ag corresponding to these Ab were found in the recipient. A chest x-ray was not carried out due to the acuteness of the situation. Although the immunological prerequisites for a TRALI were present, the case can only be assessed as probable, since the detection of pulmonary infiltrates is missing and a pulmonary embolism is a differential diagnosis. Again, the apheresis PC involved came from a donor with a history of pregnancy.

(7) An 84-year-old patient received two RBCs due to tumour anaemia and suffered a circulatory collapse with dyspnoea, bronchospasm and pulmonary oedema about two hours after the end of the transfusion. New infiltrates were detected in x-ray diagnostics. In one of the donors involved, HLA class I and II antibodies were found, the other donor showed a weak positive in the GIFT. Both donors had a history of pregnancy. The recipient was not HLA-typed to assess the presence of corresponding Ag. A TACO could not be ruled out by differential diagnosis because of a previous heart failure. The case was therefore assessed as probable in relation to a TRALI.

(8) A 60-year-old patient with Child-C liver cirrhosis received nine FFP, four RBCs, two PCs, and 200 mg human albumin due to a haemorrhagic shock in a pelvic ring fracture. After completion of the transfusion series, she developed an oxygenation impairment within the relevant time window. Radiological evidence of alveolar pulmonary oedema was obtained. Pneumonia, circulatory overload (TACO) or ARDS after trauma were other causes considered as differential diagnosis. In the TRALI assessment, HLA class II antibodies were found in one of the FFP donors and HLA class I and II antibodies were found in a donor of one of the pooled PCs. The HLA typing of the recipient for the detection of corresponding Ag is missing for diagnosis, so that the case could only be assessed as probable. The patient died ten days after symptom onset in acute-on-chronic liver failure (ACLF). Taking into account both the severe underlying condition of the patient, the HLA-Ab

findings, and the clinical course, the TRALI is assessed as a contributory factor for the fatal course and thus the case is considered possible.

(9) A 72-year-old patient with haematemesis primarily characterised by reflux esophagitis received two RBCs to treat anaemia caused by bleeding. She subsequently developed malaise, dyspnoea, and a drop in oxygen saturation below 90 percent. New bilateral infiltrates and acute pulmonary oedema were found in x-ray diagnostics. HLA class I and II antibodies were detected in one of the two donors involved. The prerequisites for an immunogenic TRALI were thus met. Since an HLA typing of the recipient was also missing here and no differentiation of the positive HLA-Ab screening result was made, the case can only be assessed as probable.

Table 4.4a: Number of reported suspected cases of transfusion-related acute lung injury (TRALI), confirmed cases after administration of RBC, PC, and plasma, and SAR rates per 106 transfused units (2021)

TRALI	2021	TRALI rate per 10^6 units
Number of reports	55	
Confirmed cases after administration of		
RBCs	4	1.23
PCs	2	4.0
Plasma	0	0
Combination	3	
Total confirmed cases	**9**	

Table 4.4b: Confirmed TRALI cases in 2021

TRALI	Donor			Recipient	
Evaluation	**Donor findings (Ab/Ag)**	**Blood component**	**Gender**	**Recipient findings (corresponding Ag/Ab)**	**Underlying condition**
Certain	**HLA-Ak:** HLA-Ak: anti-HLA-A66, **B7,** B13, B27, B47, B48, B57, B60, B61, B62, B63, B73, B75, B76, B77, B81	A-PC	female, 6 pregnancies in history	**HLA-Ag: B7**	Post-ET myelofibrosis
Certain	Anti-HLA-A11, A25, B5, B13, B18, B22, B39, B40, B42	RBC	female, pregnancy in history	**Ag:** corresponding Ag present **Ak*:** HLA-A1, A11, A23, A24, A36; B8, B44, B45, B76, B82; Cw7	Haemangioma of the cavernous sinus, surgical removal
Certain	Anti-HLA-**DR13** and -**DQ6**	P-PC	female, pregnancy in history	HLA-**DR13** and -**DQ6**	Coronary bypass surgery due to heart disease
Certain	**Anti-HNA 3a,** anti-HLA A2, -A68, -A69, -DQ5, -DQ6, DPA1 or DPB1	P-PC FFP	2 female donor with pregnancy in history 2 male donors, immunisation history unknown	**HNA 3a** and others	intraspinal mass, surgical removal
Probable	Anti-HLA I and II	RBC	female, pregnancy in history	not tested	right cerebral ischemia, LAE, anaemia
Probable	Anti-HLA I and II including anti HLA **DQA1*05**	A-PC	female, pregnancy in history	HLA-**DQA1*05,** -DQB1, -DRB1	Adenocarcinoma of the lung
Probable	Anti-HLA I and II	RBC	female, pregnancy in history	not tested	Tumour anaemia in oral floor carcinoma
Probable	Anti-HLA I and II	RBC, P-PC, FFP	1 male donor 1 female donor, 2 pregnancies	not tested	Child-C liver cirrhosis, haemorrhagic shock in pelvic ring fracture
Probable	Anti-HLA-A29, -A34, -A43, CW2, CW4, CW7, CW14	RBC	female, no pregnancy in history	not tested	Haematemesis characterised by reflux esophagitis, COVID-19, acute-on-chronic kidney failure

* Reverse TRALI also possible, but not confirmed: detection of HLA-Ab in the recipient; status regarding corresponding Ag in the donors known

Deaths:

In 2021, there were two confirmed deaths related to a TRALI (see cases 6 and 8).

4.5 Transfusion-Associated Dyspnoea (TAD)

TAD was reported as a serious transfusion reaction in 24 reports in 2021; in 20 cases, an association with the transfusion was assessed as probable or possible.

Table 4.5: Number of reported suspected cases of TAD, confirmed cases following the administration of RBC, PC, plasma, or a combination of these and SAR rates per 10^6 transfused units (2021)

Dyspnoea	2021	TAD rate per 10^6 units
Number of reports	24	
Confirmed cases after administration of		
RBCs	18	5.55
PCs	1	2.00
Plasma	1	1.56
Combination	0	
Total confirmed cases	**20**	

Deaths:

No fatalities were reported in 2021.

4.6 Haemolytic Transfusion Reactions (HTRs)

The association of a haemolytic reaction with a transfusion is considered likely if, in addition to the typical clinical symptoms, the laboratory findings on haemoglobin, haptoglobin, bilirubin and LDH indicate haemolysis. The association with the transfusion is considered to be certain in the presence of a positive antiglobulin test or a positive crossmatch test. As in the last report, the 2021 report only lists cases as confirmed HTRs that have been assessed as probable and confirmed.

In 2021, 20 of the 77 suspected HTR cases reported were confirmed, 17 of which were due to RBC transfusions and three to PC transfusions (Table 4.6a). In an additional 20 cases, association with the transfusion was classified as possible, in 27 cases as unlikely and an assessment based on the reported data was not possible in ten cases. Of the 20 confirmed HTRs, 16 were reported as acute HTRs, three of which were due to high isoagglutinin titres in A-PCs, one case due to irregular anti-A1 Ab, five cases due to other irregular alloantibodies, and four cases due to auto-Ab. In three cases, the haemolysis was not immunological. The three HTRs were due to minor-incompatible A-PC transfusions. The same donor was involved in all three cases and extremely high anti-A-isoagglutinin titres (> 1,000) were found at the follow-up.

Furthermore, four cases of delayed HTRs were reported, all of which were triggered by alloantibodies. Thus, a total of nine of the 20 confirmed HTRs were due to alloantibodies (Table 4.6b).

Deviating from the literature [23], significantly more acute (16) than delayed (4) HTRs were reported in the 2021 reporting period.

Table 4.6a: Number of reported suspected cases of Haemolytic Transfusion Reactions (HTRs), confirmed cases following the administration of RBC and PC, deaths after administration of RBC and SAR rates per 10^6 transfused units (2021)

HTR	2021	HTR rate per 10^6 units
Number of reports	77	
Confirmed cases after administration of		
RBCs	17	5.24
PCs	3	6.00
Plasma	0	0
Combination	0	
Deaths (RBC)	0	
Total confirmed cases	**20**	

Table 4.6b: Confirmed HTR broken down by type of reaction and Ab detection (2021)

HTR 2021	Acute HTRs	Delayed HTRs	Unknown*	Total
AB0-Ab	4	0	0	4
Other Allo Ab	5	4	0	9
Auto Ab	4	0	0	4
Non-immunological	3	0	0	3
Not specified	0	0	0	0
All HTRs	**16**	**4**	**0**	**20**

* Information on the time of the transfusion is missing.

Deaths:

No deaths due to HTRs were reported in 2021.

4.7 Febrile Non-Haemolytic Transfusion Reactions (FNHTRs)

The strong increase in reports observed since 2014 has now continued into 2021 after a slight decline in 2020. It should be noted that, although the total number of reports from 2021 exceeds the value from 2019, the number of confirmed cases does not quite reach the level from 2019 (Annex, Figure 1). The rate of confirmed cases of FNHTR in 2021, unlike in previous years, was significantly higher after PC administration than after RBC administration. No cases were reported after administration of plasma.

Table 4.7: Number of reported suspected cases of febrile, non-haemolytic transfusion reactions (FNHTR), confirmed cases after administration of RBCs, PCs or a combination of these and SAR rates per 10^6 transfused units (2021)

FNHTR	2021	FNHTR rate per 10^6 units
Number of reports	200	
Confirmed cases after administration of		
RBCs	142	43.81
PCs	30	60.04
Plasma	0	0
Combination	9	
Total confirmed cases	**181**	

Deaths:
No deaths associated with an FNHTR have been reported since the systematic collection of reports began in 2012.

4.8 Other transfusion reactions

71 suspected cases of a transfusion reaction were reported during the reporting period; however, the cause of these reactions is not the transfusion, but predominantly the underlying condition. The exception among these cases subsumed under ”other transfusion reactions“ is the occurrence of an alloimmunisation after a PC transfusion:

A 63-year-old patient developed anti-E alloantibodies after transfusion of several E-positive PCs. She had not received any E-positive RBCs that could explain the immunisation. Alloimmunisation by PC is possible in principle [24], although only very rarely observed. Although anti-E Ab can also occur naturally without prior immunisation, due to the temporal correlation, the transfusion of the PC is to be assumed as the most probable cause in the present case.

4.9 Transfusion-Transmitted Bacterial Infections (TTBIs)

Of the 31 suspected cases of TTBIs reported in 2021, two transmissions of *Listeria monocytogenes* could be confirmed with certainty by sequence comparison of the samples from patients and PCs. These were twin preparations from the same apheresis PC donor that were transfused on the third and fourth days of shelf life. The donor himself was symptom-free at the time of the donation. *Listeria* was not detected in the follow-up examination or in the reserve samples, so the source of contamination (donor or secondary contamination) ultimately remained unclear. The transfusion of a pooled PC contaminated with *Serratia marcescens* was assessed to be the probable cause of sepsis with a fatal outcome. The individual donations involved (4 RBCs, 4 FFP) remained negative in post-testing, so contamination during processing is also possible in this case. Furthermore, a case of *Staphylococcus aureus* transmission by a pooled PC was classified as a probable transmission. In this case, the examination of all donors of the pooled PC also showed a positive test result for a plasma preparation

originating from one of the donors. In both cases, there was no investigation of the bacterial identity of the pathogen found both in the residual PC and in the patient's blood (Table 4.9 c). In a third case, *Staphylococcus epidermidis* with identical antibiotic resistance pattern was found in remnants of the patient's transfused RBC and blood culture. The case was also assessed as probable due to the same resistance pattern of both germs.

In four other suspected cases, the TTBI could not be confirmed on the basis of the available data, so the connection with the transfusion was assessed as possible. In three of these cases, information on the microbiology of the patient's blood or the administered product was missing. Since in these three cases the symptoms could only be explained by a TTBI, the connection with the transfusion was considered possible. In one case, the same pathogen was detected in the recipient and the product, but since the recipient had already tested positive for the relevant pathogen before the transfusion, retrograde contamination of the preparation by patient blood appears likely (Table 4.9b).

Table 4.9a: Number of reported suspected cases of transfusion-transmitted bacterial infections (TTBIs), confirmed TTBI cases after administration of RBCs, PCs and plasma, and SAR rates per 10^6 transfused units (2021)

TTBI	2021	TTBI rate per 10^6 units
Number of reports	31	
Number of transfused products with confirmed positive pathogen detection		
RBCs	1	0.31
PCs	4	8.00
Plasma	0	0
Number of which included a death	1	
Affected products total	**5**	

Table 4.9b: Transfusion-transmitted bacterial infections with possible causality (2021)

Pathogen	Product	Pathogen detection recipient/product	Outcome
Cutibacterium acnes	A-PC	not tested/positive	Restored
Cutibacterium acnes	RBC	n/a/positive	Restored
Escherichia coli	A-PC	positive even before transfusion/ positive*	Restored
Staphylococcus capitis	RBC	positive/not tested	Restored

* Retrograde contamination of the preparation by the patient possible

Table 4.9c: Transfusion-transmitted bacterial infections with confirmed causality (2021)

Pathogen	Product	Pathogen detection recipient/product	Outcome	Evaluation
Listeria monocytogenes	A-PC	Both	Restored	Certain
Listeria monocytogenes	A-PC	Both	Restored	Certain
Serratia marcescens	P-PC	Both	Death	Probable
Staphylococcus aureus	P-TK	Both	n/a	Probable
Staphylococcus epidermidis	RBC	Both	n/a	Probable

Deaths:

The death in the reporting year 2021 was due to the transfusion of a P-PC contaminated with *Serratia marcescens.* The P-PC was transfused three days after donation. The recipient, a 26-year-old patient with myelodysplastic syndrome, subsequently developed sepsis, in the course of which he died. The first symptoms appeared about an hour after the start of the transfusion, but were initially interpreted as anaphylactic events in the absence of a temperature increase.

4.10 Transfusion-Transmitted Viral Infections (TTVIs)

Viral transmission was confirmed on the basis of the criteria pursuant to vote 48 of the German National Advisory Committee Blood (AK Blut) [11] or on the basis of comparable criteria for pathogens not listed within that criteria.

One of the four suspected cases of transfusion-transmitted HEV transmission reported in 2021 was confirmed. A connection to transfusion was assessed as unlikely in nine suspected cases of HBV transmission and three suspected cases of HCV transmission. No suspected cases of HIV transmission were reported in 2021.

Table 4.10: Number of reported suspected cases of transfusion-transmitted viral infections (TTVIs), confirmed positive detection of pathogen after administration of RBC, PC and plasma as well as rates per product with positive pathogen detection per 10^6 transfused units (2021)

TTVI (HIV, HCV, HBV, HEV)	2021	TTVI rate per 10^6 units
Number of reports	16	
Transfused products with positive pathogen detection		
RBCs	0	0
PCs	0	0
Plasma	2*	3.12
Total Affected Products	**2**	

* Both plasmas from different donors were transfused to the same patient, resulting in only one case.

HEV

The HEV transmission confirmed in 2021 was due to the transfusion of two contaminated plasma preparations. Both products were manufactured in the period before the introduction of mandatory HEV-NAT donor screening. The patient tested positive for HEV IgG and IgM approximately three months after the transfusion and was also positive in the NAT screening. In the period in question, the patient had received a total of 14 RBCs, three pooled PCs and nine units of LyoPlas. Two follow-up samples of plasma donations from this group of transfused products also tested positive for HEV during the NAT. Sequencing was not possible, as both donors already had negative NAT results from subsequent donations, so the case could only be assessed as probable.

Deaths:

No deaths due to TTVI were reported in the 2021 reporting year.

Other transfusion-transmitted infections

A suspected case of Epstein-Barr virus (EBV) transmission via an RBC as well as a suspected case of CMV transmission via a combined component administration (1 RBC, 2 PCs, 1 FFP) was not confirmed. Furthermore, no transmissions of viral pathogens such as West Nile virus (WNV), chikungunya virus, dengue virus, Zika virus or other arthropod-transmissible viruses could be detected.

4.11 Donor Initiated Look-Back Procedures (LBPs)

In the 2021 reporting year, a total of 3,248 confirmed suspected donor infections were reported. These reports trigger an LBP. Compared to the previous years, the number of procedures began to decline again slightly. There were 867 confirmed positive screening results in 2018, 1,692 in 2019, and 3,675 in 2020. The increase in LBPs in the recent past was mainly due to a sharp increase in LBPs regarding HEV. HEV-NAT testing has been a mandatory part of blood donor screening since 1 January 2020 and was increasingly carried out by blood establishments on a voluntary basis even before this date [25]. As expected, the number of LBPs has now stabilised at a higher level in the second year after the introduction of mandatory HEV-NAT testing.

In the majority of the 3,248 reported cases, either the follow-up samples (FUS) tested negative (2,272), the previous donations were outside the LBP period or no products were transfused (692). The 116 cases in which follow-up samples tested positively were completed without report of transmission. Final information is missing in 165 cases due to lack of sample material or other reasons.

Table 4.11: Donor initiated look-back procedures (LBPs) in 2021, triggered by confirmed or repeatedly indeterminate laboratory results in line with the AK-Blut vote 48 [11]

2021	Confirmed positive index donations	NUP				
Pathogen	Reports	negative[1]	positive, no transmission reported	positive, confirmed transmission	Testing not-required[2]	other[3]
CMV	15	14	1	0	0	0
EBV	1	0	0	0	0	1
HAV	0	0	0	0	0	0
HBV	363	291	5	0	45	22
HBV+HCV	1	0	0	0	1	0
HCV	78	37	4	0	9	28
HEV	2,660	1,888	104	0	577	91
HIV	42	31	0	0	10	1
HIV+Syphilis	0	0	0	0	0	0
Syphilis	75	10	2	0	48	15
Parvo B19	7	0	0	0	0	7
WNV[4]	4	1	0	0	2	1
Total	**3,246**	**2,272**	**116**	**0**	**692**	**166**

[1] for HIV/HCV/Syphilis there were also repeated indeterminate results

[2] products not transfused/plasma for fractionation /previous donation outside the LBP period/Syphilis: storage duration of PC>5days

[3] no material/procedure still open, e.g. no feedback from hospital, USUV

[4] WNV: one confirmed WNV infection, one confirmed USUV infection (under ”other“), twice neither USUV nor WNV confirmed (no follow-up examination)

4.12 Incorrect Blood Components Transfused (IBCT)

The IBCT complex includes not only the incorrect transfusion of a blood component from the wrong blood group, but also all faulty processes that lead to a planned or completed transfusion of blood components that are not intended for the recipient concerned. These faulty processes include the administration of non-irradiated instead of irradiated blood components, a blood group-compatible IBCT of a patient without a transfusion indication, or an IBCT of a blood component with a coincidentally compatible blood group. Various causes can lie behind a faulty process, including the incorrect transmission of patient data, a mix-up of patients in the clinic, or switching the blood components before use.

In the following summary, IBCTs with a detectable transfusion reaction are therefore presented as an IBCT-SAR. Incompatible IBCTs in which no detectable transfusion reaction occurred despite the transfusion are presented as IBCT-SAEs. The term SAE (when used on its own) refers, as in previous haemovigilance reports, to adverse events or near-IBCTs in which no IBCT occurred. The following

presentation of the frequency of IBCTs (SAR as well as SAE) therefore differs from the presentations in previous haemovigilance reports.

In the 2021 reporting year, the following suspected cases were reported and confirmed with the exception of one case: 24 suspected cases of a transfusion reaction (SAR) due to an IBCT of RBC, five suspected cases due to IBCTs of plasma preparations and one suspected case of an IBCT with a combination of components (RBC blood type A to O and a compatible FFP intended for another patient).

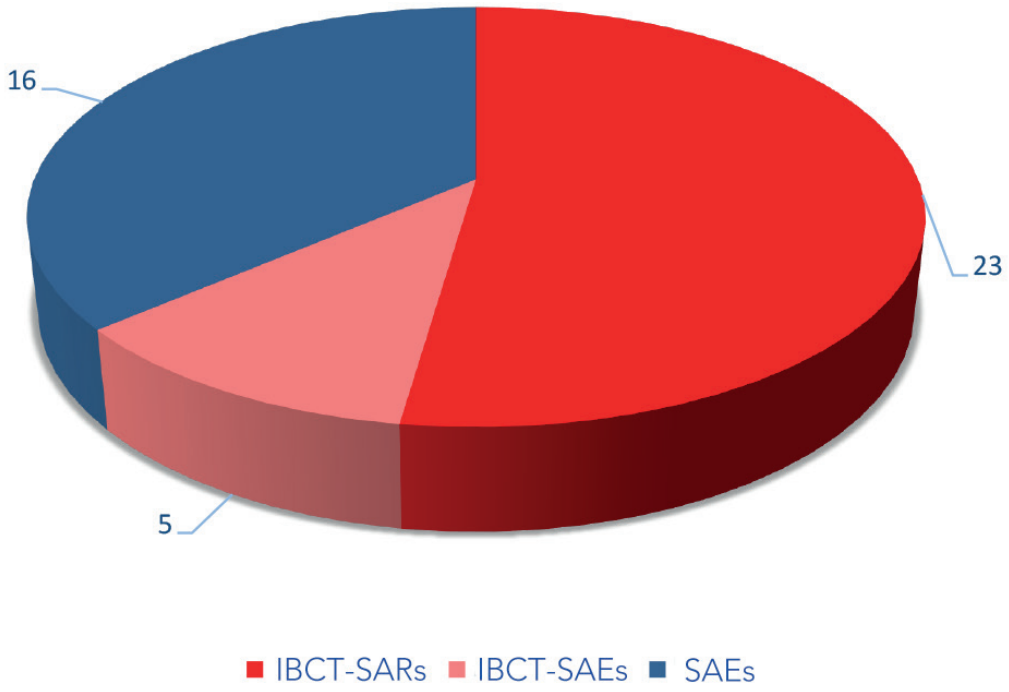

Figure 4.12a: ABO-Incompatible IBCT-SARs, IBCT-SAEs and SAEs Reported in 2021

In 2021, a total of 44 ABO-incompatible SARs and SAEs were reported in connection with the transfusion of RBCs. In 23 cases, an ABO-incompatible RBC transfusion (IBCT-SAR) led to a transfusion reaction. In five cases, different amounts of ABO-incompatible RBCs were transfused, which, due to various circumstances, did not result in a reaction from the RBC recipient (IBCT-SAE). In 16 other cases, SAEs were reported in which the RBC was not transfused because the error was discovered before transfusion. In these cases, an ABO-incompatible RBC transfusion could have occurred if it had not been corrected in time.

The severity of the reported transfusion reactions after ABO-incompatible RBC transfusion was categorised into levels 0–4 (see Fig. 4.12 b). Level 0 includes all IBCTs for which there were no laboratory indications of an IBCT and no symptoms of haemolysis reported to the PEI. Level 1 includes all IBCTs (IBCT-SARs) for which only mild adverse reactions and less pronounced laboratory indications have been reported. All serious and/or long-lasting reactions are placed at level 2, all life-threatening IBCT-SARs are placed at level 3, and all fatalities are placed at level 4.

Figure 4.12b: Definition of the severity of transfusion reactions after an IBCT

Definition	Severity Level
no laboratory indications of an IBCT	0
mild course with less pronounced clinical and laboratory indications of IBCT	1
severe and/or long-lasting course, invasive therapy necessary	2
life-threatening transfusion reaction	3
fatal course	4

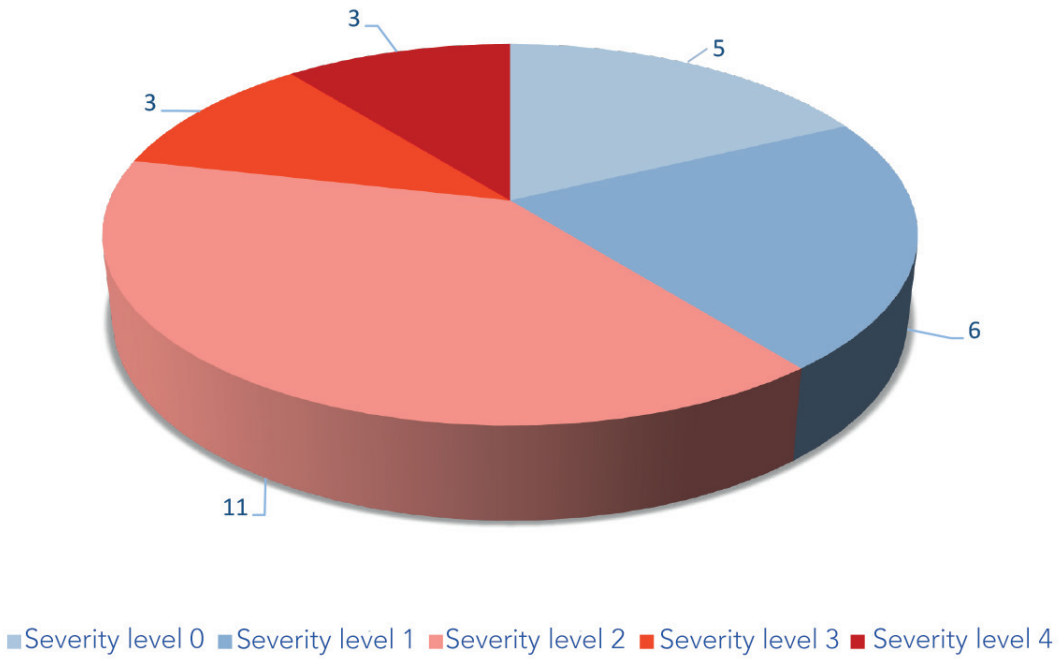

Figure 4.12c: Severity of reported ABO-incompatible RBC transfusions (SAR) in 2021

Figure 4.12c shows that five IBCT-SAEs were reported in 2021 in which no recipient response could be observed. The cases were therefore assigned to level 0. Six IBCT-SARs were assigned to level 1, eleven IBCT-SARs were assigned to level 2, and three IBCT-SARs were assigned to level 3. In the case of three IBCT-SARs in 2021, the causality between the IBCT and the death of the patient was classified as probable and the cases were thus assigned to level 4.

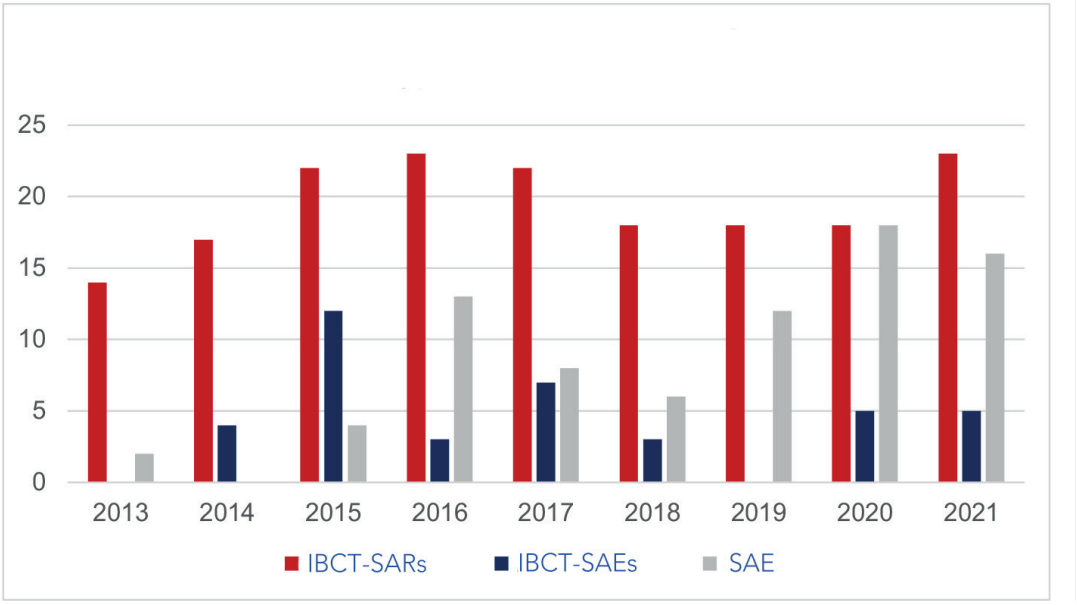

Figure 4.12 d: Reported ABO-incompatible SARs and SAEs involving RBCs each year from 2013 to 2021

Reports of ABO-incompatible RBC transfusions that triggered a serious transfusion reaction (IBCT-SARs) have increased from 14 reports in 2013 to 23 reports in 2021. In 2015 there were 12 reported IBCT-SAEs and between zero and five in the years following (2021). According to institutions reporting to the PEI, there was no evidence of a haemolytic transfusion reaction in the laboratory parameters for these IBCT-SAEs reports despite the administration of RBCs from incompatible blood groups. In the SAE category, which includes all near-IBCTs that could have led to an ABO-incompatible RBC transfusion, a significant increase can be seen between 2013 and 2021. While only two SAE cases were reported in 2013, there were 18 cases in 2020 and 16 cases in 2021. This increase can be explained by the introduction of the SAE reporting obligation in 2012 in the 16th AMG amendment [7].

Deaths:

In 2021, three deaths resulted from IBCTs using RBCs.

(1) A 75-year-old patient with blood group O Rh(D) negative was transfused with an RBC from blood group A Rh(D) positive. He then developed bradycardia, haemoglobinuria, macrohaematuria, and kidney failure. The patient died twelve days after the IBCT. The reporting facility did not see a direct link to the ABO-incompatible transfusion, but did not provide information on the underlying conditions or cause of death even after repeated inquiries. However, the available documents show that the patient had kidney failure, which required dialysis from the time of the IBCT until his death. Therefore, it can be assumed that the IBCT resulted in kidney failure requiring dialysis or contributed to the worsening of an underlying condition and ultimately to the fatal course in the presence of already impaired renal function.

(2) A 53-year-old patient with Child B-C liver cirrhosis and haemorrhagic shock due to variceal bleeding received an ABO-incompatible RBC (A to O) as part of a mass transfusion. This resulted in protracted shock and macrohaematuria. The patient died the same day.

(3) A 44-year-old patient with blood group O Rh(D) positive and anaemia as a transfusion indication was erroneously transfused with an RBC from the blood group B Rh(D) positive. Immediately after the end of the transfusion, the patient reacted with malaise, nausea, abdominal pain, haemoglobinuria/anuria and shock. The patient was transferred to the intensive care unit. Despite deployment of maximum therapy, multi-organ failure developed with pronounced vascular dysfunction, especially of the liver and kidneys. The patient died with multiple organ failure from the consequences of the IBCT.

4.13 Serious Adverse Events (SAEs)

Serious adverse events within the meaning of section 63i subsection 6 of the AMG [6] are primarily repeated adverse events that suggest a faulty work process or faulty materials and that could have led to serious reactions on the part of the recipient [12].

The number of SAE notifications has increased significantly since 2012, the year that the 16th AMG amendment entered into force. After the number of reports remained the same in 2019 and 2020, there was again a significant increase in SAE reports for 2021 (see Table 4.13 a). During this period, both the number of processed blood donations [9] and the total number of transfused blood components (Table 1 Annex) remained approximately the same.

Table 4.13a: Number of SAE reports, total number of allogenic blood donations and total number of transfused units of RBC, PC and plasma in the period from 2012 to 2021

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
SAE	26	29	64	79	99	96	113	171	176	266
Donations (10^6)	7,447	7,366	7,300	6,864	6,758	6,742	6,477	6,566	6,388	6,497
BCs transfused (10^6)	5,853	5,486	5,320	5,017	4,799	4,771	4,599	4,559	4,400	4,380

BCs=blood components

4.14 Serious Adverse Donor Reactions (Donor SARs)

Since 2015, the number of donor SARs reported annually has been in a comparable range (Table 4.14 a). In accordance with the reports pursuant to section 21 of the TFG, 69 blood establishments were identified as blood establishments collecting blood components in the reporting year 2021. 41 of these establishments reported donor SARs, including nine German Red Cross Blood Donor Services (with their own graduated plan officers), four blood establishments that exclusively collect plasma for fractionation and 28 state, municipal, religious, and private blood establishments. A total of five BEs indicated that no serious reactions were observed during the donation; no reports of donor SARs were received from 25 institutions.

A total of 5,081,279 donations (78.21 %) were made in the BEs that reported donor SARs; 47,526 donations (0.74 %) in BEs without donor SAR (zero reporting); and 1,368,016 (21.05 %) donations in the establishments for which no donor SAR information is available.

Table 4.14a: Reporting figures for donor SARs 2011–2021

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
confirmed donor SARs	1	3	13	24	531	459	527	444	423	463	444
reporting blood establishments	1	1	3	5	35	40	26	30	60	53	41

Based on the definition of the Haemovigilance Working Party of the ISBT [26], SARs occurring during the donation were divided into A) local symptoms attributable to the puncture, B) generalised symptoms, C) apheresis-specific complications, D) allergic reactions, E) cardiovascular events and F) other events. Figure 4.14a shows the percentages of each reaction type based on all donor SARs reported in 2021. Three cardiovascular reactions, each occurring in the context of a whole blood donation, were reported in 2021 as rare but particularly serious reactions. The reactions comprise a cardiac arrhythmia with short-term unconsciousness and seizure; pulmonary artery embolism within a week of donation, in which unusual pain had already occurred during use of the tourniquet; and cardiac arrest. Cardiac arrest occurred in a 27-year-old male donor; the patient's status after the reaction was reported as recovered. Further information on the course of the reaction is not available. The category "other" includes reports where further information on the type of reaction is missing.

A total of 84 first-time donors and 355 repeat donors were affected. In five cases, no information on donor status was provided.

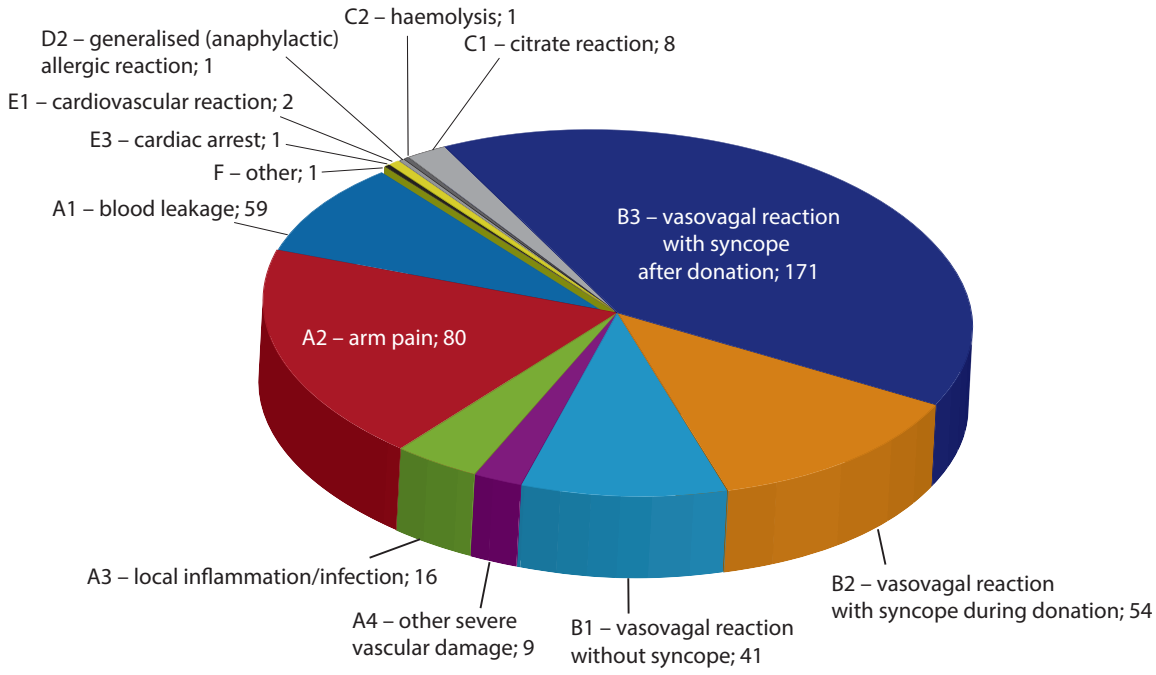

Figure 4.14a: Percentages of donor SARs 2021

As in the previous reports, there are variations in the percentages of the SARs. The percentages of vasovagal reactions with loss of consciousness during and particularly also after donation (54 % and 46 %, respectively) predominate when it comes to whole blood samples and plasmapheresis. Vasovagal reactions without loss of consciousness (24 %) and citrate reactions (27 %) predominate for cell apheresis (Table 4.14 b). When whole blood is taken, a significant proportion (36 %) of serious reactions at the injection site are added, mostly nerve injuries.

Table 4.14b: Serious donor reactions sorted by type of donation (2021)

Spende-SAR 2021	Whole blood donation	Plasma-pheresis	Zyta-pheresis	Total
A1 – blood leakage*	53	5	1	**59**
A2 – arm pain	65	9	6	**80**
A3 – local inflammation/infection	12	3	1	**16**
A4 – other severe vascular damage	8	1	0	**9**
B1 – vasovagal reaction without syncope	26	8	7	**41**
B2 – vasovagal reaction with syncope during donation	39	12	3	**54**
B3 – vasovagal reaction with syncope after donation	156	12	3	**171**
C1 – citrate reaction	0	0	8	**8**
C2 – haemolysis	0	1	0	**1**
C3 – air embolism	0	0	0	**0**
D1 – local allergic reaction	0	0	0	**0**
D2 – generalised (anaphylactic) allergic reaction	0	1	0	**1**
E1 – cardiovascular reaction	2	0	0	**2**
E3 – cardiac arrest	1	0	0	**1**
F – other	1	0	0	**1**
Total	**363**	**52**	**29**	**444**

* includes haematoma/arterial puncture /post-donation bleeding

The reporting rates on SARs based on 106 donations also vary between the donation types (Figure 4.14b) and thus confirm the data from previous years and from the literature [27, 28]. Unfortunately, the number of reporting BEs has decreased significantly compared to the previous year (41 BEs in 2021 versus 53 BEs in 2020, see Table 4.14a) and thus also the percentage of donations covered by the reports (79 % in 2021 versus 96 % in 2020). Compared to the previous year, the data from 2021 continues to provide a good assessment of the distribution and connections with the donation type, but it is less representative than in 2020.

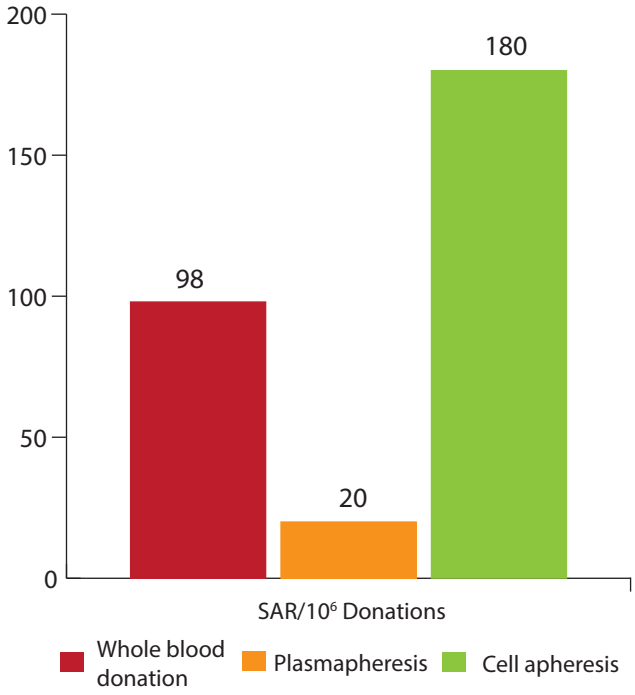

Figure 4.14b: Rates of confirmed donor SARs per million donations in 2021, based on data from 41 establishments reporting donor SARs; cell apheresis includes thrombocytapheresis, erythrocytapheresis, and multicomponent donation

// 5. Summary //

- As a general rule, it should be noted that haemovigilance data based on spontaneous reports can only allow for a determination of the reporting frequency and not the incidence of serious transfusion reactions.
- Once again, in 2021, the highest SAR rates per 10^6 transfused units were reports of ATRs after PR administration.
- The reporting rate of cases of transfusion-associated circulatory overload after RBC administration has increased significantly in recent years (2016–2019: 12.96 per 10^6 RBCs, 2020–2021: 21.27 per 10^6 RBCs).
- In the 28 cases of a confirmed blood group-incompatible RBC transfusion, six recipients experienced life-threatening complications or fatalities.
- With regard to transfusion-transmitted of pathogens, there was one case of HEV transmission via two plasmas from different donors and five confirmed transmissions of bacterial pathogens, with a fatal course after PC administration. No transfusion-transmitted HIV, HCV, or HBV transmissions were confirmed.
- The most common serious donor SARs were vasovagal reactions with syncope in 171 of 444 confirmed reactions, the most serious reactions were three cardiovascular reactions (including a pronounced cardiac arrhythmia and cardiac arrest with subsequent resuscitation), each in the context of whole blood donations.
- Seven deaths with a confirmed causal relationship to transfusion were reported in 2021. Three cases involved blood group-incompatible IBCTs of RBCs, two involved TRALIs after PC administration, one case involved a bacterial infection after transfusion of a pooled PC, and one case involved a TACO after RBC transfusion.

// 6. References //

1. Corman VM et al.: SARS-CoV-2 asymptomatic and symptomatic patients and risk for transfusion transmission. Transfusion 2020;60:1119-1122
2. Richter E et al.: Detectable SARS-CoV-2 RNAemia in Critically Ill Patients, but Not in Mild and Asymptomatic Infections. Transfus Med Hemother 2021;48:154-160
3. Directive 2002/98/EG of the European Parliament and of the Council. https://www.pei.de/SharedDocs/Downloads/DE/service/rechtliches/richtlinie-2002-98-eg-blutrichtlinie-2003-01-27.pdf?__blob=publicationFile&v=2
4. https://www.pei.de/DE/newsroom/dossier/coronavirus/coronavirus-inhalt.html?nn=169466&cms_pos=4
5. Funk MB et al.: 2021: Haemovigilance Report of the Paul-Ehrlich-Institut 2019: Assessment of the Reports of Serious Adverse Transfusion Reactions Pursuant to Section 63i AMG: www.pei.de/haemovigilanzbericht
6. https://www.pei.de/DE/arzneimittelsicherheit/haemovigilanz/meldeformulare-online-meldung/meldeformulare-online-meldung-node.html
7. https://www.gesetze-im-internet.de/amg_1976/
8. COMMISSION DIRECTIVE 2005/61/EC OF 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and reporting of serious adverse events and reactions. http://data.europa.eu/eli/dir/2005/61/oj
9. https://www.pei.de/DE/newsroom/pflichtberichte/21tfg/21-tfg-berichte-node.htmlwww.pei.de/haemovigilanz-formulare
10. https://www.gesetze-im-internet.de/tfg/
11. AK Blut Vote 48: Message from the German National Advisory Committee Blood of the Federal Ministry of Health. Look-back procedures pursuant to section 19 of the Transfusion Act. Federal Health Bulletin Health Research – Health Protection 2021;64:108-125
12. Funk MB, Frech M, Lohmann A, Keller-Stanislawski B: Law – Haemovigilance. Overview of the legal requirements vis-à-vis the higher federal authority in Germany. Transfusionsmedizin. 2015;5(2):102-107
13. ISBT Working Party on Haemovigilance: Proposed Standard definitions for surveillance of non-infectious adverse transfusion reactions. https://www.isbtweb.org/isbt-working-parties/haemovigilance/resources.html
14. Defence against drug risks – Order of requirements for the approvals of therapeutic individual plasma (plasma stored in quarantine or treated with a method for pathogen inactivation) (from 08. May 2009). Federal Gazette No. 84 from 10.06.2009, page 2064
15. Ring J et al.: Guideline on Acute Therapy and Management of Anaphylaxis. Allergo J Int. 2014;23:36-54
16. Li G et al.: Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. Transfusion. 2011;51(2):338-343
17. Klandermann RB et al.: Transfusion-associated circulatory overload-a systematic review of diagnostic biomarkers. Transfusion. 2019;59:795-805
18. De Clippel D, Emonds MP, Compernolle V: Are we underestimating reverse TRALI? Transfusion. 2019;59(9):2788-2793
19. Funk MB et al.: 2015. Haemovigilance Report of the Paul-Ehrlich-Institut 2013/14: Assessment of the Reports of Serious Adverse Transfusion Reactions Pursuant to Section 63i AMG: www.pei.de/haemovigilanzbericht
20. Vlaar APJ, Juffermans NP: Transfusion-related acute lung injury: a clinical review. Lancet. 2013; 382:984-994
21. Vlaar APJ et al.: A consensus redefinition of transfusion-related acute lung injury. Transfusion. 2019;59:2465-2476
22. Wiersum-Osselton JC et al.: Revised international surveillance case definition of transfusion-associated circulatory overload: a classification agreement validation study. Lancet Haematol. 2019;6:e350-e358. doi: 10.1016/S2352-3026(19)30080-8
23. SHOT reports. www.shotuk.org/shot-reports
24. Rajeswari Subramaniyan: Non-RhD (anti-E) red cell alloimmunization following platelet transfusion: a case report and implications on quality of the platelet concentrates and antibody screening protocols. Hematology, Transfusion and Cell Therapy. 2022; 44 (2):272-274
25. Notice on the authorisation of medicinal products – Defence against drug risks – Arrangement of testing of blood donors to prevent transmission of hepatitis E virus by blood components for transfusion and stem cell preparations for hematopoietic reconstitution. 5 February 2019, Federal Gazette Federal Gazette AT 17.05.2019 B7
26. ISBT Working Party on Haemovigilance. Standard for Surveillance of Complications Related to Blood Donation. http://www.isbtweb.org/working-parties/haemovigilance/
27. Daurat A et al.: Apheresis platelets are more frequently associated with adverse reactions than pooled platelets both in recipients and in donors: a study from French hemovigilance data. Transfusion 2016;56:1295-1303
28. Orru' S et al.: Blood Donation-Related Adverse Reactions: Results of an Online Survey among Donors in Germany (2018). Transfus Med Hemother. 2021; https://doi.org/10.1159/000516049
29. Orru' S et al.: Analysis of Transfusion-Transmitted Bacterial Infections according to German Hemovigilance Data (2011–2020). Transfus Med Hemother. 2022; https://doi.org/10.1159/000526761

// 7. Figures and Tables //

Figure 1: Annual total of confirmed serious adverse transfusion reactions (2000–2021)

TACOs have been systematically recorded since 2009, FNHTRs and TADs since 2012. Beginning in 2009, only Grade III and IV ATRs are included. Starting in 2013, only probable and confirmed TRALIs are considered as confirmed transfusion reactions. As of 2020, only probable and confirmed HTRs are considered as confirmed transfusion reactions.

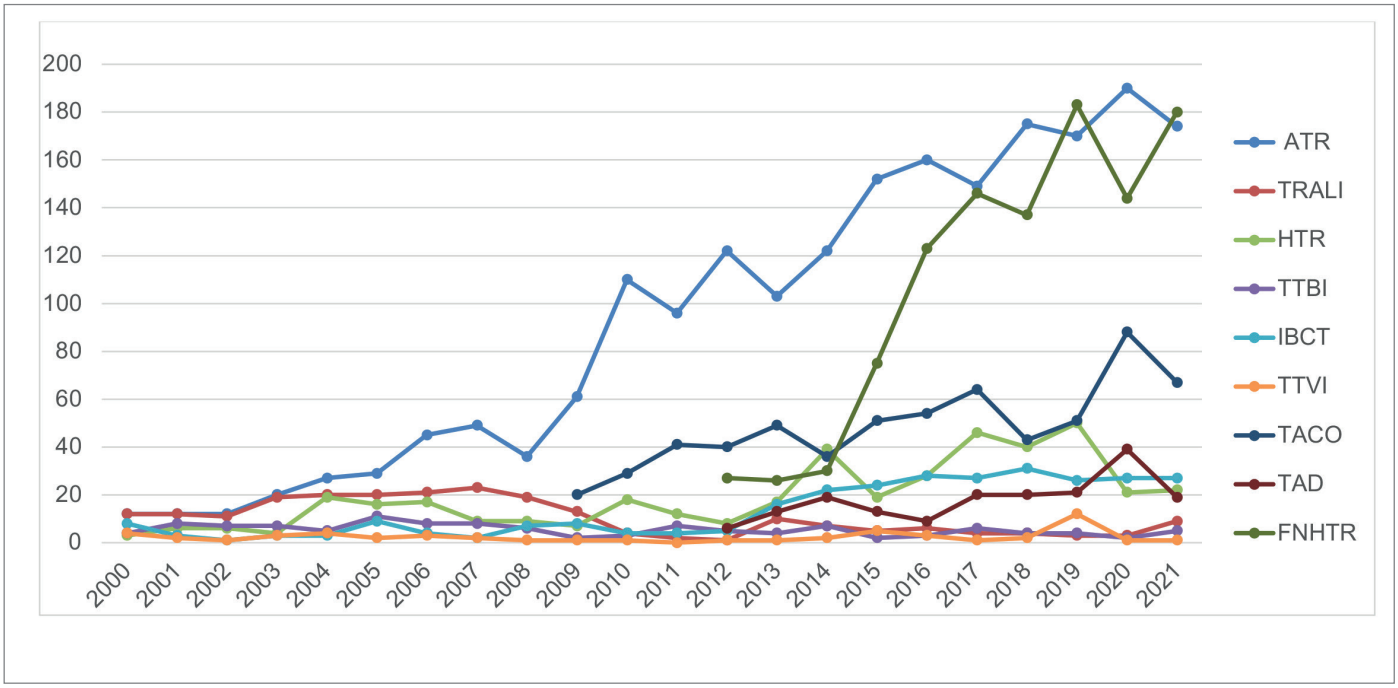

Figure 2: Percentage change in consumption of blood components (2000–2021)

Consumption in 2000 corresponds to 100 percent. The consumption of PC steadily increased to 161 percent in 2011. Since then, PC consumption has stagnated with slight fluctuations. Consumption of RBC and plasma has been falling since 2011.

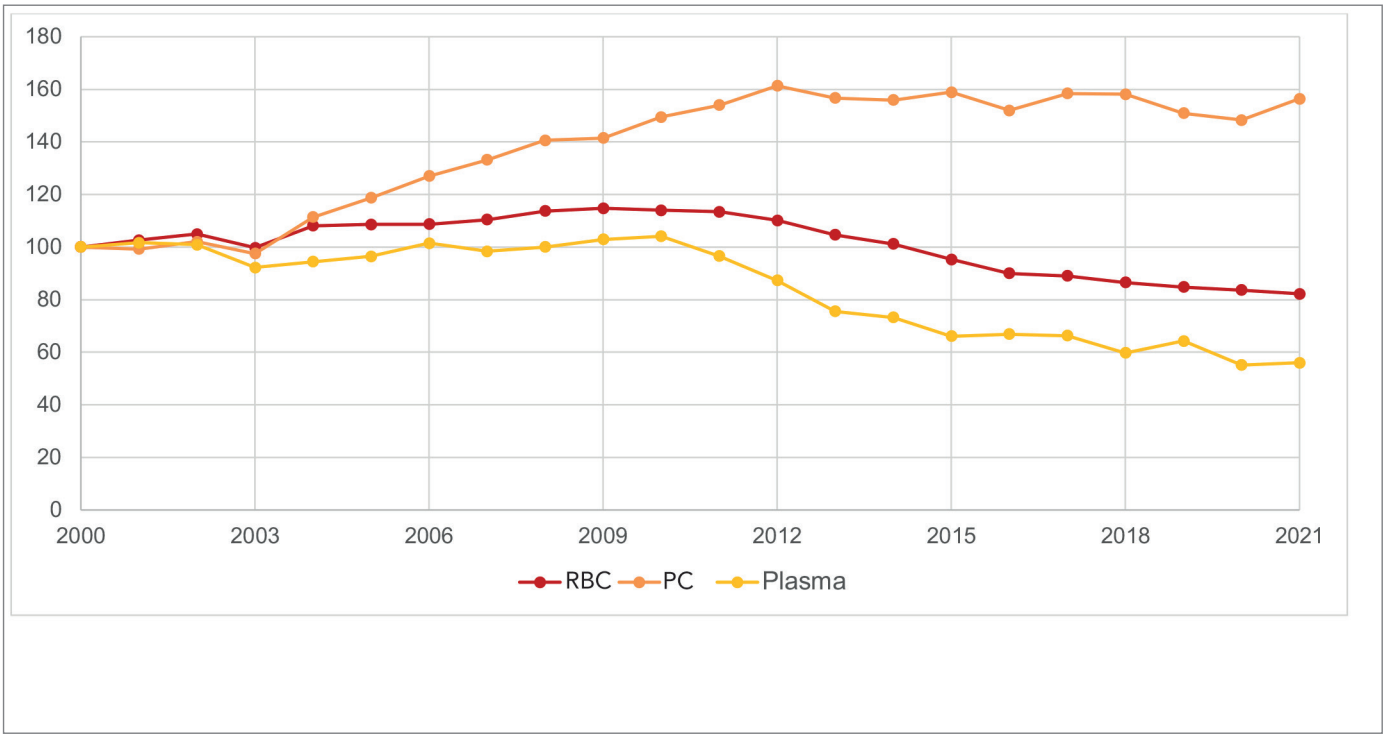

Table 1: Consumption of blood components (2000–2021), calculated from the user-reported data on sale and expiry submitted in accordance with section 21 of the TFG (as of 08.09.2022 [9])

The usage figures used for the calculation of TACOs (reports since 2009) and for FNHTRs, TADs and HEV (reports since 2012) are listed separately.

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2020–2021	2000–2021
RBC	16,051,470	17,173,130	17,964,825	16,202,065	13,807,351	6,536,483	87,734,178
PC	1,274,659	1,566,873	1,870,911	2,022,453	1,979,632	973,527	9,687,151
Plasma	4,515,718	4,469,498	4,616,104	3,453,264	2,941,921	1,270,588	21,269,076

TACO	2009–2021	TAD, FNHTR, HEV	2012–2021
RBC	50,027,589	**RBC**	36,545,445
PC	6,397,339	**PC**	4,975,608
Plasma	11,140,214	**Plasma**	7,667,756

Table 2: Total number of reported serious transfusion reactions (SARs), confirmed transfusion reactions, and proportion of associated deaths (1997–2021)

Serious Transfusion Reactions (SAR) 1997–2021	Reported Suspected cases	Confirmed cases	Share of cases with fatal outcome
Acute allergic/anaphylactic transfusion reactions (ATRs)[1]	4,104	2,040	34
Transfusion-related acute lung injury (TRALI)[2]	1,389	255	25
Haemolytic transfusion reactions (HTRs)[3]	931	458	25
Transfusion-transmitted bacterial infections (TTBIs)	635	139	21
Incorrect blood components transfused (IBCT)	304	300	21
Transfusion-transmitted viral infections (TTVIs)[4]	3,702	78	3
Post-transfusion purpura (PTP)	35	20	0
Transfusion-associated graft-versus-host disease (GVHD)	4	3	1
Transfusion-associated circulatory overload (TACO)[5]	706	633	16
Transfusion-associated dyspnoea (TAD)[6]	230	182	0
Febrile non-haemolytic transfusion reactions (FNHTRs)[6]	1,172	1,057	0
Other SARs	321	52	0
Total	**13,533**	**5,217**	**146**

[1] as of 2009 only ATR grades III and IV included in the assessment

[2] as of 2013 only probable and confirmed TRALI included

[3] as of 2020 only probable and confirmed HTR included

[4] contains reports on HCV, HIV, HBV, HAV, HEV

[5] TACOs systematically recorded as of 2009

[6] TADs and FNHTRs recorded as of 2012

Table 3: Confirmed suspected Reports of serious grade III and IV allergic/anaphylactic transfusion reactions (ATR), associated deaths, and confirmed ATR rate per 10^6 transfused units (2000–2021)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2020–2021	2000–2021
confirmed ATR after administration of							
RBC	27	99	160	277	368	202	1.133
PC	12	20	49	108	167	101	457
Plasma	9	16	54	57	70	34	240
Combination	8	15	40	57	49	28	197
Total	**56**	**150**	**303**	**499**	**654**	**365**	**2.027**
Deaths							
RBC	4	2	6	4	1	0	17
PC	1	1	2	1	1	0	6
Plasma	1	1	2	0	1	0	5
Combination	2	0	1	1	0	0	4
Total	**8**	**4**	**11**	**6**	**3**	**0**	**32**
Rates of confirmed ATRs per 10^6 transfused units							
RBC	1.68	5.76	8.91	17.10	26.56	31.37	12.91
PC	9.41	12.76	26.19	53.40	84.36	103.75	47.18
Plasma	1.99	3.58	11.70	16.51	23.79	26.76	11.28

Before 2009, ATR grades I and II were also recorded.

Table 4: Confirmed suspected reports of serious transfusion-associated circulatory overload (TACO), associated deaths and rate of confirmed TACOs, per 10^6 transfused units (2009–2021)

	2009–2011	2012–2015	2016–2019	2020–2021	2009–2021
RBC	57	146	179	139	521
PC	6	8	9	4	27
Plasma	6	6	7	4	23
Combination	22	16	17	8	63
Total	**91**	**176**	**212**	**155**	**634**
Deaths					
Totalled	**5**	**6**	**3**	**2**	**16**
Rates of confirmed TACOs per 10^6 transfused units					
RBC	4.23	9.01	12.96	21.27	10.41
PC	4.22	3.96	4.55	4.11	4.22
Plasma	1.73	1.74	2.38	3.15	2.06

Table 5: Confirmed suspected reports of serious transfusion-related acute lung injury TRALI, associated deaths and rate of confirmed TRALIs, per 10^6 transfused units (2000–2021)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2020–2021	2000–2021
TRALI, donor examination for HLA/HNA-Ab positive for							
RBC donors	5	9	5	13	7	5	44
PC donors	2	3	5	6	7	3	26
Plasma donors	17	48	18	5	3	1	92
Combination	0	0	0	0	1	3	4
Total	**24**	**60**	**28**	**24**	**18***	**12**	**166**
TRALI with fatalities after administration of							
RBC	1	2	0	0	1	0	4
PC	0	0	1	1	1	1	4
Plasma	1	10	5	0	0	0	16
Combination	0	0	0	0	0	1	1
Total	**2**	**12**	**6**	**1**	**2**	**1**	**25**
Rates of confirmed TRALIs per 10^6 transfused units							
RBC	0.31	0.52	0.28	0.80	0.51	0.76	2.68
PC	1.57	1.91	2.67	2.97	3.54	3.08	2.68
Plasma	3.76	10.74	3.90	1.45	0.68	0.79	4.33

* Includes contains a pooled-PC-induced non-immunogenic TRALI.

Since 1 September 2009, a specific donor selection process or test must be used [14] when plasma for transfusion will be produced from the donation.

Table 6: Confirmed suspected reports of serious transfusion-associated dyspnoea (TAD) and rate of confirmed TADs, per 10^6 transfused units (2012–2021)

TAD	2012–2015	2016–2019	2020–2021	2012–2021
TAD after administration of				
RBC	38	54	53	145
PC	5	13	3	21
Plasma	2	3	2	7
Combination	6	3	1	10
Total	**51**	**73**	**59**	**183**
Rates of confirmed TADs per 10^6 transfused units				
RBC	2.35	3.91	8.23	3.96
PC	2.47	6.57	3.08	4.22
Plasma	0.58	1.02	1.57	0.91

Table 7: Confirmed suspected reports of serious haemolytic transfusion reactions (HTR), associated deaths and rate of HTRs, per 10^6 transfused units (2000–2021)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2020–2021*	2000–2021
haemolytic transfusion reactions after administration of							
RBC	11	50	41	71	152	36	**361**
PC	2	4	4	3	1	5	**19**
Plasma	0	0	0	0	1	0	**1**
Combination	6	7	1	9	10	0	**33**
Total	**19**	**61**	**46**	**83**	**164**	**41**	**414**
number of which were delayed haemolytic transfusion reactions and HTRs with some evidence of irregular antibodies							
Delayed HTRs	3	6	21	14	55	13	**112**
number of which were haemolytic transfusion reactions with fatal courses after administration of							
RBC	0	3	2	0	9	3	**14**
Combination	0	1	0	0	0	0	**1**
Total	**0**	**4**	**2**	**0**	**9**	**3**	**15**
Rates of confirmed HTRs per 10^6 transfused units							
RBC	0.69	2.91	2.28	4.38	11.01	5.59	4.11
PC	1.57	2.55	2.14	1.48	0.51	5.14	1.96
Plasma	0	0	0	0	0.34	0	0.05

* Since 2020, only probable and confirmed HTRs have been recorded as confirmed cases.

Table 8: Confirmed suspected reports of febrile non-haemolytic transfusion reactions (FNHTR) and rate of confirmed FNHTR per 10^6 transfused units (2000–2021)

FNHTR	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2012–2021
FNHTR after administration of											
RBC	11	19	22	61	108	125	121	151	124	142	**884**
PC	1	4	5	7	14	14	12	23	13	30	**123**
Plasma	0	0	0	2	1	0	0	0	0	0	**3**
Combination	1	3	3	5	0	7	4	0	7	9	**48**
Total	**13**	**26**	**30**	**75**	**123**	**146**	**137**	**183**	**144**	**181**	**1,058**
Rates of confirmed FNHTRs per 10^6 transfused units											
RBC	2.53	4.61	5.52	16.25	30.44	35.64	35.48	45.19	37.62	43.81	**24.18**
PC	1.94	7.99	10.04	13.78	28.83	27.65	23.75	47.68	27.44	60.04	**24.72**
Plasma	0.00	0.00	0.00	2.64	1.31	0.00	0.00	0.00	0.00	0.00	**0.39**

Table 9: Confirmed suspected reports of serious transfusion-transmitted bacterial infections (TTBI), associated deaths and rate of TTBIs per 10^6 transfused units (2000–2021)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2020–2021	2000–2021
bacterial infections after administration of							
RBC	7	13	7	8	4	2	**41**
PC	19	18	11	10	13	5	**76**
involving P-PC	*8*	*9*	*5*	*1*	*6*	*2*	*29*
involving A-PC	*11*	*9*	*6*	*9*	*7*	*3*	*43*
Plasma	0	1	0	0	0	0	**1**
Total	**26**	**32**	**18**	**18**	**17**	**7**	**118**
number of which were bacterial infections with fatal courses after administration of							
RBC	0	0	0	0	0	0	**0**
PC	3	3	2	1	5	2	**16**
involving P-PC	*1*	*1*	*2*	*0*	*2*	*1*	*6*
involving A-PC	*2*	*2*	*0*	*1*	*3*	*1*	*9*
Plasma	0	0	0	0	0	0	**0**
Total	**3**	**3**	**2**	**1**	**5**	**2**	**16**
Rates of confirmed TTBIs per 10^6 transfused units							
RBC	0.44	0.76	0.39	0.49	0.29	0.31	**0.47**
PC	14.91	11.49	5.88	4.94	6.57	5.14	**7.85**
Plasma	0.00	0.22	0.00	0.00	0.00	0.00	**0.05**

Table 10: Pathogens detected in 45 blood donation recipients with confirmed TTBIs reported in the 2011–2021 period [29]

Course of the recipient's illness		not fatal [n=36]		fatal [n=9]	
after administration of		**RBC [n=15]**	**PC [n=21]**	**RBC [n=1]**	**PC [n=8]**
Pathogens with low (human) pathogenicity [n=9]					
Cutibacterium acnes	(gram-positive)	1	0	0	0
Staphylococcus epidermidis	(gram-positive)	2	4	0	0
Staphylococcus saprophyticus	(gram-positive)	1	0	0	0
Pasteurella multocida	(gram-negative)	0	1	0	0
Pathogens with medium/high (human) pathogenicity [n=33]					
Bacillus cereus	(gram-positive)	0	1	0	0
Listeria monocytogenes	(gram-positive)	0	2	0	0
Staphylococcus aureus	(gram-positive)	2	2	1	1
Streptococcus agalactiae	(gram-positive)	0	1	0	0
Streptococcus dysgalactiae	(gram-positive)	0	2	0	2
Streptococcus gallolyticus subsp. Gallolyticus	(gram-positive)	0	1	0	0
Streptococcus pneumoniae	(gram-positive)	0	2	0	0
Escherichia coli	(gram-negative)	3	3	2	2
Klebsiella oxytoca	(gram-negative)	1	0	0	0
Klebsiella pneumoniae	(gram-negative)	3	1	1	1
Serratia marcescens	(gram-negative)	0	1	1	1
Pathogens without clear (human) pathogenicity [n=3]					
Streptococcus – Group G	(gram-positive)	0	0	0	1
spore-forming bacteria		1	0	0	0
multiple bacteria		1	0	0	0

Table 11a: Confirmed suspected reports of transfusion-transmitted viral and bacterial infections (TTVI and TTBI) (2000–2021)

Confirmed transfusion-transmitted Infections	HBV	HCV	HIV	HEV	HAV	WNV, DENV, CHIKV	TTBI
2000	**1**	0	**3**	0	**1**	0	5
2001	**2**	0	0	0	**1**	0	8
2002	**1**	0	0	0	0	0	6
2003	**3**	0	0	0	0	0	7
2004	**3**	**1**	0	0	0	0	5
2005	**2**	0	0	0	0	0	11
2006	**3**	0	0	0	0	0	8
2007	**1**	0	**1**	0	0	0	8
2008	**1**	0	0	0	0	0	6
2009	**1**	0	0	0	0	0	2
2010	0	0	**1**	0	0	0	3
2011	0	0	0	0	0	0	7
2012	**1**	0	0	0	0	0	5
2013	0	0	0	**1**	0	0	4
2014	0	0	0	**2**	0	0	7
2015	**1**	0	0	**4**	0	0	2
2016	0	0	0	**3**	0	0	3
2017	0	0	0	**1**	0	0	6
2018	0	0	0	**2**	0	0	4
2019	0	**2**	0	**10**	0	0	4
2020	0	0	0	**1***	0	0	2
2021	**0**	**0**	**0**	**1****	0	0	5
Total	**20**	**3**	**5**	**25**	**2**	**0**	**118**

* An HEV transmission to a patient after massive transfusion via contaminated pooled PC and contaminated plasma. This TTVI is not yet included in the transmission rate overview.

** A patient received two HEV-positive plasmas from different donors during a massive transfusion.

Table 11b: Rate of TTVI per 10^6 transfused units (2000–2021)*

Rates of confirmed transfusion-transmitted HBV, HCV and HIV infections per 10^6 transfused units							
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2020–2021	2000–2021
RBC	0.37	0.58	0.11	0.06	0.07	0.00	0.23
PC	1.57	0.00	0.53	0.49	0.51	0.00	0.52
Plasma	0.44	0.22	0.00	0.00	0.00	0.00	0.14
Rates of confirmed transfusion-transmitted HEV infections per 10^6 transfused units							
				2012–2015	2016–2019	2020–2021	2012–2021
RBC				0.19	0.36	0.00	0.22
PC				1.98	4.04	0.00	1.24
Plasma				0.00	1.52	1.57	0.65

* Since multiple HEV transmissions involving two HEV-positive products have been reported, since 2021 all positive products for one pathogen have been recorded individually and not counted per case as before. This method allows for a more realistic representation of the transmission risk per 10^6 transfused units.

From 1997 through 2021, the entire time period in which the PEI has collected transfusion reaction reports, there have been no suspected reports of the transmission of viral pathogens such as West Nile virus (WNV), chikungunya virus (CHIKV), dengue virus (DENV), Zika virus or other arthropod-transmissible viruses. A total of six HIV, 22 HCV, 25 HBV, two HAV, 25 HEV and one malaria transmission via transfusion were confirmed during this period.

Table 12: Reports of IBCT with serious adverse reactions (SAR) in the recipient (2000–2021)

	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2020–2021	2000–2021
SAR RBC	15	18	23	63	101	44	264
SAR PC			0	1	3	0	4
SAR Plasma			0	3	8	10	21
SAR Total	**15**	**18**	**23**	**67**	**112**	**54**	**289**
Number of which were fatal (RBC administration)	0	1	4	5	3	5	**18**

Reports of IBCTs with serious adverse reactions (SAR) were categorised as ABO incompatibilities until 2014.

Rates of confirmed IBCT SARs per 10^6 transfused units							
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019	2020–2021	2000-2021
RBC	0.93	1.05	1.28	3.89	7.31	6.83	3.01
PC	0.00	0.00	0.00	0.49	1.52	0.00	0.41
Plasma	0.00	0.00	0.00	0.87	2.72	7.87	0.99

Table 13: Rates of confirmed suspected serious adverse transfusion reactions (SAR), for the period 2000–2021, each rate per 10^6 transfused units of RBC, PC, and plasma

SAR rates per 10^6 transfused units												
	Units transfused 2000–2021	ATR	HTR	TRALI	TTBI	TTVI[1]	IBCT	Units transfused 2009–2021[2]	TACO[2]	Units transfused 2012–2021[3]	FNHTR[3]	TAD[3]
EK	87,734,178	12.90	4.13	0.50	0.47	0.32	3.00	50,027,589	10.41	36,545,445	24.16	3.94
TK	9,687,151	47.18	1.96	2.68	7.85	1.75	0.41	6,397,338	4.22	4,975,607	24.72	4.22
Plas-ma	21,269,076	11.28	0.05	4.33	0.05	0.38	0.99	11,140,214	2.06	7,667,756	0.39	0.91

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

TACOs[2] were systematically recorded beginning in 2009, FNHTR[3] and TAD[3] from 2012; accordingly, the rates for TACOs refer to the consumption of transfused units from 2009–2021, the rates for FHNTRs and TADs refer to consumption from 2012–2021.

Table 14: Assessment of serious adverse transfusion reactions [5]

Probability of connection to transfusion	Criteria
assessment not possible	Insufficient data, for example, when there is no longer any data available on donors or recipients.
excluded or unlikely	Data, temporal relationship, underlying conditions exclude the transfused blood component as the cause of the reaction or speak against it.
possible	Clinical course of the reaction and temporal relationship with the transfusion suggests transfusion as the cause, but other factors, such as the patient‘s underlying conditions, a known septicaemia before the transfusion, or another source of contamination, cannot be ruled out as influencing factors or as the cause of the reaction.
probable	Clinical course of the reaction and data suggest transfusion as the cause of the SAR, but the data is not conclusive due to various circumstances, such as as the lack of a comparative antibiogram of the bacterial strain found in the product and recipient, or that evidence of the sequence homology of the virus found in the donor and recipient or of corresponding antigens or antibodies could not be provided due to a lack of test material.
certain	Clinical course of the SAR and laboratory data prove the connection.

Table 15: Definition of serious adverse transfusion reactions according to the Haemovigilance Working Party of the International Society of Blood Transfusion (ISBT) [13]

Acute allergic/anaphylactic transfusion reaction (ATR), no obligatory symptoms:

Symptoms

- Start: during transfusion or within **4 hours** of transfusion
- *Allergic:*
  - primarily mucocutaneous symptoms: not serious
    - rash, itching, hives (urticaria), local angioedema (e.g. lips, tongue, uvula, eyelids)
- *Anaphylaktoid:* always serious, additional symptoms:
  - *cardiovascular: d*rop in systolic blood pressure (>20 mmHg) as well as increase in heart rate (>20/min), shock/cardiac arrest
  - *respiratory:* hoarseness, stridor, cough, dyspnoea, cyanosis

Transfusion-related acute lung injury (TRALI):

- **Acute** onset during or within a maximum of **6 hours** after the end of transfusion
- Hypoxemia (PaO2/FiO2 <300 mmHg or oxygen saturation ≤90 % indoors)
- new bilateral lung infiltrates, radiologically confirmed
- Exclusion of pre-transfusion acute lung insufficiency (ALI) and alternative risk factors for ALI
- Differential diagnosis always excludes hypervolaemia (cardiac, renal, iatrogenic), determination of NT-proBNP level (course)

(All five criteria must be met.)

Haemolytic transfusion reaction (HTR):

Symptoms

- Acute: onset within 24 hours after end of transfusion, delayed: onset 1–28 days after end of transfusion
- Fever, chills, hot flush
- Pain in the flank, back, chest or abdomen
- Nausea/vomiting, diarrhoea
- Hypotension, pallor, jaundice, oligoanuria, dark urine, diffuse bleeding

Laboratory

- Inadequate increase or decrease in haemoglobin (>2 g/dL within 24 hours), haemoglobinaemia
- Increase in LDH (>50 % in 24 hours) and bilirubin
- Decrease in haptoglobin
- Haemoglobinuria

For immune-mediated HTR, laboratory confirmation by:

- Positive direct antiglobulin test, positive elution
- Positive cross test
- Possible appearance of new alloantibodies in the recipient

Transfusion-transmitted bacterial infection (TTBI):

- Start within 24 hours of the end of the transfusion
- Fever ≥ 39°C or a ≥ 2° C increase from baseline temperature, chills, tachycardia
- Detection of the bacterium/the same bacterial strain in the transfused blood product and the recipient; no pre-existing infection with the pathogen detected in the transfused product

Transfusion-transmitted viral infection (TTVI):

Evidence of infection in the recipient with exclusion of a pre-transfusion infection, other cause of the infection and clinical symptoms in temporal relation to the transfusion

Transfusion-associated circulatory overload (TACO):

Symptomes / laboratory (a total of ≥ 3 criteria must be met)

Within 12 hours of the end of the transfusion

- Required criteria (at least one criterion must apply):
  - acute or worsening impairment of breathing and/or
  - signs of acute or worsening pulmonary oedema based on:
    - clinical physical examination and/or
    - chest X-rays and/or other non-invasive assessment of cardiac function
- Additional criteria:
  - changes in the cardiovascular system (including tachycardia, hypertension, enlargement of the jugular veins, enlarged cardiac silhouette and/or peripheral oedema) that cannot be explained by the patient's underlying condition
  - signs of fluid overload, including positive fluid balance; clinical improvement after diuresis
  - supporting result involving a relevant biomarker, e.g. increase of NT-pro BNP by more than 1.5 times the value before transfusion

IBCT:

Transfusion of ABO-incompatible blood components; with coincidentally ABO-compatible or identical blood components; with blood components whose alloantibody compatibility has not been ensured; with blood components that have not been manufactured according to requirements (e.g. not radiated); with untested blood components as well as the transfusion of blood components without an indication for transfusion. IBCTs without recipient reactions are to be reported by the pharmaceutical company as serious adverse events (SAE) (section 63i subsection 7 of the AMG).

Transfusion-associated dyspnoea (TAD):

Symptoms

- Start in temporal relation to the transfusion (<24 hours after the transfusion)
- Exclusion of TRALI, TACO or allergic reaction

Post-transfusion purpura (PTP):

Symptoms

- Start within 5–12 days of transfusion
- Petechiae lab test
- Thrombocytopoenia
- HPA antibodies detectable in the recipient

Serious febrile non-haemolytic transfusion reaction (FNHTR):

Symptoms

- Start within 4 hours of the end of the transfusion
- Fever >38°C or an increase of ≥1°C (can also occur without fever)
- Chills
- Possibly combined with headache and nausea
- Exclusion of another cause, such as HTR, TTBI or underlying condition

  Only **serious** cases (fever ≥39°C and an increase of ≥2°C from baseline temperature and chills/rigor) should be reported.

Transfusion-associated graft-versus-host disease (TA-GVHD):

Symptoms

- Start 1–6 weeks after transfusion
- Fever, rash, liver dysfunction, diarrhoea, pancytopenia lab test
- Chimerism
- Characteristic histological appearances

No other cause identifiable.