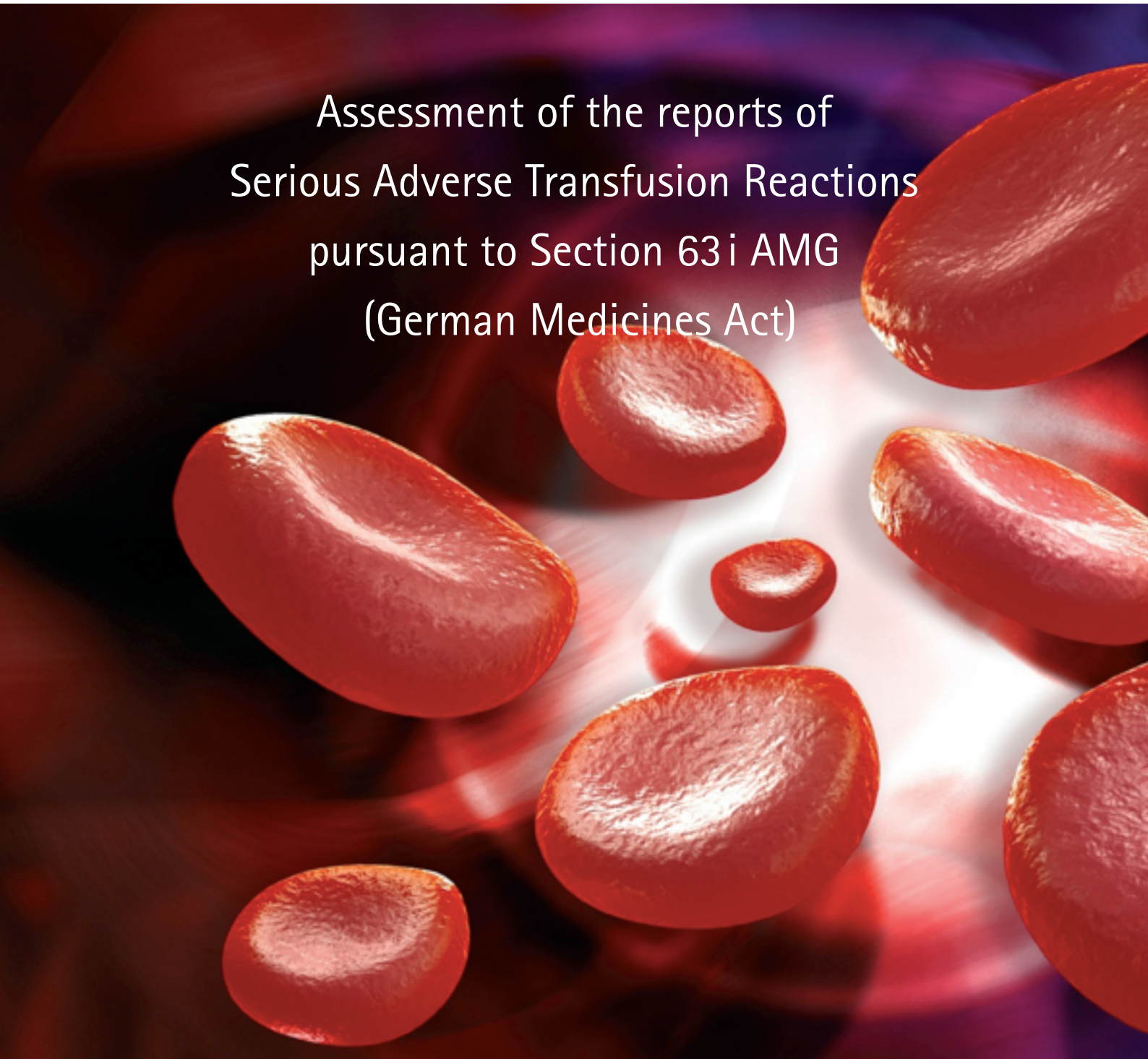
Federal Institute for Vaccines
and Biomedicines

Paul-Ehrlich-Institut

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

## 2013/14



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

# // Impressum //


### Published by

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The pdf version can be downloaded from
the website of the Paul-Ehrlich-Institut
www.pei.de/haemovigilance-report
For a subscription please contact
presse@pei.de
ISSN (Internet) 2192-2314


The Paul-Ehrlich-Institut is an
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# // Contents //

# // 1. Introduction //

The current haemovigilance report from the Paul-Ehrlich-Institute summarises the notifications of serious adverse transfusion reactions and serious adverse events from 2013 and 2014 and compares them with the reporting data from the years before (1979–2012). A comparison of the data from Germany with those of other haemovigilance systems (UK and Switzerland) shows that a similar standard exists in these countries with regard to risks and safety of blood components. [1, 2].

In the current report, the evaluation algorithm for reported cases of TRALI was changed to assure a better presentation of possible, likely and confirmed immunogenic and non-immunogenic reactions. The result is a higher number of registered cases of TRALI compared with the previous years.

Since the 16th amendment of the AMG (Arzneimittelgesetz, German Medicines Act) of 2012, a distinction is made between transfusion reactions and adverse events when recording incorrect transfusions. Adverse events are defined as incorrect processes without the occurrence of transfusions reactions. Altogether, the cumulative reporting rates for TR and adverse events have increased compared with the previous period.

Because of the current discussion concerning safety of platelet concentrates, a separate presentation of reporting rates was chosen for transfusion reactions after administration of apheresis platelet concentrates (APC) and of pooled platelet concentrates (PPC). In addition the reporting pattern for university as compared with that of non-university facilities was determined.

For the first time, the report also contains a detailed presentation of the transmission of HEV infections in 2013/14 in addition to the established TTVI reports.

An accurate documentation of adverse events by the treating doctors and the blood establishments involved as well as a standardised and transparent evaluation by the Paul-Ehrlich-Institut of the data reported is essential to identify so far unknown risks and to discuss the steps to be taken to improve the transfusion system. Since 2001 the German haemovigilance data are regularly reported to the Council of Europe and also to the European Commission since Directive 2005/61/EC became operative (www.edqm.eu/en/blood-transfusion-reports-70.html).

# // 2. Abbreviations //

| | |
|---|---|
| **Ab** | Antibody |
| **ACVB** | Aortocoronary vain bypass |
| **AK Blut** | German Advisory Committee “Blood”/national advisory board of transfusion |
| **AMG** | Arzneimittelgesetz (German Medicines Act) |
| **AML** | Acute myeloid leukaemia |
| **Anti-HBc** | Antibodies against hepatitis B-core antigen |
| **ARDS** | Acute respiratory distress syndrome |
| **APC** | Apheresis platelet concentrate(s) |
| **ATG** | Antithymocyte globulin |
| **ATR** | Acute transfusion reactions |
| **AWMF** | Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies in Germany) |
| **BNP** | Brain Natriuretic Peptide |
| **CJD** | Creuzfeld-Jakob-Desease |
| **CML** | Chronic myelogenous leukaemia |
| **CMV** | Cytomegaly virus enzyme immunoassay |
| **DCGMA** | Drug Commission of the German Medical Association |
| **EIA** | Enzyme immunoassay |
| **FFP** | Fresh frozen plasma |
| **GvHD** | Graft vs. Host Disease |
| **HAV** | Hepatitis-A virus |
| **Hb** | Haemoglobin |
| **HBV** | Hepatitis-B virus |
| **HCV** | Hepatitis-C virus |
| **HIV** | Human immunodeficiency virus |
| **HLA** | Human leucocyte antigen |
| **HNA** | Human neutrophil antigen |
| **HPA** | Human platelet antigen |
| **HTR** | Haemolytic transfusion reaction |
| **IHN** | International Haemovigilance Network |
| **LDH** | Lactate dehydrogenase |
| **MAIPA** | Monoclonal antibody immobilization of platelet antigens |
| **NAT** | Nucleic acid amplification test technology |
| **PCR** | Polymerase chain reaction |
| **PC** | Platelet concentrate(s) |
| **PEI** | Paul-Ehrlich-Institut |
| **PPC** | Pool platelet concentrate(s) |
| **PTP** | post-transfusion purpura |
| **RBC** | Red blood cell concentrate(s) |
| **STR** | Serious transfusion reaction |
| **TACO** | Transfusion-associated circulatory overload/transfusion-associated volume overload |
| **TTBI** | Transfusion-transmitted bacterial infection |
| **TTVI** | Transfusion-transmitted viral infection |
| **TFG** | Transfusionsgesetz (German Tranfusion Act) |
| **TPHA** | Treponema pallidum haemagglutination |
| **TRALI** | Transfusion-related acute lung injury |
| **TX** | transplantation |
| **WG** | Week of gestation |
| **S.a.** | State after |

# // 3. Methods //

All reports of serious transfusion reactions notified to the PEI based on Section 16 TFG and/or Section 63i AMG are entered in the database of the PEI. By using reporting forms, the reporting physician documents recipient-specific data such as the blood components administered, date of birth, gender, underlying disease and all relevant accompanying diseases of the patient as well as the course of the transfusion reaction. The blood establishments involved complete this information by specific data on the donations, lab tests performed and look-back procedures if required. All transfusion reactions reported are categorised in compliance with the criteria of the International Haemovigilance Network (IHN). Pursuant to Section 63i AMG, the pharmaceutical company has to notify incorrect transfusions without a transfusion reaction as serious adverse event to the PEI as competent senior federal authority (16th amendment of the German Medicines Act – Arzneimittelgesetz). For incorrect transfusions with a transfusion reaction, a reporting obligation pursuant to Section 16 (2) TFG (Transfusionsgesetz, Transfusion Act) applies [3, 4]. This obligation must be fulfilled by the treating doctor. Incorrect transfusions without a transfusion reaction are not subject to the reporting obligation on the part of the treating doctor pursuant to Section 16 (2) TFG, and are not reported to the pharmaceutical company and thus cannot be recorded and included in the haemovigilance report.

## 3.1 Categorisation of transfusion reactions (TR)

Basically, the definitions of serious transfusion reactions used in this report agree with those also used by the IHN [5]. The transfusion reactions are categorised and rated based on the criteria in Box 1: Definition of serious transfusion reactions (based on the criteria of the IHN).

Primarily changes in the reporting frequency of serious transfusion reactions were used to judge the usefulness of safety relevant action. The cases of acute (allergic) transfusion reactions reported in 2011 and 2012 were further subdivided according to the classification of Ring and Mesmer [6] conceived by the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF, Association of the Scientific Medical Societies in Germany). Based on this classification, a distinction was made between Grades I and II allergic transfusion reactions, and Grades III and IV serious allergic and/or anaphylactoid transfusion reactions.

In assessing suspected cases of TRALI, a distinction was made between possible and likely/confirmed TRALI events. The category of likely/confirmed cases was then subdivided into immunogenic and non-immunogenic events [7, 8]. There is a higher number of registered TRALI cases compared with the previous years, above all after the administration of RBCs.

Transfusion-associated dyspnoea was presented separately, since it is not comparable to other transfusion reactions which concur with dyspnoea such as a TRALI event or bronchospasm during an acute transfusion reaction. As it does not represent a serious transfusion reaction, it was not included in the respective Tables 1a and 1b. Based on the usually mild symptoms, febrile non haemolytic transfusion reactions were not included in the current haemovigilance report either.

The amount of blood components prepared by German blood establishments as well as the loss at manufacturers and users has been reported to the PEI since 1998 pursuant to Section 21 TFG [4]. The real consumption of the individual blood components can be calculated as an approximate

figure, and is also published in the report of the PEI on reports pursuant to Section 21 TFG on a regular basis (see Table 9). In Tables 2 to 5 and 7 to 8, the reporting frequencies of the transfusion reactions per blood component are determined for a period of four years each. Four four-year periods in total are compared with each other.

### Box 1: Definition of serious transfusion reactions (by IHN criteria)

Acute Transfusion reaction (ATR):

Skin rash, itching, exanthema, allergic dyspnoea, angiooedema, laryngeal oedema, drop in systolic blood pressure >30 mm Hg, rise in heart rate >30/min (definition tachycardia), bronchospasm/cyanosis, shock/circulatory arrest, occurrence of the symptoms within 24 hours after transfusion, exclusion of other transfusion reaction.

Transfusion-related acute lung injury (TRALI):

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

Haemolytic transfusion reaction (HTR):

Fever accompanied by other symptoms (respiratory distress, hypotension, tachycardia, pain in the region of the kidneys), macrohaematuria, inadequate rise in the haemogobulin level following transfusion, drop in the haemoglobulin level >2g/dl within 24 hours, rise in the lactate dehydrogenase level (LDH level) >50% within 24 hours, rise in the bilirubin level, haemoglobinaemia, drop in haptoglobin in temporal connection with the transfusion. The reaction is confirmed by a positive antiglobulin test or a positive cross 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 four hours accompanied by chills and tachycardia. Suspected transfusion transmitted bacterial infections are verified by detection of the bacterium in the transfused blood product or in the recipient and confirmed by detection of the same bacteria strain in the blood of the recipient and the transfused blood components.

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

TTVI is suspected in the case of seroconversion of the recipient post transfusion. To establish a causal relationship, the recipient triggered look-back procedure must be performed (pursuant to Opinion 34/35 of the AK Blut).

Transfusion associated circulatory overload (TACO):

Respiratory distress, tachycardia, typical signs of cardiogenic lung oedema in the chest radiograph, evidence of a positive liquid balance and/or cardiac injury during or within twelve hours post transfusion.

Administration of AB0-incompatible blood components (incorrect transfusion):

Incorrect transfusion in a more precise meaning is defined as treatment with AB0-incompatible blood components, transfusion of AB0 compatible blood components by chance, of blood components the allo-ab compatibility of which has not been confirmed, and transfusion of untested blood components. Depending on the cause and the effects, an incorrect transfusion can be reported as serious adverse event or serious adverse reaction (Section 63i (7) AMG).

Transfusion related dyspnoea:

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

Post-transfusion purpura (PTP):

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

## 3.2 Measures taken to improve safety standards

Between 1997 and 2012, the following measures to improve the quality and safety of blood components had been mandated by the PEI and/or recommended by the AK blood (German Advisory Committee Blood):

| Time of announcement | Measures prescribed or recommended |
|---|---|
| 1998 | Since April 1999 introduction of HCV screening for donors of red blood cell and platelet concentrates by NAT-pool testing (limit of detection of the HCV-RNA concentration of 5,000 IU/ml referring to a single donation). |
| 1999 | Since October 1999 HCV screening of donors of FFP by means of NAT pool testing (detection limit of HCV-RNA concentration of 5,000 IU/ml). |
| 2000 | Since August 2000 introduction of leucocyte depletion in the manufacture of red blood cell and platelet concentrates (residual concentration of leukocytes $< 1 \times 10^6$ per unit). |
| 2000 | Since February 2001 exclusion of blood donors who have lived in countries in which an increased number of variant Creutzfeldt–Jakob disease (vCJD) patients was registered. |
| 2002 | Since June 2003 introduction of pre-donation sampling to reduce the number of microbial contaminated blood components (voluntary measure taken by the blood donation centres in accordance with Opinion 27 of the "AK Blut"). |
| 2003 | Since May 2004 introduction of HIV donor screening for cellular blood components and fresh frozen plasma using NAT pool testing (detection limit for the HIV-RNA concentration 10,000 IU/ml). |
| 2006 | Since 2006 introduction of donor screening for cellular blood components and fresh frozen plasma using hepatitis-B core antibody single testing (Anti-HBc-Test). |
| 2008 | Since 2008, as voluntary measure to be taken by the blood donation centre: limitation of the shelf life of platelet concentrates to 4 x 24 hours plus the date of manufacture with the aim of reducing life-threatening septic transfusion reactions caused by bacterial contamination (Opinion 38 of the "AK Blut"). |
| 2009 | Since September 2009 introduction of donor screening to reduce the risk of TRALI: Blood from female donors may only be admitted to the preparation of plasma if the donors do not have a history of pregnancy and/or if the test for leucocyte antibodies is negative. |
| 2010 | Instructions for the consideration of the manufacturer's recommendations in using the ARCHITEKT-Anti-HCV test in the donor screening. |
| 2012 | Introduction of HIV-1-NAT test systems with two target regions.<br>Since 1 Jan 2015 in donor screening. |
| 2012/13 | Since 2013 update of Opinions 34 and 35 "Look-back procedures with regard to hepatitis B infections" (Opinion 42). |
| 2014 | Testing for antibodies against hepatitis-B core antigen (Anti-HBc) in the blood donation system (notification from the PEI of 7 February 2014). |
| 2014 | Conditions for a donor deferral after travelling to endemic areas for West Nile Virus (WNV) |

# // 4. Results //

## 4.1 Serious transfusion reactions in accordance with the IHN criteria

494 suspected cases of serious transfusion reactions were reported to the PEI in 2013, and altogether 589 in 2014. The number of reports per year has amounted to between 298 and 702 cases (mean value: 458 cases) and has thus remained constant in the past few years.

The 281 and 371 likely or confirmed acute transfusion reactions in 2013 and 2014 respectively refer to 79 and 120 allergic reactions, Grade I and II, 103 and 122 serious allergic reactions (Grade III and IV), 49 and 36 cases of transfusion-associated circulatory overload (TACO), 17 and 39 haemolytic reactions, ten and seven TRALI reactions, 16 and 22 incorrect transfusions with serious transfusion reactions, four and seven transfusion-transmitted bacterial infections, two and three transfusion-transmitted viral infections, and two cases of post-transfusion purpura. Suspected cases of transfusion-associated graft vs. host disease (GvHD) have not been confirmed.

In the current periods, increases in reported incorrect transfusions could be found, likewise, an increase in the total number of TRALI events. In this context, changes in the reporting behaviour in the case of incorrect transfusions as well as the change in the evaluation algorithm for TRALI reports must be taken into account.

In the period of 2013/14, reporting rates of serious allergic transfusion reactions add up to 15 cases per $10^6$ transfused red blood cell concentrates (RBC), 15 cases per $10^6$ fresh frozen plasma (FFP) units, and 52 cases per $10^6$ platelet concentrates (PC). They are thus higher than the reporting rates of the last four year period (2009–2012). Reporting rates of HTR and TTBI have remained unchanged compared with the previous years. For TTVI five HEV transmissions have been reported in the past few years.

In the two years referenced, altogether 15 deadly courses of a transfusion reaction were documented, four deaths each following acute allergic reactions and cases of transfusion-associated circulatory overload, two deaths each following incorrect transfusions and haemolytic transfusion reactions, and one death each following TRALI, TTBI, and TTVI.

In the observation period of 18 years (1997–2014) 104 deaths can be attributed to the administration of blood components. Serious allergic reactions (31 cases) were documented as the most frequent cause of death, followed by TRALI reactions (21 cases). Thirteen cases can be attributed to haemolytic transfusion reactions, 14 to TTBI, and ten to incorrect transfusions. In addition, eleven deaths were reported following TACO, three following TTVI, and one following GvHD.

## 4.2 Allergic transfusion reactions

*IHN criteria for less serious courses:* Skin reactions, drop in blood pressure < 30 mmHg, mild dyspnoea.

*IHN criteria for serious courses:* Drop in blood pressure ≥ 30 mmHg, pronounced dyspnoea, shock symptoms, clinical action taken in intensive care.

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

**Classification of the severity of allergic (transfusion) reactions according to Ring and Messmer**

| Grade | Skin | Abdomen | Respiratory tract | Cardiovascular system |
|---|---|---|---|---|
| I | Itching<br>Flush<br>Urticaria<br>Angioedema | | | |
| II | | Nausea<br>Colic | Rhinorrhoea<br>Hoarseness<br>Dyspnoea<br>Arrhythmia | Tachycardia<br>(increase ≥ 20/min)<br>Hypotonia<br>(drop > 20 mm Hg sys.) |
| III | | Vomiting<br>Defecation | Larynx oedema<br>Bronchospasm<br>Cyanosis | Shock |
| IV | | | Respiratory arrest | Cardio-vascular arrest |

The number of confirmed allergic and anaphylactoid transfusion reactions has largely remained constant in the period from 2011–2013, however, it rose to 252 cases in the last year (see Table). The number of cases with increased monitoring or extended period of hospitalisation varied from 146 to 178 per year and amounted to 835 in total in the past five years. 285 of these cases were categorised as Grade I or II and 550 as Grade III or IV. The number of grade III and grade IV reactions was between 96 and 122 cases per year (2010–2014). For the reporting rates of serious allergic reactions in the two year period, slight increases were observed following RBC and FFP administration and a marked increase following administration of PC. The number of fatal outcomes, on the other hand, remained more or less constant with three cases in 2013 and one case in 2014.

The table below only takes into account allergic reactions of Grades III and IV.

### Overview of ATR cases (see also Table 2, Section 7)

| | | 2010 | 2011 | 2012 | 2013 | 2014 | 2010–2014 | |
|---|---|---|---|---|---|---|---|---|
| Number of reports | | 329 | 208 | 195 | 206 | 288* | 1,226 | |
| IHN criteria fulfilled | | 178 | 199 | 183 | 182 | 252* | 994 | |
| Without additional monitoring | | 3 | 53 | 14 | 15 | 74* | 159 | |
| With hospitalisation and monitoring | Grade I | 4 | 1 | 2 | 7 | 8 | 285 | |
| | Grade II | 64 | 49 | 45 | 57 | 48 | | |
| | Grade III | 95 | 88 | 101 | 92 | 118 | 550 | |
| | Grade IV | 12 | 8 | 21 | 11 | 4 | | |
| | **Total** | **175** | **146** | **169** | **167** | **178** | **835** | |
| ATR following administration of RBC | Grade I | 1 | 1 | 2 | 3 | 5 | 158 | 453 |
| | Grade II | 35 | 23 | 28 | 32 | 28 | | |
| | Grade III | 49 | 45 | 53 | 56 | 53 | 295 | |
| | Grade IV | 8 | 5 | 15 | 9 | 2 | | |
| | Deaths | 2 | 3 | 7 | 2 | 0 | | |
| ATR following administration of PC | Grade I | 0 | 0 | 0 | 3 | 2 | 73 | 180 |
| | Grade II | 18 | 13 | 10 | 15 | 12 | | |
| | Grade III | 13 | 15 | 21 | 14 | 35 | 107 | |
| | Grade IV | 1 | 2 | 4 | 1 | 1 | | |
| | Deaths | 0 | 1 | 0 | 1 | 0 | | |
| ATR following administration of FFP | Grade I | 1 | 0 | 0 | 0 | 0 | 34 | 113 |
| | Grade II | 8 | 8 | 4 | 8 | 5 | | |
| | Grade III | 18 | 16 | 16 | 13 | 12 | 79 | |
| | Grade IV | 2 | 0 | 1 | 1 | 0 | | |
| ATR following combined administration | Grade I | 2 | 0 | 0 | 1 | 1 | 20 | 89 |
| | Grade II | 3 | 5 | 3 | 2 | 3 | | |
| | Grade III | 15 | 12 | 11 | 9 | 18 | 69 | |
| | Grade IV | 1 | 1 | 1 | 0 | 1 | | |
| | Deaths | 1 | 0 | 0 | 0 | 1 | | |

* Since 2014, all DCGMA (AKdÄ) reports have been forwarded to the PEI.

The rise in ATR reported in 2014 can primarily attributed to the fact that an increased number of reports received by the Drug Commission of the German Medical Association (DCGMA) were forwarded to the Paul-Ehrlich-Institut. 74 cases were non serious acute transfusion reactions which did not require hospitalisation and monitoring and were thus not taken into account in calculating the reporting frequency of ATRs.

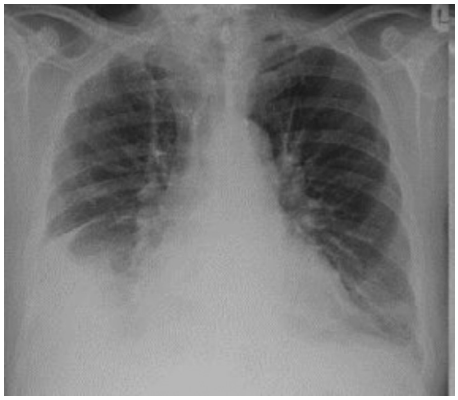
### Reporting rate of confirmed Grade III and IV cases per $10^6$ transfused units referring to the appropriate period

| Products | 2005–2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|
| RBC | 6.2 | 6.2 | 13.11 | 11.16 | 15.67 | 16.50 | 14.44 |
| PC | 13.2 | 31.6 | 29.72 | 34.69 | 51.02 | 31.25 | 73.47 |
| FFP | 2.91 | 13.69 | 17.36 | 14.04 | 11.33 | 16.67 | 14.46 |

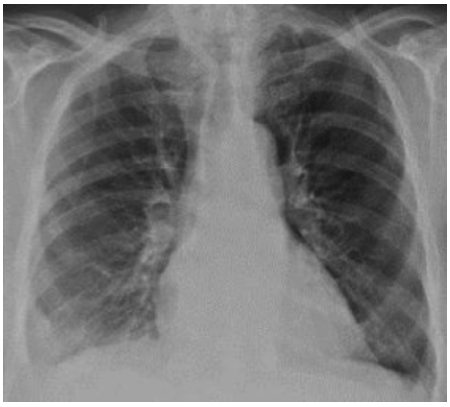
## 4.3 Transfusion associated circulatory overload (TACO) [9]

*IHN criteria:* Dyspnoea, tachycardia, hypertension, typical signs of cardiogenic lung oedema in the x-ray of the thorax, evidence of positive balance of the fluid chemistry and/or cardiac damage during or within twelve hours post transfusion.

**Radiological findings:**
**Lung oedema**



**Monitoring after diureses**



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

TACO has been recorded systematically by the PEI as transfusion complication since 2009.

**Overview of cases with transfusion associated circulatory overload**

| | 2011 | 2012 | 2013 | 2014 | 2011–2014 |
|---|---|---|---|---|---|
| Total number of cases reported | 42 | 41 | 50 | 42 | 175 |
| Confirmed cases (IHN criteria) | 42 | 40 | 49 | 36 | 167 |
| Following administration of RBC | 28 | 33 | 36 | 30 | 127 |
| Following administration of PC | 3 | 3 | 3 | 2 | 11 |
| Following administration of FFP | 3 | 0 | 4 | 2 | 9 |
| Following combined administration | 7 | 4 | 6 | 2 | 19 |
| Deaths | 2 | 1 | 1 | 3 | 7 |
| Details on previous underlying diseases: Previous cardiovascular damage, DIC, haemorrhagic shock, known liver cirrhosis, renal damage | 21 (50%) | 31 (77.5%) | 29 (59%) | 26 (72.2%) | 107 (64.1%) |
| Age of recipient; mean value (range) | 68 (23–88) | 68.5 (6–92) | 68.8 (7–94) | 69.7 (13–92) | 68.7 (6–94) |

**Confirmed cases of TACO per $10^6$ transfused units in the appropriate reporting year**

| Products | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|
| RBC | 7.11 | 8.66 | 9.14 | 7.87 |
| PC | 6.25 | 6.12 | 6.25 | 4.08 |
| FFP | 3.57 | 0.00 | 4.76 | 2.41 |

As in the preceding years, the majority of the patients affected in 2013 and 2014 were reported to have displayed predisposing factors in the form of underlying diseases, such as cardiovascular diseases, DIC, haemorrhagic shock, liver cirrhosis in the history, renal damage [9].

Moreover, in most cases, elderly patients were affected (>60$^{th}$ year), who partly received large volumes within a short time period (volume: >2ml/m in total or >2 ml/kg/h). As a preventive measure, a reduced transfusion rate of 1 ml/kg/h is therefore recommended for the entire RBC volume in patients where the above mentioned criteria apply.

### Case history 2013

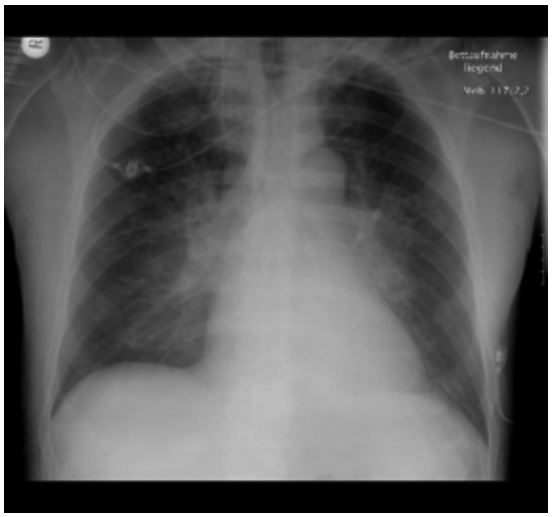
Relapsing gastro-intestinal bleeding occurred in a 71-year old male patient with coronary heart disease under treatment with anti-coagulants. Because of his pronounced anaemia, the patient received two RBC transfused within a short period of time (first RBC within 90 minutes). The administration of the second RBC was performed at the same transfusion rate. Dyspnoea, tachycardia, sweating, and a decrease in $O_2$ saturation occurred 60 minutes after the beginning of the second transfusion. The X-Ray of the thorax showed signs of lung oedema with existing cardiac insufficiency. His symptoms subsided rapidly following the administration of diuretics. The criteria for transfusion associated circulatory overload were thus fulfilled.

## 4.4 Transfusion-related acute lung injury (TRALI)

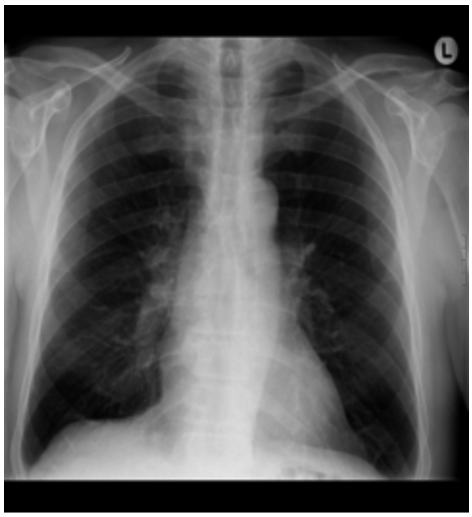
*IHN criteria:* Acute respiratory distress, i.e. dyspnoea (symptoms occur within six hours following the beginning of transfusion), recurring bilateral lung oedema (confirmed radiologically), and the exclusion of hypervolaemia (cardiac, renal, iatrogenic).

**Radiological findings: TRALI following administration of FFP in patients post prostatectomy**

**Bilateral lung infiltrates**



**Control (day 5) after machine-assisted ventilation**



There are currently no clear parameters suitable to confirm a TRALI diagnosis. A distinction between other causes of acute lung injury or transfusion associated circulatory overload remains difficult in the individual cases due to the great number of different relevant factors involved. In the past, several suspected cases reported could not be confirmed since essential information was missing, especially such information that could have been used to rule out other causes. The following algorithm was therefore used for an acute assessment of a TRALI reaction:

1. Investigation as to whether conditions of TRALI are fulfilled:
   a) Reaction occurring within six hours post transfusion and new bilateral lung infiltrates
      → TRALI possible
   b) As in 1a, however, in addition no evidence of other causes of lung oedema
      → TRALI likely
2. Examination of the donors for HLA or HNA-Ab
   a) Detection of a leucocyte Ab: immunogenic TRALI
   b) No evidence of leucocyte Ab: non-immunogenic TRALI
      (Assumed causes: bioactive lipids, complement activation, vascular endothelial growth factor (VEGF) in PC donors [10, 11])
3. Examination of the recipient
   a) Antigen(s) corresponding to Ab(s) of the donor: TRALI confirmed
   b) HLA- or HNA-Ab → inverse TRALI

### Overview of TRALI cases using the above mentioned algorithm (see also Table 3)

| Classification | 2013 | 2014 |
|---|---|---|
| Number of reports | 54 | 58 |
| Two IHN criteria fulfilled (within 6 h, bilateral lung infiltrates) | 14 | 20 |
| TRALI possible | 4 | 13 |
| Number of non-immunogenic TRALI cases | 2 | 8 |
| Number of immunogenic TRALI cases | 2** | 5 |
| TRALI likely/confirmed (within 6 h, bilateral Infiltrates, no other cause) | 10 | 7 |
| Number of non-immunogenic TRALI cases | 0 | 2 |
| Number of immunogenic TRALI cases | 10 | 5 |
| Age of patients with TRALI | 56.1 (23–80) | 65.7 (50–79) |
| Number of cases with Ab-positive FFP donors* | 3 | 1 |
| Number of cases with Ab-positive RBC donors* | 7 | 4 |
| Number of cases with Ab-positive PC donors* | 4 | 0 |
| Number of Ab positive female donors | 7 | 1 |
| Number of Ab positive male donors | 10 | 2 |
| Fatal outcomes following non-immunogenic TRALI | 0 | 0 |
| Fatal outcomes following immunogenic TRALI | 1 | 0 |
| TRALI-associated deaths following administration of FFP | 0 | 0 |
| TRALI-associated deaths following administration of RBC | 0 | 0 |
| TRALI-associated deaths following administration of PC | 1 | 0 |

* The total of cases in which individual products were listed varies with the number of the overall cases, since in several cases antibodies were found in different products. Thus, products from three categories were involved in two cases with immunogenic TRALI in 2013. For altogether three cases (two in 2013 and one in 2014) the causal relation was assessed as confirmed, because the corresponding antibodies and antigens were in each case found in both the donors and the recipients.

** In one case: HLA-Ab was detected in a recipient.

TRALI cases from 2013/2014 with a likely/confirmed causal relationship

| | Recipient | Donor | | | |
|---|---|---|---|---|---|
| Case No | Diagnosis/course | Blood components (sex of donor) | | | Antibodies |
| 2013 | | RBC | PC | FFP | |
| 1 | 49-yr old pat. with autoimmune anaemia. Bilateral lung oedema 6 h following 1 RBC and 12 FFP. No initial chest X-Ray. Other causes of lung oedema possible. | | | X (m) | HNA-Ab in 1 FFP |
| 2 | 23-yr old pat. with anorexia nervosa, Cardiac and renal insufficiency, liver cirrhosis, received RBC due to drop in Hb. TRALI within 4 hours. Other causes could be ruled out. | X (f) | | | HLA-Ab |
| 3 | 67-yr. old pat. undergoing gastric resection due to tumour disease. TRALI 4 h following RBC. Other causes could be ruled out. | X (m) | | | HLA cat. II Ab |
| 4 | 64-yr. old pat.: Condition after by-pass surgery developed TRALI following administration of PC within 2 h. Other causes could be ruled out. | | X (all 3 m) | | HLA cat. I and II Ab in 3 APC donors |
| 5 | 80-yr. old pat.: Condition after by-pass surgery and valve replacement received 5 RBC, 2 PC and 3 FFP due to bleeding post extracorporeal circulation. Lung oedema due to other causes could be ruled out. TRALI confirmed. Female donors, with HLA cat. I (PC) and HLA cat. II Ab (RBC) and HNA-Ab CD 16 (FFP) respectively were involved. | X (f) | X (f) | X (f) | HLA cat. I and II, HNA-Ab CD16 |
| 6 | 71-yr. old pat. with dens fracture & thrombocytopenia developed TRALI following administration of 8 PC. Most serious ARDS intraoperatively, multiple organ failure, death in septic shock, possibly caused by TRALI. | | X (2 f, 1 m) | | 1 PC HLA cat. I & II and HNA-Ab (anti CD 16), 2 PK HLA I u. II |
| 7 | 57-yr. old pat. undergoing liver transplantation and diffused bleeding developed TRALI during mass transfusion intraoperative. Respiratory recovery. 4 months later death due to sepsis. | X (m) | X (m) | X (m) | HNA-Ab, anti CD1, CD11a, CD177. CD32, HLA cat. I &. II Ab |
| 8 | 59-yr. old pat.: cond. after intestine surgery and postoperative anaemia developed TRALI 4 h following RBC TRALI. Non-serious course. | X (?) | | | HLA DR Ab with correspond. Ag |
| 9 | 47-yr. old pat. with postoperative anaemia developed TRALI 6 h post RBC. Other causes could be ruled out. | X (f) | | | HLA DQ5–Ab with correspond. Ag |
| 10 | 44-yr. old pat. with ACI stenosis developed TRALI intraoperative following 4 RBC and 3 PC. DD: TACO, Granulocyte Ab in the plasma of the donor of the RBCs. | X (m) | | | HNA-Ab |

| | Recipient | Donor | | | |
|---|---|---|---|---|---|
| Case No | Diagnosis/course | Blood components (sex of donor) | | | Antibodies |
| 2014 | | RBC | PC | FFP | |
| 1 | Pat. with metastasising prostate cancer suffered TRALI with hypoxic seizure. Initial chest X-Ray not available. | X (m) | | | HLA DR7 and HLA DR 9 Ab |
| 2 | Pat. with Ileus and postoperative anaemia. | X (?) | | | HLA-Kl. II Ab, Recpt. Ab K II IgG |
| 3 | 63-yr. pat with lung fibrosis and condition after lung TX developed TRALI symptoms and rejection reaction following plasma replacement. Female donor repeatedly denied pregnancy, miscarriage or transfusions. | | | X (f) | HLA DR 13 Ab corresponding antigen in patient |
| 4 | 79-yr. old pat. received 2 RBC due to anaemia. TRALI within 1 h. No other cause. | X (?) | | | HNA-Ab in corresponding serum of a RBC |
| 5 | 52-yr. old pat. received 4 RBC and 2 FFP due to haemorrhagic shock. TRALI within 2 h. DD TACO. | X (m) | | | Weak HLA and HNA-Ab in 3 RBC |
| 6 | 63-yr.old. pat. with B-cell lymphoma and anaemia developed TRALI within 2 h post administration of RBC without any possible other causes. Donor: No Ab (non-immunogenic TRALI). | | | | non-immunogenic |
| 7 | 78-yr. old pat. with fracture of the femoral neck received 3 FFP and 2 PC intraoperatively and developed TRALI symptoms within 3 h. No other cause for lung oedema possible. 2 PC donors are HLA and HNA-Ab negative. The two male donors of the FFP cannot be examined. They are deferred from future donations. | | | | non-immunogenic |

Cat = category; CD = cluster of differentiation; Hb = haemoglobin; recpt. = recipient; h = hours; pat. = patient; DD = differential diagnosis

### 2013: Cases of TRALI with possible causality

In four reports from 2013, only a possible causality between the symptoms and the administration of blood components could be seen due to other potential causes. HLA-Ab were detected in a donor of RBC involved; in two other cases, the categorisation of a possible non-immunogenic TRALI event was made, since no Ab could be detected. In a fourth case, a possible inverse TRALI reaction was discussed.

A 21-year old female patient with liver cirrhosis and haemorrhagic anaemia, thrombocytopenia, and plasmatic coagulation disorder under immunosuppressive treatment developed TRALI symptoms within six hours following administration of FFP. Due to concomitant sepsis under immunosuppressive treatment, the causal relationship was categorised as "possible". In the further course, HNA2a-Ab was detected in the female patient, so that inverse TRALI reaction could be assumed. No leucocyte antibodies were found in the FFP donor.

### 2014: TRALI with possible causal relationship

In eight of the 13 cases rated as possible TRALI reactions, no leukocyte antibodies could be found in the donors involved. In five other cases, HLA Category I and Category II antibodies were detected in four RBC donors and one FFP donor, respectively. In one case, platelet-reactive antibodies against glycoprotein complex were also found in the recipient of one RBC.

### Confirmed immunogenic cases of TRALI (likely/confirmed) per $10^6$ transfused units in relation to the appropriate period of time

| Products | 2005-2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|
| RBC | 0.46 | 0.88 | 0.22 | 0 | 0.23 | 1.78 | 1.05 |
| PC | 1.8 | 6.77 | 0 | 2.04 | 0 | 8.33 | 0 |
| FFP | 11.18 | 4.56 | 0 | 0 | 0 | 3.57 | 1.20 |

In 2013, the rate of reported TRALI cases following administration of PC increased because of three confirmed cases, while in 2014 no additional case could be confirmed. Thus, since 2009, the reporting rate has varied between zero and eight cases per to $10^6$ transfused PC units. Altogether four immunogenic TRALI events were confirmed following administration of FFP in the period of 2013/2014. Two male and two female FFP donors were involved altogether. In both cases, the female donors had denied all risk factors in the donor interview (pregnancy, miscarriage, or transfusions), so that the reason for the development of antibodies remains unclear.

One death in connection with a TRALI reaction (immunogenic) was reported. In 2013, one patient died of septic shock following multiple organ failure with most severe ARDS after the administration of eight PCs. HLA and HNA antibodies were found in two female and one male APC donor.

## 4.5 Transfusion related dyspnoea

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

**Presentation of the cases of transfusion related dyspnoea**

| | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|
| Total number of all reported cases | 17 | 14 | 19 | 25 |
| Confirmed cases (IHN-criteria) | 11 | 6 | 13 | 19 |
| RBC | 6 | 3 | 9 | 17 |
| PC | 1 | 1 | 2 | 0 |
| FFP | 0 | 0 | 1 | 0 |
| Combination | 4 | 2 | 1 | 2 |
| Deaths | 0 | 0 | 0 | 0 |
| Age of recipients<br>Mean value (range) | 70<br>(53–90) | 67<br>(48–68) | 63<br>(45–93) | 69.68<br>(38–89) |

## 4.6 Haemolytic transfusion reaction (HTR)

*IHN criteria:* Fever concomitantly with other symptoms (respiratory distress, hypotension, tachycardia, pain in the renal area), macro haematuria, drop in the haemoglobin level >2g/dl within 24 hours, increase in LDH >50% in 24 hours, increase in the bilirubin level, positive antiglobulin test, positive cross sample.

**Presentation of cases of haemolytic transfusion reactions (see also Table 4)**

| | 1997–2010 | 2011 | 2012 | 2013 | 2014 | 1997–2014 |
|---|---|---|---|---|---|---|
| Number of reports | 278 | 45 | 37 | 36 | 60 | 456 |
| IHN criteria fulfilled | 157 | 12 | 8 | 17 | 39 | 233 |
| Acute HTR | 130 | 3 | 5 | 11 | 36 | 185 |
| Delayed HTR | 27 | 9 | 3 | 6 | 3 | 48 |
| Delayed HTR with evidence of irregular anti-RBC-Ab | 22 | 9 | 3 | 6 | 3 | 43 |
| HTR after admin. of RBC | 131 | 11 | 7 | 16 | 33 | 198 |
| HTR after admin. of PC | 9 | 1 | 1 | 0 | 1 | 12 |
| HTR after combined admin. | 17 | 0 | 0 | 1 | 5 | 23 |
| Fatal outcomes after HTR | 9 | 0 | 0 | 0 | 2 | 11 |
| HTR associated deaths after admin. of RBC | 7 | 0 | 0 | 0 | 2 | 9 |

In 2014, both an increase in suspected reports and in confirmed transfusion related haemolytic reactions following administration of PC was seen compared with 2013. In most of the cases, these were acute haemolytic reactions. In contrast to the data of other haemovigilance systems (SHOT, Swissmedic), the proportion of reports on delayed reactions with evidence of irregular anti-RBC-Ab is low.

**HTR with evidence of irregular anti-RBC-Ab (2013/2014)**

| Delayed HR | Symptoms | Hb course (g/dl) | Lab | Cause | Other informationen |
|---|---|---|---|---|---|
| 1 | Pain in the renal area, renal insufficiency | 8.0 to 10.5 to 7.5 g/dl | Increased LDH and bilirubin | Anti-Jk(a) | Renal failure, lethal |
| 2 | Somnolence | ? | LDH >4,000 U/l<br>Bilirubin >40 mg/dl | Anti-Jk(a) | Multiple organ failure, lethal |
| 3 | Nausea, fainting, shock | Drop to 9 per g/dl | LDH >3000 U/l<br>Bilirubin 4.51 | Anti-Jk(b) | Reanimation, restitution |
| 4 | Transition syndrome | 7.6 to 8.2 g/dl | LDH 340 U/l<br>Bilirubin 2.6 mg/dl | Anti-C, Anti-Fy(a), Anti-P1, Anti-Jk(a), Anti-S | Restitution |
| 5 | Icterus, Haemoglobinuria | ? | Increased LDH and bilirubin | Anti-Jk(b) | Restitution |
| 6 | Rise in body temperature, Icterus | Drop in Hb | LDH 457 U/l | Anti-S,-Jk(b), -C(w) | Restitution |
| 7 | Chills, sweating | ? | ? | Anti-C, Anti-E | Unknown |
| 8 | Icterus | Drop in Hb | ? | Anti-Fy(a), Anti-S, Anti-M, | Restitution |
| 9 | Icterus, massive haematoma on the upper thigh | 9 to 7 g/dl | LDH 485/U/l<br>Bilirubin 2,5 mg/dl | Anti-Fy(a) | Restitution |

Two cases of delayed haemolytic transfusion reactions led to death.

The first case was a 73-year male patient who, among other things, suffered from dilated cardiomyopathy, atrial fibrillation, and a status after nephrectomy in 2013, extensive renal cell carcinoma, and renal insufficiency, and received two RBC in early March 2014. Two weeks later, he was hospitalised for increasing somnolence, and decreased Hb. Laboratory findings included a positive direct antibody search test and a positive direct Coomb test. Anti-Jk(a) could be detected in the serum and the eluate. In the following course, the patient developed progressive renal insufficiency and finally died of acute renal failure. Haemolysis can be considered as a co-factor for the development of the acute renal failure. Based on an antigen frequency of 75 percent, it was regarded as likely, due to the patient's reaction, that one of the RBC antigens were positive. There was no material left for examination at the time when the reaction became known.

The second case of death referred also to a delayed haemolytic transfusion reaction in a 75-year old female patient with thoraco-abdominal aorta replacement after aorta aneurysm. Recovery was pro-

longed in the patient post-operatively. Within the framework of a revision and re-anastomosis, 16 RBC, 4 PC and 10 FFP were administered. Increasing somnolence and signs of multiple organ failure occurred. Five days later, irregular Jk (a) Ab were found in the patient for the first time. In the later course, haemolysis parameters increased to extreme values (LDH > 4,000 U/l and bilirubin > 40 mg/dl). The patient died following multiple organ failure and sepsis.

**Confirmed cases of HTR per $10^6$ transfused units referred to the respective period of time**

| Produkte | 2005–2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|
| RBC | 2.41 | 1.32 | 3.55 | 2.46 | 1.61 | 4.06 | 8.66 |
| PC | 1.80 | 0 | 4.25 | 2.04 | 2.04 | 0 | 2.04 |

## 4.7. Transfusion transmitted bacterial infections (TTBI)

*IHN criteria:* Fever > 39 °C or a rise in the temperature by 2 °C within four hours, chills, tachycardia, and detection of the same bacteria strain in the recipient's blood and in the transfused blood component.

The frequency and degrees of severity of TTBI in the past few years (1997–2014) and the results of the detection of the pathogens can also be found in Tables 5 and 6.

### System of evaluation

The cases are categorised as "unlikely", "possible", "likely", and "confirmed". Reports of TTBI in which no detection of a pathogen was available or the time interval was exceeded were rated as cases with an unlikely causality. If the pathogen was found only in the blood component, a possible causality was assumed. For the detection of the same pathogen in the product and in the patient, the causal relationship is considered as likely. For a confirmed TTBI, the homology of the pathogen must be available, for example as an identical antibiogram. In practice, consistent testing of the recipient and the blood components is not always feasible. The follow-up reports are therefore frequently inadequate because they are marred with gaps. The PEI currently shows all cases of transfusion transmitted bacterial infections in the haemovigilance report which are categorised as "likely" and "confirmed".

In 2013, 35 cases altogether were reported to the PEI with suspected TTBI. In 28 of the reports, the causal relationship was categorised as unlikely, and in three cases as possible. In altogether four cases, the causal relationship was likely or confirmed and the IHN criteria were fulfilled.

In 2014, 36 cases were reported to the PEI with suspected TTBI. For 20 of the reports, the causal relationship was categorised as unlikely, and for nine cases, it was categorised as possible. In six cases, the causal relationship was likely, and in one case confirmed. The latter cases fulfilled the IHN criteria and were included in the tables of confirmed serious transfusion reactions.

In the twelve cases with possible causality, nine RBC, two PC, and one FFP were involved. No information is available as to the age of the products. In nine cases, a pathogen was found only in the

products and in three cases only in the patient. In the eight cases with likely causality, three APC and five RBC were involved. The three APC were at the end of their shelf-life. One immune suppressed patient died of *S.-aureus* infection after administration of the APC.

In 2014 one *E.-coli* infection was confirmed both in the APC donor and in the recipient, and homology was confirmed by an antibiogram. A second PC was prepared from the same apheresis donation (irradiated double product). The recipient of the second PC showed no symptoms of bacterial infection. However, he was treated with antibiotics before transfusion.

### Transfusion transmitted bacterial infections with possible causality

| Year | Pathogen | Blood component | Detection of pathogen recipient/product | Outcome |
|---|---|---|---|---|
| 2013 | *Citrobacter freundii* | RBC | Recipient | Restitution |
| | *Enterococcus faecium* | RBC | Product | Restitution |
| | *Enterococcus faecium* und *Staphylococcus hominis* | FFP | Product | Restitution |
| 2014 | *Staphylococcus hominis* | RBC | Product | Restitution |
| | *Staphylococcus aureus* | RBC | Product | Restitution |
| | *Enterobacter chloacae* | RBC | Recipient | Restitution |
| | *Bacillus cereus* | PC | Product | Fatal |
| | *Staphylococcus warneri* | RBC | Product | Restitution |
| | *Propionibacterium acnes* | RBC | Product | Restitution |
| | *Propionibacterium acnes* | PC | Product | Restitution |
| | *Acinetobacter baumannii* | RBC | Product | Restitution |
| | *Escherichia coli* | RBC | Recipient | Restitution |

### Transfusion transmitted bacterial infections with likely causality

| Year | Product | Pathogen | Categorisation | Result |
|---|---|---|---|---|
| 2013 | RBC | *Klebsiella pneumoniae* | Likely | Restitution |
| | RBC | *Staphylococcus aureus* | Likely | Restitution |
| | APC, 4 days old | *Staphylococcus epidermidis* | Confirmed | Restitution |
| | APC, 4 days old | *Staphylococcus epidermidis* | Confirmed | Restitution |
| 2014 | APC, 4 days old | *Escherichia coli* | Likely | Restitution |
| | APC, 4 days old | *Staphylococcus aureus* | Likely | Restitution |
| | APC, 4 days old | *Staphylococcus aureus* | Likely | Fatal |
| | RBC | *Staphylococcus aureus* | Likely | Restitution |
| | RBC | *Klebsiella pneumoniae* | Likely | Restitution |
| | RBC | *Klebsiella oxytoca* | Likely | Restitution |
| | APC | *Escherichia coli* | Confirmed | Restitution |

## Reported and confirmed transfusion transmitted bacterial infections (1997–2014)

| Period | 1997–2010 | 2011 | 2012 | 2013 | 2014 | 1997–2012 |
|---|---|---|---|---|---|---|
| Number of reports | 220 | 45 | 33 | 35 | 36 | 369 |
| IHN criterial not fulfilled | 130 | 38 | 28 | 31 | 29 | 256 |
| IHN criterial fulfilled | 90 | 7 | 5 | 4 | 7 | 113 |
| TTBI after administration of PC | 51 | 4 | 3 | 2 | 4 | 64 |
| TTBI after administration of PPC | 26 | 2 | 0 | 0 | 0 | 28 |
| TTBI after administration of APC | 25 | 2 | 3 | 2 | 4 | 36 |
| TTBI after administration of RBC | 34 | 3 | 2 | 2 | 3 | 44 |
| TTBI after administration of FFP | 5 | 0 | 0 | 0 | 0 | 5 |
| Fatal outcome after TTBI | 12 | 1 | 0 | 0 | 1 | 14 |
| TTBI associated deaths after administration of PC | 8 | 1 | 0 | 0 | 1 | 10* |
| TTBI associated deaths after administration of RBC | 4 | 0 | 0 | 0 | 0 | 4 |
| Deadly courses in recipients with relevant immunosuppression | 9 | 1 | 0 | 0 | 1 | 11** |

* All ten platelet concentrates had reached the end of their shelf-lives at the time of transfusion (fourth day and fifth day, respectively, after donation).

** Fatal outcome in patients with malignant underlying diseases (CML, AML, aplastic anaemia, sepsis etc.).

## Reporting frequency of TTBI per $10^6$ transfused units referred to the respective period

| Produkte | 2005–2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|
| RBC | 0.80 | 0 | 0.22 | 0.67 | 0.46 | 0.51 | 0.79 |
| PC | 10.77 | 4.51 | 4.25 | 8.16 | 6.12 | 4.17 | 8.16 |
| FFP | 0.22 | 0 | 0 | 0 | 0 | 0 | 0 |

## 4.8 Transfusion transmitted viral infections (TTVI)

Viral transmission was confirmed by means of the criteria conforming to Opinion 34 (AK Blut).

### Listing of confirmed TTVI (see also Table 7)

| Period | 1997–2012 | 2013 | 2014 | 1997–2014 |
|---|---|---|---|---|
| Total number of reports | 3,283 | 57* | 75 | 3,415 |
| Total number of HAV reports | 2 | 0 | 3 | 5 |
| Total number of HBV reports | 1,212 | 20 | 30 | 1,262 |
| Total number of HCV reports | 1,879 | 24 | 22 | 1,925 |
| Total number of HEV reports | 4 | 2 | 7 | 13 |
| Total number of HIV reports | 181 | 7 | 8 | 196 |
| Total number of cases with likely or confirmed viral transmission | 52 | 2 | 3 | 57 |
| HAV | 2 | 0 | 0 | 2 |
| HBV | 24 | 0 | 0 | 24 |
| HCV | 20 | 0 | 0 | 20 |
| HEV | 0 | 2 | 3 | 5 |
| HIV | 6 | 0 | 0 | 6 |
| Transmission after administration of RBC | 31 | 0 | 1 | 31 |
| Transmission after administration of PC | 9 | 2 | 2 | 12 |
| Transmission after administration of FFP | 12 | 0 | 0 | 12 |
| Fatal outcomes after HBV transmission | 2 | 0 | 0 | 2 |
| Fatal outcomes after HEV transmission | 0 | 1 | 0 | 1 |

* Suspected transmission of HBV and HCV was reported in one case.

Other transfusion transmitted viral infections were reported to the PEI in 2013 and 2014. These included five cases of CMV infection in 2013 and four cases of CMV infection as well as one case of varicella zoster infection in 2014. None of these infections could be confirmed.

### Hepatitis E

From 1997 to 2012, a total of four suspected cases of HEV transmission were reported to the Paul-Ehrlich-Institut. However, these could not be confirmed by donor testing.

In 2013, two HEV infections were identified within the framework of a donor triggered look-back procedure. The first case was a 50-year old female donor who donated whole blood on 11 October 2013 which was processed into one RBC, one PPC, and one FFP and who was tested positive for HEV on 28 October 2013 after developing cough and fever. The recipient of the PPC was tested positive for HEV on 27 November 2013 in the serological and NAT test. In both the donor and the recipient, genotype 3c could be detected. In the further course, the recipient was tested HEV-NAT negative and did not develop clinical symptoms at any time. No HEV infection was found in the recipient of the RBC donation.

The second case was a 48-year old patient with mantle cell lymphoma, who had received one APC after allogenic stem cell transplantation on 4 July 2013. Due to elevated transaminase, hepatitis diagnostics were performed in the patient, and an HEV infection was confirmed serologically and by means of NAT testing in 12 December 2013. On that date genotype 3f was also confirmed. In the recipient triggered look-back procedure, the retain samples of the APC donor were also tested HEV-NAT positive and a genotype 3f was detected. Altogether six APC were prepared from the donations of the donor who was tested HEV positive. Apart from the index patient, a HEV infection could not be detected in any of the other recipients, however, two recipients died of their underlying disease before a test could be performed. The patient who had mantle cell lymphoma died of renal and hepatic failure in 2014. He also had pronounced symptoms of GvHD. In the final assessment, the HEV infection was considered as co-factor for the further progression of the disease.

Altogether seven suspected cases of HEV infection were reported in 2014. In four cases, a possible causal relationship could be ruled out based on negative donor testing. In three donors, the referred samples (two APC and one RBC) were tested HEV positive in the single PCR. No clinical symptoms of HEV infection developed in any of the three recipients. The recipients of other blood products of the infected donors had negative HEV test results. In two cases, the transmission of the infection was confirmed by positive gene sequence comparison.

### Hepatitis B, Hepatitis C, HIV

After the introduction of HCV-/HIV-NAT donor screening, three cases of transmission by blood components have so far been reported: one case of HCV transmission and two cases of HIV transmission (Table 7, Figure 5). In all these cases, the infection was transmitted by PC donors in whom the infection could not be confirmed in the NAT pool testing [12]. For the transfusion related HBV infections, two transmissions occurred per year between 1997 and 2006. In the six years that followed, after the introduction of donor screening by anti-HBc single testing (10/2006), a total of four cases of transfusion related HBV infections were confirmed. In 2013 and 2014, no cases of HBV, HCV, or HIV transmission following administration of blood components could be confirmed.

Confirmed transfusion related infections (1997 – 2014)

| | 1997-2002 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | 10 | 11 | 12 | 13 | 14 | 1997-2014 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bacteria | 40 | 7 | 5 | 11 | 8 | 8 | 6 | 2 | 3 | 7 | 5 | 4 | 7 | 113 |
| HBV | 9 | 3 | 3 | 2 | 3 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 24 |
| HCV | 19 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 |
| HIV | 4 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 6 |
| HAV | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| HEV | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 5 |
| Malaria | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| WNV, Dengue, Chikungunya | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Prions | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 75 | 10 | 9 | 13 | 11 | 10 | 7 | 3 | 4 | 7 | 6 | 6 | 10 | 171 |

Confirmed viral transmissions (HBV, HCV, HIV, HEV) per $10^6$ transfused units in relation to the respective period

| Products | 2005–2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|
| RBC | 0.46 | 0 | 0.22 | 0 | 0 | 0 | 0.26 |
| PC | 0 | 2.26 | 0 | 0 | 2.04 | 4.17 | 4.08 |
| FFP | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

## 4.9 Post-transfusion purpura (PTP)

A suspected case of post-transfusion purpura (PTP) refers to the occurrence of purpura and thrombocytopenia within twelve days post transfusion. PTP is considered as confirmed if platelet specific antibodies (usually anti-HPA-1a) are present in the recipient's blood and the corresponding antigen can be detected in the donor platelets, or if a thrombocyte cross match [13] tests positive.

No case of post-transfusion purpura was reported in 2013.

Six suspected cases were reported in 2014, out of which two PTP were confirmed.

## 4.10 Donor triggered look-back procedures – overview

| Reports of suspected cases | 2011 | 2012 | 2013 | 2014 | Transmissionen (confirmed) |
|---|---|---|---|---|---|
| Total | 803 | 906 | 815 | 798 | 6 |
| Transmission of | | | | | |
| HEV | | | 2 | 7 | 5 |
| HBV | 625 | 702 | 548 | 489 | 1* |
| HCV | 96 | 102 | 131 | 168 | 0 |
| HAV | | 1 | | 1 | 0 |
| HIV | 66 | 58 | 69 | 53 | 0 |
| CMV | | 2 | | 5 | 0 |
| Parvovirus B19 | | | 7 | 2 | 0 |
| HEV + HAV | | | 1 | | 0 |
| HBV + HIV, HCV, HAV and Syphilis | 4 | 2 | 3 | 2 | 0 |
| HCV + Syphilis | | 1 | | | 0 |
| HIV + Syphilis | 1 | | 2 | 2 | 0 |
| Syphilis | 7 | 34 | 52 | 68 | 0 |
| CJK | | 3 | | | 0 |
| Toxoplasmosis | | 1 | | | 0 |
| Leishmaniosis | 1 | | | | 0 |
| Lyme arthritis | 2 | | | | 0 |
| Transient bacteraemia | 1 | | | | |
| Malaria | | | | 1 | 0 |

* confirmed in 2012

With around 800 reports of donor triggered look-back procedures in 2013 and 2014, there was a slight decline in the reports notified to the PEI. Compared with the figures of 2012 the number of look-back procedures triggered by a HBV infection of donors, decreased by >150 cases per year.

As in the preceding years, in 2013 and 2014, too, a positive anti-HBc test in the donor was by far the major reason for performing a look-back procedure.

The Table below shows a more detailed breakdown of the test results that led to a look-back procedure.

**Look-back procedure in HBV positive donors**

| Lab results from the HBV positive donors | Number of cases | | | |
|---|---|---|---|---|
| | 2011 | 2012 | 2013 | 2014 |
| Total number of reports | 625 | 702 | 548 | 489 |
| Anti-HBc-positive, HBsAg-positive and/or HBV-PCR-positive | 125 | 49 | 65 | 68 |
| Anti-HBc-positive, HBsAg-negative, HBV-PCR-negative | 500 | 653 | 483 | 421 |
| out of these: anti-HBs-negative | | | | |
| Number | 107 | 314 | 177 | 106 |
| Portion of total number [%] | 21.4 | 48.1 | 36.6 | 25.2 |
| out of these: anti-HBs-positive | 102 | 277 | 215 | 143 |
| with anti-HBs > 100 IU/ml | 63 | 188 | 150 | 85 |
| with anti-HBs < 100 IU/ml | 39 | 89 | 65 | 58 |
| No information on anti-HBs | 291 | 62 | 91 | 172 |

In 2013 and 2014 the combination of anti-HBc-positive plus HBsAg-negative plus HBV-PCR-negative test results caused 483 and 421 donor triggered look-back procedures. In the group tested for Anti-HBs about half of the donors had no measurable anti-HBs antibody titre. In the past four years, the number of anti-HBc-positive donors that tested negative for anti-HBs was between 214 and 106 cases. Due to the revision of Opinion 34, a look-back procedure can be dispensed if two test results are negative in the supplementary anti-HBc test. (2:1 Rule of Opinion 42) [14].The data referenced provide evidence for a slight decline in the procedures performed after the introduction of the Opinion 42 regulation.

Reports of a treponema pallidum (syphilis) infection of the donor rose sharply in 2014. However, an infection of the recipient was not confirmed in any of the cases. For the products involved that were stored at cool temperatures (4 °C), a transmission of the pathogen can be ruled out, so that no additional testing of the recipient became necessary [15]. In all other cases, the recipients were tested negative by means of TPHA-EIA, or the previous donation was more than five years prior to the one referenced.

## 4.11 Serious adverse events (SAE)

Based on the requirements of the Paul-Ehrlich-Institut, incidents are considered as serious and notifiable pursuant to Section 63i (6) [16], if one of the criteria below applies:

1) Delivery of faulty products
2) Events to be rated as critical, even if a delivery did not take place
3) Events which occur repeatedly in a facility, and which can therefore be attributed to a non-conforming working process
4) Incorrect transfusions without a reaction in the recipient based on incorrect manufacture/assignment (such as incorrect labelling etc.)

Based on the criteria which apply throughout Europe, incidents are categorised as follows (see Annex III of COMMISSION DIRECTIVE 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and the Council as regards traceability requirements and notification of serious adverse reactions and events):

I. After localising of the occurrence of the serious adverse event
   1. During whole blood collection
   2. During apheresis collection
   3. During testing of donations
   4. During processing
   5. During storage
   6. During distribution
   7. No assignment

II. By type of serious adverse event
   1. Product defect
   2. Equipment failure
   3. Human error
   4. Other

Around 29 incidents were reported to the PEI in 2013. The total number was thus equivalent to the reporting frequency obtained in 2012. In 2014, reports of adverse events increased to 64. Most of the adverse events (approx. 40 percent) referred to incorrect transfusions based on incorrect assignments of the products at the manufacturer and in isolated cases also at the user side. These were twelve of the 29 reported cases in 2013 and 29 of the 64 reported cases in 2014. In 2013 and in 2014, five and twelve post-donation information cases with diseases or exclusion criteria of a donor that became known in retrospect were reported. These were mainly bacterial diseases of the donor (chlamydia, borrelia, malaria or tuberculosis), or viral infections such as varicella or herpes zoster. In one case, the donor indicated in retrospect a past sexual contact with a HIV infected person. The retain sample from the donation involved tested negative in the single HIV-NAT. A transmission of the infections to the recipients by the products already transfused was not detected.

### Reports on serious adverse events (2013 and 2014)

| Located upon | 2013 | 2014 | Type of serious event | Number |
|---|---|---|---|---|
| Donation | 1 | 6 | Product defect | 1 |
| | | | Human error | 6 |
| Production by means of apheresis | 3 | 4 | Product defect | 3 |
| | | | Human error | 2 |
| | | | Equipment failure | 2 |
| Production from whole blood donations | 1 | 4 | Product defect | 2 |
| | | | Human error | 3 |
| Processing | 4 | 8 | Product defect | 5 |
| | | | Human error | 4 |
| | | | Equipment failure | 3 |
| Storage | 2 | 1 | Product defect | 2 |
| | | | Equipment failure | 1 |
| Distribution | 12 | 29 | Human error | 41 |
| No assignment | 6 | 12 | Other | 18 |
| Total | 29 | 64 | | 93 |

### Listing of the type of reports on serious adverse events from 2011 to 2014

| Serious adverse events | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|
| **Total number of cases reported** | **21** | **26** | **29** | **64** |
| Donor exclusion criteria that became known in retrospect | 8 | 5 | 5 | 12 |
| Storage problems (interruption of the cooling-chain) | 2 | 2 | 2 | 1 |
| Data processing error | 2 | 0 | 1 | 2 |
| Incorrect labelling/human error | 6 | 1 | 5 | 10 |
| Incorrect transfusion without reaction of the recipient | 1 | 1 | 12 | 29 |
| Error as part of the production (including the formation of clotting in the apheresis) | 2 | 6 | 2 | 5 |
| Leak in the bag | 0 | 7 | 2 | 3 |
| Contamination before delivery | 0 | 3 | 0 | 2 |
| Suspected CJD in the donor | 0 | 1 | 0 | 0 |

### Number of undesirable donor reactions reported from 2011 to 2014

| | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|
| **Undesirable donor reactions** | 1 | 3 | 13 | 24 |

Since the coming into force of the 16th amendment of the AMG, serious donor reactions (such as pronounced orthostatic complaints, compartment syndrome, haematoma formation, lesions of the nerve etc.) must be reported to the Paul-Ehrlich-Institut separately as serious donor reactions pursuant to Section 63i (7). Even though the number of reports has increased, it must be assumed that underreporting persists.

## 4.12 Incorrect transfusions

An incorrect transfusion without a transfusion reaction in the recipient is also a serious adverse event pursuant to the AMG. For the pharmaceutical company, it involves a reporting obligation pursuant to Section 63i (6) AMG. The treating physician exclusively is subject to an in-house reporting obligation pursuant to Section 16 (1) TFG.

The incorrect transfusion in the narrow sense of the term is defined as treatment with AB0 incompatible blood components, as incorrect but by chance AB0 compatible transfusion of blood components, as transfusion of blood components the alloantibody compatibility of which is not confirmed, and as transfusion of untested blood components. If a reaction occurs, the pharmaceutical manufacturer is subject to a reporting obligation pursuant to Section 63i (7) AMG, and the treating physician is subject to a reporting duty pursuant to Section 16 (2) TFG to the pharmaceutical company and the Paul-Ehrlich-Institut. In this context, the degree of severity of the reaction is of no importance, since an incorrect transfusion always represents a severe adverse event. Furthermore, it is also irrelevant whether the mix up of the product occurred in the blood establishment or at the hospital [4].

Since 1997, about five incorrect transfusions were reported to the PEI per year. In 2013, a total of 15 incorrect transfusions were reported. In 2014, the number of reports rose to 22 cases (two of these with fatal outcome following the administration of RBC). While the reporting rate for incorrect transfusions was 1.62 per $10^6$ RBC units in the period from 2009 to 2012, there was an increase to 10.19 per $10^6$ RBC units in the period of 2013/2014 (see Table 8).

## 4.13 Transfusion reactions following administration of platelet concentrates

Based on the discussion on the safety of APC versus PPC, defined transfusion reactions for the number of confirmed transfusion reactions of the past four years are shown separately for APC and PPC for the last four years (2011 to 2014).

### Transfusion reactions for APC and PPC in the period from 2011 to 2014

| | Transfusion reactions | PPC | APC | Comparison of the reporting frequency of PPC vs. APC p-value** |
|---|---|---|---|---|
| **Transfused units** | | 905,700 | 1,417,400 | |
| | ATR* | 52 | 78 | 0.8119 |
| | HTR | 0 | 3 | 0.9595 |
| | TRALI | 4 | 1 | 0.6542 |
| | TACO | 4 | 7 | 0.8585 |
| | TTBI | 2 | 11 | 0.1020 |
| | TTVI | 1 | 4 | 0.4013 |
| | All TR | 63 | 104 | 0.5542 |

* 18 additional reports on ATR, no other information was given on the type of manufacture of the PC.
** Chi square test according to Wald.

In a haemovigilance system, the reporting frequency can be determined for specific transfusion reactions, however, their incidence cannot. Altogether, the development (trend) for transfusion risks can be described with the aid of the haemovigilance data. A comparison of the reporting rates of transfusion reactions shows that no statistically significant difference can be determined between APC and PPC in the period from 2011 to 2014.

### Reporting behaviour of university and non-university facilities

Differences in the reporting behaviour between the treating physicians in university and non-university facilities may influence the reporting rate of the platelet concentrates tested with regard to transfusion related infections. To provide an assessment of the reporting behaviour, the following Table shows a comparison between the number of reported suspected cases of a serious adverse reaction and the reported suspected cases of a transfusion related infection (reports pursuant to Section 63i AMG) in the calendar year 2013 for the number of transfused blood components (reports pursuant to Section 21 TFG) between the respective facilities. In determining the reporting frequencies referring to the number of blood components used (RBC, PC, and therapeutic single plasms) no significant difference can be seen between university and non-university facilities with regard to viral and bacterial transmissions for the period of 2013/2014. A bias of the reporting rate to the detriment of blood components used to a larger extent in university facilities compared with other health care facilities cannot be assumed on the basis of these data.

Listing of the suspected cases reported from university versus non university facilities (2013)

| 2013 | University hospital | Hospital | Other health care facilities |
|---|---|---|---|
| Number of facilities | 41 | 1,381 | 1,175 |
| Number of transfused RBCs | 844,296 | 2,817,633 | 349,779 |
| Number of transfused PCs | 230,781 | 222,799 | 35,903 |
| Number of transfused plasma units | 355,263 | 478,835 | 2,658 |
| Total number of transfused RBC/PC/plasma units | 1,430,340 | 3,519,267 | 388,340 |
| Number of suspected cases reported (total) | 155 | 261 | 22 |
| Number of suspected cases reported* (viral/bacterial) | 22 | 38 | 6 |
| Reports of suspected cases (viral, bacterial) per $10^6$ transfused RBC/TC/plasma units | 15 | 11 | 15 |
| Lower 95% confidence interval (CI), Reports of suspected cases per $10^6$ transfused RBC/PC/plasma units | 10 | 8 | 6 |
| Upper 95% CI, reports of suspected cases per $10^6$ transfused RBC/PC/plasma unit | 23 | 15 | 34 |
| $Chi^2$ p-value: 0.36, p >0.05, non-significant, degree of freedom: 2 | | | |

* The number of suspected cases does not match with the total from the tables in the above sections, since some cases could not be assigned to a specific facility.

# // 5. Summary/Conclusion //

### Referring to the data of the haemovigilance system

- Only the reporting frequency but not the incidence of serious transfusion reactions can be determined based on the haemovigilance data.

### Referring to the data for the period from 2013 to 2014

- The most frequent complications following administration of PC were approximately:

  52.6 ATR and 6.2 TTBI per $10^6$ units
- The most frequent complications following administration of RBC were:

  15.5 ATR, 8.5 TACO and 6.3 HTR per $10^6$ units
- The most frequent complications following administration of FFP were:

  15.6 ATR and 3.6 TACO per $10^6$ units

### Referring to the period from 2013 to 2014

- The most frequently confirmed suspected diagnoses were:
- ATR > TACO > HTR > AB0 incompatibility > TRALI > TTBI > TTVI
- The most frequent transfusion related deaths were:

  ATR = TACO > HTR = AB0 Inkompatibilität > TRALI = TTBI = TTVI

### Referring to the acute transfusion reactions

- The number of reported suspected cases and that of the confirmed serious ATR has remained unchanged for 2013/2014 as compared to 2011/2012.
- The reporting frequency of ATR following the administration of PC has risen essentially in the period of 2013/14 and has risen slightly following administration of RBC and FFP in that period.
- Underlying and concomitant diseases also have to be taken into account as additional causes. To be able to judge the allergic reactions better, additional data from the patient's history should be collected, including allergies against foods, other medicines, and pollen/grasses.

### Referring to the transfusion-related acute lung injury

- After the measures for the reduction of immunogenic TRALI to be implemented by September 2009, reporting of TRALI reactions and associated deaths has decreased.
- In the period of 2013/2014, a total of 15 immunogenic and two non-immunogenic TRALI cases were reported.
- One TRALI associated case of death following the administration of PC was reported.

### Referring to the haemolytic transfusion reactions

- The reporting frequency of haemolytic transfusion reactions following administration of RBCs has risen in 2014.

### Referring to the transfusion transmitted bacterial infections

- The reporting frequency of bacterial infections following administration of PC remained constant during the twelve-year period from 1999 to 2008 with more than ten cases per $10^6$ units [17].
- Fatal courses in most of the cases were caused by pathogens with high human pathogenicity.
- After the limitation of the shelf-life of PC to 4 x 24 hours plus the date of donation in 2008, one death occurred following the administration of one PPC and one death following the administration of one APC in the period from 2009 to 2014.
- Since the limitation of the shelf-life, the rate of confirmed bacterial infections following administration of PC has been 5.8 per $10^6$ units for the period from 2009 to 2012 and 6.2 per $10^6$ units for the period from 2013 to 2014.

### Referring to the transfusion transmitted viral infections

- With the introduction of serologic single donor screening by the end of the 1990s, viral transmission could largely be prevented [17].
- Since 1999, HCV transmission could be reduced to up to now one case thanks to HCV-NAT pool testing. HIV-NAT pool testing helped reducing HIV transmission to up to now two cases since 2004.
- By means of HBsAg single donor screening, the reporting rate for HBV transmissions could be reduced to less than one case per year.
- In 2013/2014 altogether five HEV transmission were confirmed, which led to complications in one recipient during the later course following transmission.
- Complete detection of all infected donors is not possible due to the diagnostic window phase and the variability of the pathogens tested.
- After the introduction of HCV-NAT pool testing, around 40 million donors were tested in the period from 1999 to 2009, of those 92 tested positive with NAT and negative with ELISA. After the introduction of HIV NAT pool testing, around 17 million donations were tested in the period from 2004 to 2009, of which eleven tested positive with NAT but negative with ELISA [12].

### Referring to transfusion associated circulatory overload (TACO)

- The evaluations of the reports from 2011 to 2014 confirm a higher risk of circulatory overload in elderly patients with cardio-vascular diseases and renal insufficiency [9].
- As a preventative measure, a reduced transfusion rate (1 ml/minute total volume) is therefore recommended for patients to whom the above mentioned criteria apply.

### Referring to the data of donor triggered look-back procedures

- Because of the high number of look-back procedures for non-specific positive anti-HBc results, it became necessary to review the criteria laid down in Opinion 34/35. The changes were adopted in Opinion 42 of the AK Blut on 7 November 2012 [14] and specified in more detail in the order of the PEI (2014). The number of HBV-related look-back procedures has since then decreased slightly.
- The data document also a slight decrease in the look-back procedure for isolated anti-HBc positive donors after the introduction of the regulation governed by Opinion 42.
- Reports of syphilis infections in the donor have increased 5-fold since 2011.

### Referring to serious adverse events

- Reports of serious adverse events to the PEI have increased in the period of 2013/2014.
- The classification was made in accordance with the requirements of the European Commission.
- The serious adverse events primarily referred to failures during processing and distribution of the blood products.
- Referring to German law incorrect transfusions of blood components relating to mistakes in the manufacturing or distribution without the occurrence of reactions in the recipient represent a special type of serious adverse events.
- The reporting rate of incorrect transfusions has increased tenfold in 2013/2014 compared with the previous reporting period.

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# // 7. Figures and Tables //

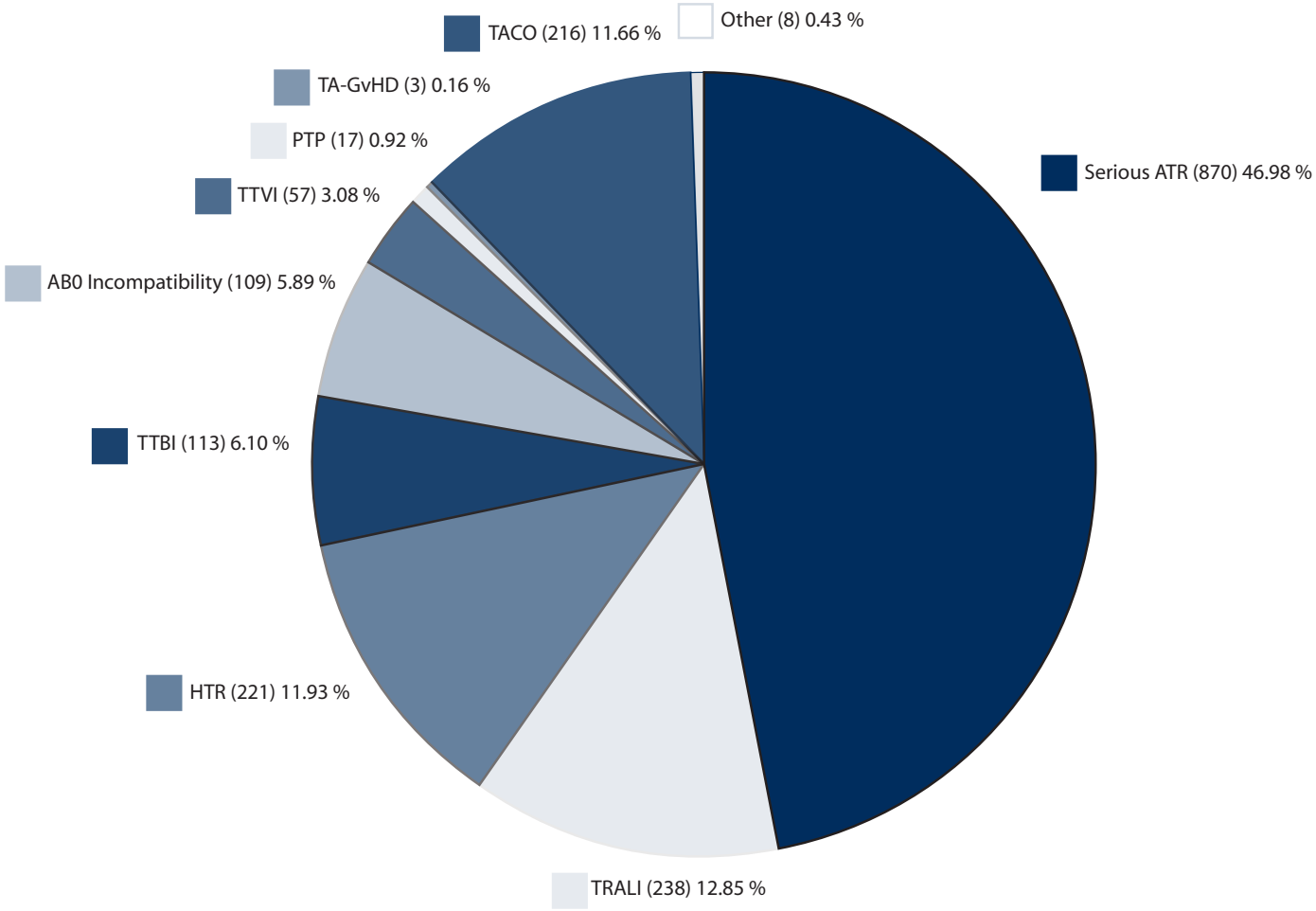


**Figure 1:**
Cumulative number of confirmed transfusion reactions (based on the IHN criteria), 1997 to 2014

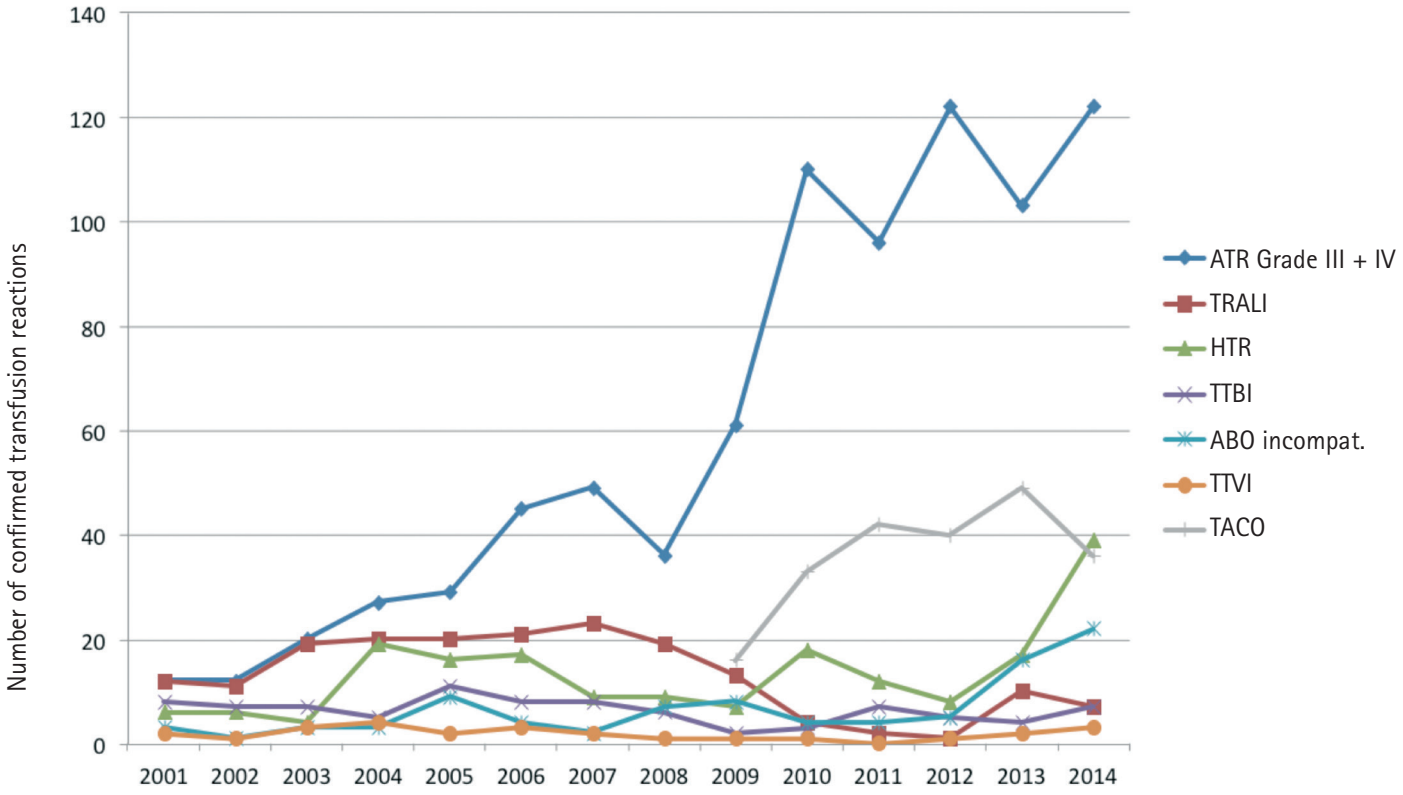


**Figure 2:**
Number of transfusion reactions confirmed per year (2001–2014)
From 2014, the TRALI graph contains only likely/confirmed cases (new definition)

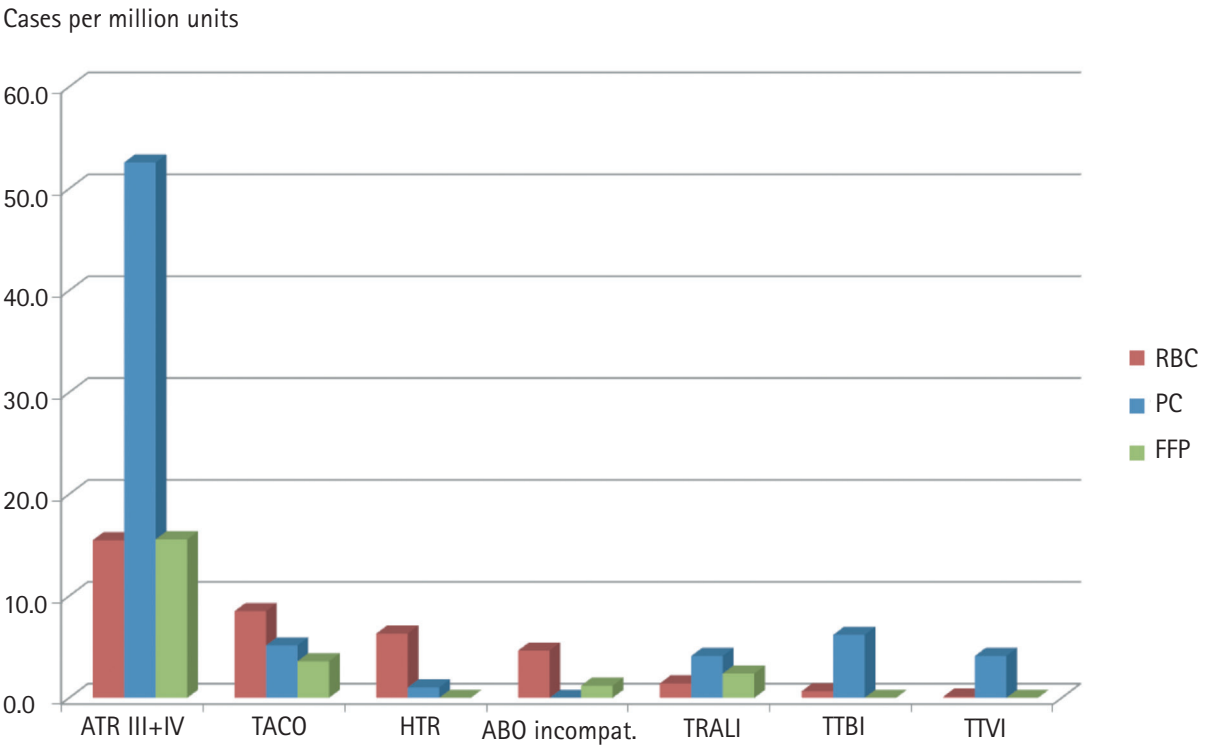


**Figure 3:**
Product-related rate of transfusion reactions (2013–2014)
Cases where different blood products were involved are not shown in the figure

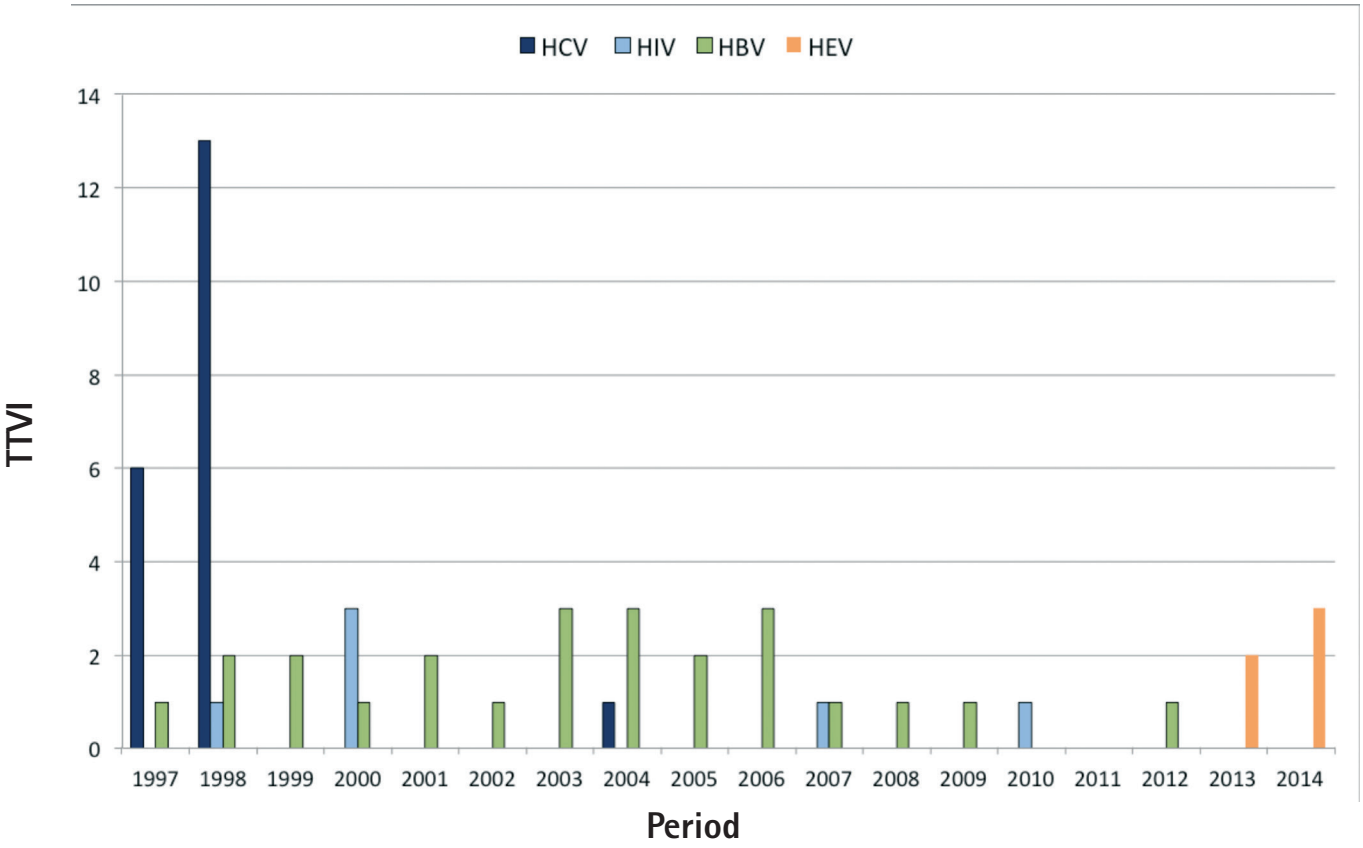


**Figure 4:**
Transfusion transmitted viral infections (1997–2014)
In compliance with Opinion 34

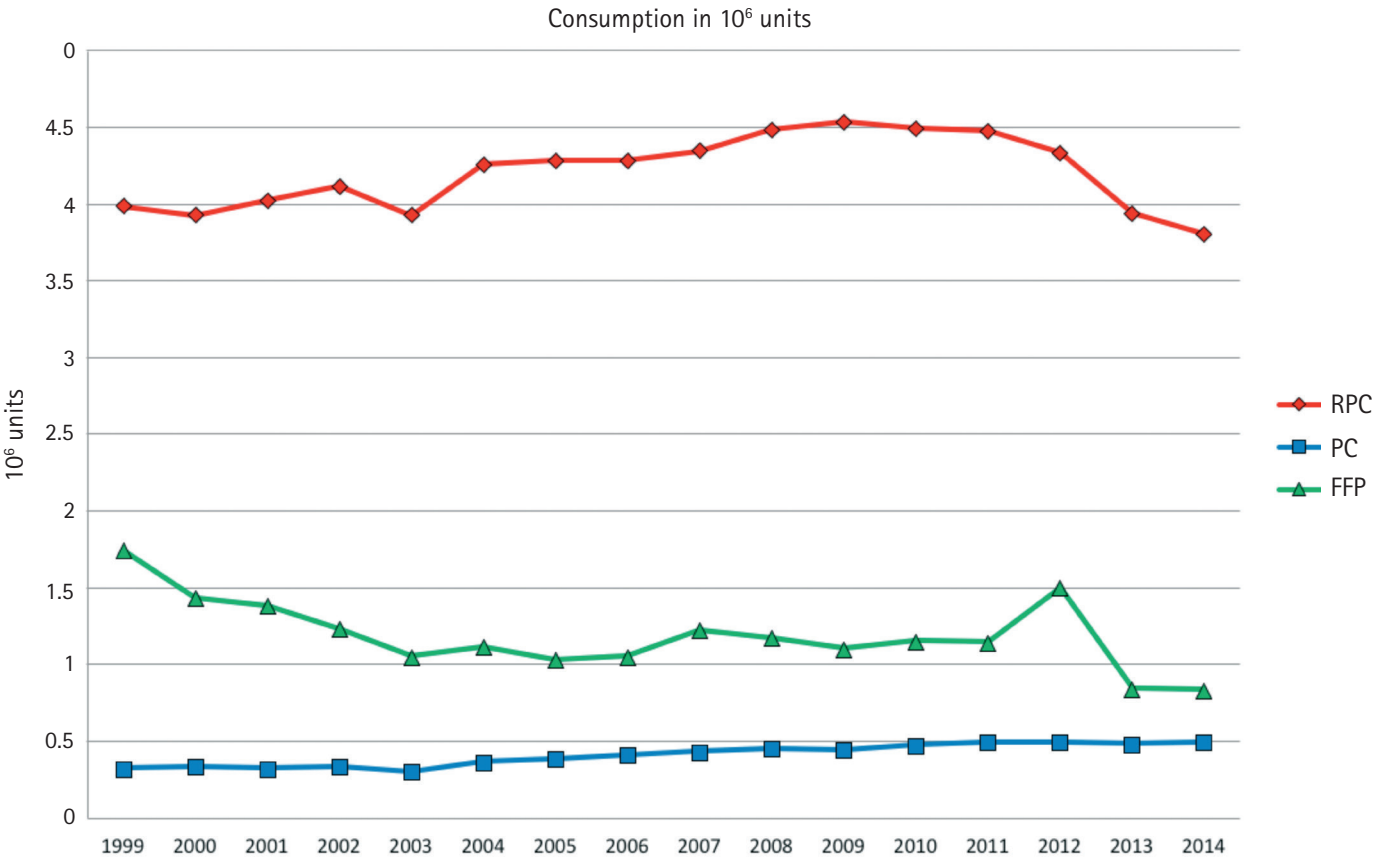


**Figure 5:**
Consumption of blood components in $10^6$ units (1999–2014)

**Table 1a:** Total number of reported and confirmed transfusion reactions (IHN criteria), 1997–2014

| | Reported suspected cases | | | | Based on IHN- criteria: confirmed suspected cases | | | |
|---|---|---|---|---|---|---|---|---|
| | 1997–2012 | 2013 | 2014 | 1997–2014 | 1997–2012 | 2013 | 2014 | 1997–2014 |
| Allergic transfusion reactions (ATR) (Grade I–Grade IV) | 2,222 | 206 | 288 | 2,716 | 1,854 | 182 | 252 | 2,288 |
| ATR (Grade I and II) | | 85 | 147 | | | 79 | 130 | |
| ATR (Grade III and IV) | | 121 | 141 | | | 103 | 122 | |
| Transfusion-related acute lung injury (TRALI) | 870 | 54 | 58 | 982 | 204 | 10 | 7 | 221 |
| Haemolytic transfusion reaction (HTR) | 360 | 36 | 60 | 456 | 177 | 17 | 39 | 233 |
| Transfusion transmitted bacterial infection (TTBI) | 298 | 35 | 36 | 369 | 102 | 4 | 7 | 113 |
| ABO incompatibility | 71 | 16 | 22 | 109 | 71 | 16 | 22 | 109 |
| Transfusion transmitted viral infection (TTVI) | 3,283 | 57 | 75 | 3,415 | 52 | 2 | 3 | 57 |
| Post-transfusion purpura (PTP) | 18 | 0 | 6 | 24 | 15 | 0 | 2 | 17 |
| Transfusion associated GVHD (TA-GVHD) | 4 | 0 | 0 | 4 | 3 | 0 | 0 | 3 |
| TACO | 137 | 50 | 42 | 229 | 131 | 49 | 36 | 216 |
| Other | 63 | 11 | 10 | 84 | 4 | 1 | 3 | 8 |
| **Total** | **7,326** | **465** | **597** | **8,388** | **2,613** | **281** | **371** | **3,265** |

**Table 1b:** Total number of confirmed transfusion reactions, associated deaths (IHN criteria), 1997–2014

| Serious transfusion reactions (STR) | STR with deadly course Total number | | | |
|---|---|---|---|---|
| | 1997–2012 | 2013 | 2014 | 1997–2014 |
| Acute (allergic) transfusion reactions (ATR) | 27 | 3 | 1 | 31 |
| Transfusion related acute lung injury (TRALI) | 20 | 1 | 0 | 21 |
| Haemolytic transfusion reaction (HTR) | 11 | 0 | 2 | 13 |
| Transfusion transmitted bacterial infection (TTBI) | 13 | 0 | 1 | 14 |
| ABO incompatibility | 8 | 0 | 2 | 10 |
| Transfusion transmitted viral infection (TTVI) | 2 | 1 | 0 | 3 |
| Post-transfusion purpura (PTP) | 0 | 0 | 0 | 0 |
| Transfusion associated GVHD (TA-GVHD) | 1 | 0 | 0 | 1 |
| TACO | 7 | 1 | 3 | 11 |
| Other | 0 | 0 | 0 | 0 |
| **Total** | **89** | **6** | **9** | **104** |

**Table 2:** Serious allergic transfusion reactions (Grades III and IV), associated deaths, and reporting frequencies (before 2010 serious reactions of Grade II are also included)

| | 1997–2002* | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 1997–2014 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Serious allergic reactions after administration of | | | | | | | | | | | | | | |
| RBC | 25 | 9 | 14 | 18 | 35 | 32 | 23 | 28 | 59 | 50 | 68 | 65 | 55 | 481 |
| PC | 6 | 8 | 2 | 7 | 4 | 7 | 4 | 14 | 14 | 17 | 25 | 15 | 36 | 159 |
| FFP | 9 | 1 | 6 | 1 | 2 | 7 | 3 | 15 | 20 | 16 | 17 | 14 | 12 | 123 |
| Combi-nation | 10 | 2 | 5 | 3 | 4 | 3 | 6 | 4 | 17 | 13 | 12 | 9 | 19 | 107 |
| **Total** | **50** | **20** | **27** | **29** | **45** | **49** | **36** | **61** | **110** | **96** | **122** | **103** | **122** | **870** |
| Fatal outcome after administration of | | | | | | | | | | | | | | |
| RBC | 3 | 1 | 0 | 2 | 0 | 0 | 1 | 2 | 2 | 1 | 2 | 2 | 0 | 16 |
| PC | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 5 |
| FFP | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 4 |
| Combi-nation | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 6 |
| **Total** | **8** | **2** | **0** | **2** | **1** | **1** | **1** | **5**** | **3** | **2** | **2** | **3** | **1** | **31** |

| Reporting frequency of confirmed serious allergic reactions for the period of | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2001 – 2004 | | 2005 – 2008 | | 2009–2012 | | 2013+2014 | |
| | Transfused units*** x $10^6$ | ATR (total) per $10^6$ | Transfused units*** x $10^6$ | ATR (total) per $10^6$ | Transfused units*** x $10^6$ | ATR (total) per $10^6$ | Transfused units*** x $10^6$ | ATR (total) per $10^6$ |
| RBC | 16.340 | (35) **2.14** | 17.417 | (108) **6.20** | 17.855 | (205) **11.48** | 7.75 | (120) **15.48** |
| PC | 1.311 | (12) **9.15** | 1.671 | (22) **13.17** | 1.894 | (70) **36.96** | 0.97 | (51) **52.58** |
| FFP | 4.781 | (12) **2.51** | 4.474 | (13) **2.91** | 4.888 | (68) **13.91** | 1.67 | (26) **15.57** |

The column in light blue marks the introduction of the subdivision of acute transfusion reactions into allergic and anaphylactic transfusion reactions.

* Introduction of leucocyte depletion

** These cases are patients with serious underlying diseases. A connection between the transfusion reaction and the deadly course cannot be ruled out.

*** calculated consumption

**Table 3:** TRALI cases (immunogenic and non-immunogenic), associated deaths, and reporting frequencies

| | 1997–2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013** | 2014 | 1997–2014 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TRALI based on IHN criteria, testing for HLA-/HNA antibodies | | | | | | | | | | | | | | |
| Negative | 7 | 3 | 4 | 5 | 4 | 5 | 5 | 3 | 3 | 1 | 0 | 0 | 2 | 42 |
| Donor positive | 22 | 14 | 13 | 12 | 17 | 18 | 14 | 10 | 1 | 1 | 1 | 10 | 5 | 138 |
| not done | 33 | 2 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 41 |
| Total | 62 | 19 | 20 | 20 | 21 | 23 | 19 | 13 | 4 | 2 | 1 | 10 | 7 | 221 |
| TRALI, donor examination for HLA-/HNA antibodies, positive in | | | | | | | | | | | | | | |
| RBC donors | 8 | 2 | 1 | 5 | 2 | 1 | 0 | 4 | 1 | 0 | 1 | 7 | 4 | 36 |
| PC donors | 1 | 2 | 1 | 0 | 1 | 1 | 1 | 3 | 0 | 1 | 0 | 4 | 0 | 15 |
| FFP donors | 13 | 10 | 11 | 7 | 14 | 16 | 13 | 5 | 0 | 0 | 0 | 3 | 1 | 93 |
| Total | 22 | 14 | 13 | 12 | 17 | 18 | 14 | 12 | 1 | 1 | 1 | 14 | 5 | 144 |
| TRALI with fatal outcome caused by | | | | | | | | | | | | | | |
| RBC donors | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| PC donors | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 2 |
| FFP donors | 0 | 1 | 1 | 2 | 2 | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 16 |
| Total | 0 | 2 | 2 | 2 | 3 | 5 | 5 | 1 | 0 | 0 | 0 | 1 | 0 | 21 |

| Reporting frequency of confirmed serious immunogenic reactions for the period of | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2001–2004 | | 2005–2008 | | 2009–2012 | | 2013–2014 | |
| | Transfused units* x $10^6$ | TRALI (total) per $10^6$ | Transfused units* x $10^6$ | TRALI (total) per $10^6$ | Transfused units* x $10^6$ | TRALI (total) per $10^6$ | Transfused units* x $10^6$ | TRALI (total) per $10^6$ |
| RBC | 16.340 | (5) **0.31** | 17.417 | (8) **0.46** | 17.855 | (6) **0.34** | 7.75 | (11) **1.42** |
| PC | 1.311 | (3) **2.28** | 1.671 | (3) **1.80** | 1.894 | (4) **2.11** | 0.97 | (4) **4.12** |
| FFP | 4.781 | (25) **5.23** | 4.474 | (50) **11.18** | 4.888 | (5) **1.00** | 1.67 | (4) **2.40** |

The first column highlighted in light blue marks the introduction of leukocyte depletion (2000). The second column highlighted in light blue marks the beginning of intensified monitoring by the PEI. The third column highlighted in light blue marks the introduction of risk minimising measures taken in the manufacture of therapeutic fresh frozen plasma (09/2009).

* calculated consumption

** As from 2013, rating values were changed, and only likely and confirmed cases are shown in the Table for periods as from that date.

**Table 4:** Haemolytic transfusion reactions, associated deaths, and reporting frequencies

| | 1997–2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 1997–2014 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Haemolytic transfusion reactions after the administration of | | | | | | | | | | | | | | |
| RBC | 49 | 2 | 16 | 14 | 14 | 6 | 8 | 6 | 16 | 11 | 7 | 16 | 33 | **198** |
| PC | 2 | 0 | 2 | 0 | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 0 | 1 | **12** |
| Combination | 7 | 2 | 1 | 2 | 2 | 2 | 0 | 1 | 0 | 0 | 0 | 1 | 5 | **23** |
| **Total** | **58** | **4** | **19** | **16** | **17** | **9** | **9** | **7** | **18** | **12** | **8** | **17** | **39** | **233** |
| Acute and delayed haemolytic transfusion reactions and HTR with evidence of Ab | | | | | | | | | | | | | | |
| Acute HTR | 49 | 4 | 18 | 14 | 16 | 7 | 8 | 5 | 9 | 3 | 5 | 11 | 36 | **185** |
| Delayed HTR | 9 | 0 | 1 | 2 | 1 | 2 | 1 | 2 | 9 | 9 | 3 | 6 | 3 | **48** |
| Irregular red blood cell Ab | 6 | 0 | 1 | 1 | 1 | 1 | 1 | 2 | 16 | 9 | 3 | 6 | 3 | **50** |
| **Total** | 58 | 4 | 19 | 16 | 17 | 9 | 9 | 7 | 18 | 12 | 8 | 17 | 39 | **233** |
| Haemolytic transfusion reactions with fatal outcome after the administration of | | | | | | | | | | | | | | |
| RBC | 4 | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 2 | **11** |
| Combination | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **2** |
| **Total** | **5** | **0** | **2** | **0** | **2** | **0** | **0** | **0** | **0** | **2** | **0** | **0** | **2** | **13** |

| Reporting frequency of confirmed haemolytic transfusion reactions for the period of | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2001–2004 | | 2005–2008 | | 2009–2012 | | 2013+2014 | |
| | Transfused units* x $10^6$ | HTR (total) per $10^6$ | Transfused units* x $10^6$ | HTR (total) per $10^6$ | Transfused units* x $10^6$ | HTR (total) per $10^6$ | Transfused units* x $10^6$ | HTR (total) per $10^6$ |
| RBC | 16.340 | (25) **1.53** | 17.417 | (42) **2.41** | 17.855 | (40) **2.24** | 7.75 | (49) **6.32** |
| PC | 1.311 | (4) **3.05** | 1.671 | (3) **1.80** | 1.894 | (4) **2.11** | 0.97 | (1) **1.03** |

* calculated consumption

**Table 5:** Transfusion transmitted bacterial infections, reporting frequencies

| | 1997–2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 1997–2014 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bacterial infections following the administration of | | | | | | | | | | | | | | |
| RBC | 15 | 2 | 2 | 3 | 2 | 6 | 3 | 0 | 1 | 3 | 2 | 2 | 3 | 44 |
| PPC | 11 | 3 | 1 | 4 | 3 | 1 | 2 | 1 | 0 | 2 | 0 | 0 | 0 | 28 |
| APC | 10 | 2 | 2 | 3 | 3 | 1 | 1 | 1 | 2 | 2 | 3 | 2 | 4 | 36 |
| FFP | 4 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 |
| Total | **40** | **7** | **5** | **11** | **8** | **8** | **6** | **2** | **3** | **7** | **5** | **4** | **7** | **113** |
| Bacterial infections with fatal outcome following the administration of | | | | | | | | | | | | | | |
| RBC | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 |
| PPC | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 5 |
| APC | 2 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 5 |
| FFP | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | **7** | **1** | **1** | **1** | **1** | **0** | **0** | **1** | **0** | **1** | **0** | **0** | **1** | **14** |

| Reporting frequency of confirmed transfusion related bacterial infections for the period of | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2001–2004 | | 2005–2008 | | 2009–2012 | | 2013+2014 | |
| | Transfused units* x $10^6$ | TTBI (total) per $10^6$ | Transfused units* x $10^6$ | TTBI (total) per $10^6$ | Transfused units* x $10^6$ | TTBI (total) per $10^6$ | Transfused units* x $10^6$ | TTBI (total) per $10^6$ |
| RBC | 16.340 | (9) **0.55** | 17.417 | (14) **0.80** | 17.855 | (6) **0.34** | 7.75 | (5) **0.65** |
| PC | 1.311 | (18) **13.73** | 1.671 | (18) **10.77** | 1.894 | (11) **5.81** | 0.97 | (6) **6.19** |
| FFP | 4.781 | (0) **0.00** | 4.474 | (1) **0.22** | 4.88 | (0) **0.00** | 1.67 | (0) **0** |

The column highlighted in light blue marks the introduction of pre-donation sampling (2002). The boxes highlighted mark the recommendation by "AK Blut" to reduce the shelf-life of PCs to four days (2008).

* calculated consumption

**Table 6:** Results of the microbiological analysis in confirmed TTBI (1997–2014)

| Microorganism | Number of blood components with evidence of pathogen in the recipient/blood product | | | | Course of disease in the recipient | | Deaths after administration of | |
|---|---|---|---|---|---|---|---|---|
| Type/species | RBC | PC | FFP | Total | Non-fatal | Fatal | RBC | PC |
| **Pathogen with low (human) pathogenicity** | | | | | | | | |
| *Staphylococcus capitis, epidermidis, hominis, saprophyticus und spp. Micrococcus luteus, Corynebacterium spp. Propionibacterium acnes* | 18 | 27 | 2 | 47 | 46 | 1 | 0 | 1 |
| **Pathogen with medium/high pathogenicity** | | | | | | | | |
| *Staphylococcus aureus Streptococcus pyogenes und agalactiae Bacillus cereus, Escherichia coli Enterobacter aerogenes, amnigenus Klebsiella oxytoca, pneumonia Pantoea agglomerans, Serratia marcescens, Yersinia enterocolitica, Enterococcus spp. Acinetobacter Iwoffii, Pseudomonas aeruginosa Stenotrophomonas maltophilia* | 26 | 37 | 3 | 66 | 53 | 13 | 4 | 9 |
| Total | 44 | 64 | 5 | 113 | 99 | 14 | 4 | 10* |

* Transfusion of PC on the fourth and fifth day after manufacture

**Table 7:** Transfusion transmitted viral infections (HBV, HCV, HEV, HIV), reporting frequencies (HCV, HIV, HBV, HEV)

| | 1997–2003 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 1997–2014 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HCV infections following the administration of | | | | | | | | | | | | | | |
| RBC | 7 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8 |
| PPC | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| APC | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| FFP | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 |
| **Total** | **19** | **0** | **1** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **20** |
| HIV infections following the administration of | | | | | | | | | | | | | | |
| RBC | 4 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 6 |
| PC | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| FFP | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | **4** | **0** | **0** | **0** | **0** | **1** | **0** | **0** | **1** | **0** | **0** | **0** | **0** | **6** |
| HBV infections following the administration of | | | | | | | | | | | | | | |
| RBC | 6 | 1 | 2 | 2 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 16 |
| PPC | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| APC | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 5 |
| FFP | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| **Total** | 9 | 3 | 3 | 2 | 3 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 24 |
| HEV infections following the administration of | | | | | | | | | | | | | | |
| RBC | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| PC | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 4 |
| FFP | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 3 | 5 |

| Reporting frequency of confirmed transfusion transmitted viral infections for the period of | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2001 – 2004 | | 2005 – 2008 | | 2009 – 2012 | | 2013 + 2014 | |
| | Transfused units* x $10^6$ | TTVI (total) per $10^6$ | Transfused units* x $10^6$ | TTVI (total) per $10^6$ | Transfused units* x $10^6$ | TTVI (total) per $10^6$ | Transfused units* x $10^6$ | TTVI (total) per $10^6$ |
| RBC | 16.340 | (5) **0.31** | 17.417 | (8) **0.46** | 17.855 | (1) **0.06** | 7.75 | (1) **0.13** |
| PC | 1.311 | (2) **1.53** | 1.671 | (0) **0.00** | 1.894 | (2) **1.06** | 0.97 | (4) **4.12** |
| FFP | 4.781 | (3) **0.63** | 4.474 | (0) **0.00** | 4.88 | (0) **0.00** | 1.67 | (0) **0.00** |

The first column highlighted in light blue marks the introduction of HCV-NAT pool testing. The second column highlighted in light blue marks the introduction of HIV-NAT pool testing (1999). The third column highlighted in light blue marks the introduction of anti-HBc single testing.

* calculated consumption

**Table 8:** AB0 incompatibility, associated deaths and reporting frequencies

| | | 97 | 98 | 99 | 00 | 01 | 02 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | 10 | 11 | 12 | 13* | 14 | 1997–2014 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cases with confirmed administration of AB0 incompatible products | | | | | | | | | | | | | | | | | | | | |
| | HTR RBC 1a, report | 6 | 1 | 3 | 8 | 3 | 1 | 3 | 3 | 9 | 4 | 2 | 7 | 8 | 4 | 4 | 5 | 15 | 21 | 110 |
| | HTR FFP 1a, report | | | | | | | | | | | | | | | | | 1 | 1 | 2 |
| | Serious adverse event 1b, report | | | | | | | | | | | | | 1 | 3 | 2 | 2 | 12 | 29 | 49 |
| AB0 incompatibility with fatal outcome | | | | | | | | | | | | | | | | | | | | |
| RBC | Trans. reaction 1a, report | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 2 | 0 | 0 | 2 | 10 |
| Reporting frequency of confirmed AB0 incompatibilities per $10^6$ administered RBC (transfusion reactions, reactions and serious adverse events) | | | | | | | | | | | | | | | | | | | | |
| RBC | Confirmed AB0 incompatibility | 18 | | | | 10 | | | | 22 | | | | 29 | | | | 79 | | 158 |
| | Transfused units** x $10^6$ | 15.84 | | | | 16.34 | | | | 17.42 | | | | 17.86 | | | | 7.75 | | 75.21 |
| | Cases per $10^6$ E | 1.14 | | | | 0.61 | | | | 1.26 | | | | 1.62 | | | | 10.19 | | 2.1 |

* The increased number of reports since 2013 can be explained by the so-called 16th amended version of the AMG (16. AMG-Novelle) stipulating the notification of every suspected serious adverse event by the marketing authorisation holder (Section 63i (2) AMG).

** calculated consumption

**Table 9:** Manufacture and calculated consumption of blood components (1999 to 2014, reports to the PEI pursuant to Section 21 TFG)

| Year | RBC | | PC | | FFP | | RBC, PC, FFP | |
|---|---|---|---|---|---|---|---|---|
| | Manufacture units x $10^6$ | Consumption* units x $10^6$ | Manufacture units x $10^6$ | Consumption* units x $10^6$ | Manufacture units x $10^6$ | Consumption* units x $10^6$ | Manufacture units x $10^6$ | Consumption* units x $10^6$ |
| 1999 | 4.28 | 3.99 | 0.41 | 0.32 | 1.81 | 1.74 | 6.50 | 6.05 |
| 2000 | 4.26 | 3.93 | 0.42 | 0.33 | 1.53 | 1.43 | 6.21 | 5.69 |
| 2001 | 4.32 | 4.03 | 0.39 | 0.32 | 1.45 | 1.38 | 6.16 | 5.73 |
| 2002 | 4.45 | 4.12 | 0.38 | 0.33 | 1.28 | 1.23 | 6.11 | 5.68 |
| 2003 | 4.24 | 3.93 | 0.37 | 0.30 | 1.11 | 1.05 | 5.72 | 5.28 |
| 2004 | 4.54 | 4.26 | 0.41 | 0.36 | 1.18 | 1.11 | 6.13 | 5.73 |
| 2005 | 4.56 | 4.29 | 0.43 | 0.38 | 1.09 | 1.03 | 6.08 | 5.70 |
| 2006 | 4.52 | 4.29 | 0.45 | 0.41 | 1.10 | 1.05 | 6.07 | 5.75 |
| 2007 | 4.57 | 4.35 | 0.48 | 0.43 | 1.27 | 1.22 | 6.32 | 6.00 |
| 2008 | 4.71 | 4.49 | 0.51 | 0.45 | 1.23 | 1.17 | 6.45 | 6.11 |
| 2009 | 4.74 | 4.54 | 0.52 | 0.44 | 1.14 | 1.10 | 6.40 | 6.08 |
| 2010 | 4.77 | 4.50 | 0.55 | 0.47 | 1.20 | 1.15 | 6.52 | 6.12 |
| 2011 | 4.76 | 4.48 | 0.57 | 0.49 | 1.13 | 1.14 | 6.46 | 6.11 |
| 2012 | 4.59 | 4.34 | 0.59 | 0.49 | 1.52 | 1.50 | 6.70 | 6.33 |
| 2013 | 4.40 | 3.94 | 0.58 | 0.48 | 0.99 | 0.84 | 5.97 | 5.26 |
| 2014 | 4.31 | 3.81 | 0.53 | 0.49 | 0.92 | 0.83 | 5.76 | 5.13 |

* The calculation was performed on the basis of the data on the loss at the manufacturer and the user.