Evaluation of Risk Minimisation Measures for Blood Components – Based on Reporting Rates of Transfusion-Transmitted Reactions (1997–2013)

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Keywords

Reporting rate · Risk minimisation measures ·
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Summary

Background: To assess the impact of safety measures, we compared reporting rates of transfusion-related reactions before and after the implementation of six measures in 1999, 2004, 2006, 2008 and 2009. **Methods:** Reporting rates of transfusion-transmitted bacterial infection (TTBI), viral infection (TTVI) and immune-mediated transfusion-related acute lung injury (TRALI) were calculated on the basis of confirmed annual reports and distributed blood components. **Results:** The introduction of HCV NAT testing caused a significant reduction of HCV reporting rate from 1:0.6 to 1:83.16 million administered blood components ($p < 0.0001$), donor screening for antibodies to hepatitis B core antigen caused a reduction of HBV reporting rate from 1:2.90 to 1:10.70 million units ($p = 0.0168$). A significant reduction from 1:0.094 to 1:2.42 million fresh frozen plasma (FFP) units could also be achieved by risk minimisation TRALI measures ($p < 0.0001$). Implementation of pre-donation sampling did not result in a significant decrease in TTBI, whereas limitation of shelf life for platelet concentrate (PC) minimised the TTBI reporting rate from 1:0.088 to 1:0.19 million PC units ($p = 0.041$). For HIV NAT pool testing, no significant reduction in HIV transmission was found due to very low reporting rates (1:10 million versus 1:27 million blood components, $p = 0.422$). **Conclusion:** On the basis of haemovigilance data, a significant benefit could be demonstrated for four of six implemented safety measures.

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Introduction

During the last decade (2000–2010) acute (anaphylactic) transfusion reactions, haemolytic transfusion reactions, transfusion-transmitted bacterial infections (TTBI), transfusion-transmitted viral infections (TTVI) and transfusion-related acute lung injuries (TRALI) were identified as most serious transfusion-related risks [1–4].

Various risk minimisation measures have been discussed to reduce these adverse reactions, and like other European competent authorities, the Paul-Ehrlich-Institut (PEI) imposed binding regulations on this. During the last decade the German blood establishments implemented several specific safety measures, such as HCV and HIV NAT donor testing, donor screening for antibodies to hepatitis B core antigen (anti-HBc) as well as shelf life reduction of platelet concentrates (PC) to reduce serious bacterial infections as well as TRALI risk minimisation measures.

Due to multifactorial route causes, no measures were implemented to reduce the increasing number of transfusion-related allergic reactions up to now. Whereas TTBI and TRALI are more frequent and cause immediate serious and even life-threatening complication, TTVI are very rare events and may lead to less severe reactions. However, TTVI provoke still an enhanced public awareness, and a high safety standard is required; particularly for the prevention of transfusion-transmitted HIV infections.

To evaluate the impact of safety measures, the PEI compared reporting rates of defined transfusion-related reactions before and after implementation of safety measures.

Table 1. Distribution and estimated consumption of blood components between 1997 and 2013; notification to the PEI according TFG Section 21

Year	Units $\times 10^6$							
	RBC		PC		FFP		RBC, PC, FFP	
	distribution	consumption*	distribution	consumption*	distribution	consumption*	distribution	consumption*
1997	~4.19	~3.90	~0.44	~0.30	~1.55	~1.50	~6.00	~5.70
1998	~4.22	~3.90	~0.42	~0.30	~1.59	~1.50	~6.00	~5.70
1999	4.28	3.99	0.41	0.32	1.81	1.74	6.50	6.05
2000	4.26	3.96	0.42	0.33	1.60	1.53	6.21	5.89
2001	4.32	4.06	0.39	0.32	1.47	1.45	6.16	5.83
2002	4.38	4.08	0.38	0.33	1.33	1.28	6.04	5.74
2003	4.24	3.94	0.37	0.32	1.14	1.11	5.72	5.40
2004	4.54	4.27	0.41	0.36	1.20	1.18	6.13	5.83
2005	4.56	4.29	0.43	0.38	1.14	1.09	6.08	5.81
2006	4.52	4.29	0.45	0.41	1.17	1.10	6.07	5.87
2007	4.57	4.36	0.48	0.43	1.31	1.28	6.33	6.10
2008	4.71	4.49	0.51	0.45	1.26	1.23	6.45	6.20
2009	4.75	4.53	0.53	0.46	1.24	1.22	6.50	6.23
2010	4.77	4.50	0.56	0.48	1.21	1.20	6.53	6.19
2011	4.79	4.48	0.57	0.49	1.14	1.14	6.50	6.11
2012	4.62	4.34	0.59	0.52	1.54	1.53	6.74	6.36
2013	4.40	4.13	0.58	0.50	0.99	0.97	5.97	5.60
Total	76.12	71.51	7.94	6.70	22.69	22.05	105.93	100.61

*Estimated figures.

Material and Methods

According to the German Medicinal Products Act (AMG Section 63) and the German Transfusion Act (TFG Section 16), blood establishments and treating physicians are obliged to report serious adverse reactions directly to the PEI within 15 days following their occurrence. Physicians are requested to provide any missing data such as main symptoms, clinical course and identification and categorisation of the pathogenic agent affecting the recipient as well as data of involved blood components. When a transfusion-related reaction is confirmed, further specific laboratory analysis of affected blood donors or involved blood components are usually requested.

The evaluation of a causal relationship for a suspected transfusion-related virus infection is based on the guidelines of the German Advisory Group Blood (Opinion 34). Causality assessment criteria include the categories: certain, probable, possible, unlikely and non-assessable [5].

In cases of suspected transfusion-related bacterial infections, blood samples of affected recipients and samples of transfused products need to be analysed microbiologically using aerobic and anaerobic cultures. TTBI are defined by clinical criteria associated with a culture-positive residual component and a culture-positive recipient demonstrating the same bacteria as, for instance, determined by antibiotic sensitivity.

The diagnosis of TRALI is confirmed if the criteria of acute respiratory distress during or within 6 h of transfusion, radiographic evidence of (new) bilateral pulmonary infiltrates and absence of signs of circulatory overload were fulfilled (ISBT criteria) [6]. In addition, the blood donors concerned should be analysed for leucocyte antibodies in order to distinguish between immune and non-immune TRALI. Standardised analyses of HNA and HLA antibodies have been described since 2002 [7].

Risk Minimisation Measures

A number of risk minimisation measures have been imposed by the PEI or have been recommended by the German Advisory Group Blood.

Since 1999, in addition to serological donor testing, HCV NAT testing (HCV RNA detection limit: 5,000 IU/ml) has been implemented to prevent fur-

ther transfusion-related HCV infections. HIV NAT testing (HIV RNA detection limit: 10,000 IU/ml) has been requested since May 2004 as an additional blood donor screening measure. To reduce transfusion-related hepatitis B infections, screening of blood donors with an anti-HBc test was implemented in October 2006.

Regarding transfusion-related bacterial infections, the German Advisory Committee Blood recommended risk minimisation measures in 2002 and 2008. These implementations occurred on a voluntary basis by the blood donation establishments. To achieve a reduction in microbial contamination of blood components, pre-donation sampling has been recommended since June 2003 (German Advisory Group Blood, Opinion 27). This includes the separation and removal of at least 15 ml after venepuncture before harvesting donors' blood. Since June 2008, a limitation of the shelf life of PC has been recommended (German Advisory Group Blood, Opinion 38). In 2008 it was recommended to limit the storage of PC to 4 days (4×24 h); beginning at midnight of the day the blood was collected to reduce the danger of serious or fatal bacterial infections.

Combined measures were implemented in September 2009 to reduce the reporting rate of immune-mediated TRALI. Female donors with a history of pregnancy should be excluded from fresh frozen plasma (FFP) donation. Female donors with a history of pregnancy could be accepted when tested negative for HLA class I, HLA class II, HNA 1a, HNA 1b, HNA-2 and HNA-3a antibodies.

The reporting rate of defined transfusion-related reactions was calculated on the basis of reactions fulfilling consensus criteria and the number of transfused blood components. The figures of transfused FFP, PC and red blood cells (RBC) must be reported to the PEI annually according to Section 21 of the German Transfusion Act.

Statistical Analysis

The reporting rates before and after the implementation of each risk minimisation measure were compared by means of a 2-sample Poisson test, with two-sided p values < 0.05 indicating statistically relevant differences. Reporting rate ratios (RRR) including their 95% confidence intervals (95% CI) were used to describe the corresponding effects ($RRR < 1$ indicating an effect of the intervention). R, version 3.02, was used for statistical analysis [8].

Table 2. Transfusion-transmitted HCV infections following the administration of blood components during a period of 17 years (prior and after implementation of HCV NAT pool testing)^a

	Implementation of HCV NAT testing		
	before	year of	after
Period	1997–1998	1999	2000–2013
Transfused blood component units × 10 ⁶	11.40	6.05	83.16
Confirmed HCV transmissions	19	0	1
Reporting rate: cases / 10 ⁶ units	1.67	0	0.01
1 case per X million units	1:0.6		1:83.16
^a Comparison 1997–1998 vs. 2000–2013: RRR 0.007 (95% CI 0.0002–0.0461); p < 0.0001.			

Table 3. Transfusion-transmitted HIV infections following the administration of blood components during a period of 17 years (prior and after implementation of HIV NAT pool testing)^a

	Implementation of HIV NAT testing		
	before	year of	after
Period	1997–2003	2004	2005–2013
Transfused blood component units × 10 ⁶	40.31	5.83	54.47
Confirmed HIV transmissions	4	0	2
Reporting rate: cases / 10 ⁶ units	0.1	0	0.04
1 case per X million units	1:10.08		1:27.24
^a Comparison 1997–2003 vs. 2005–2013: RRR 0.371 (95% CI 0.034–2.594); p = 0.412.			

Table 4. Transfusion-transmitted HBV infections following the administration of blood components during a period of 15 years (prior and after implementation of anti-HBc donor testing)^a

	Implementation of anti HBc testing		
	before	year of	after
Period	1999–2005	2006	2007–2013
Transfused blood component units × 10 ⁶	40.55	5.87	42.79
Confirmed HBV transmissions	14	3	4
Reporting rate: cases / 10 ⁶ units	0.35	0.51	0.09
1 case per X million units	1:2.90	1:1.96	1:10.70
^a Comparison 1999–2005 vs. 2007–2013: RRR 0.27 (95% CI 0.065–0.862); p = 0.0168.			

Results

Reporting Rates of TTVI (HBV/HCV/HIV)

A total of 106 million blood components were distributed by the German blood establishments within a period of 17 years (1997–2013), and approximately 101 million units were transfused: 71.51 million RBC concentrates 22.05 million FFP and 6.70 million PC as shown in table 1.

During the whole haemovigilance period (1997–2013), an overall amount of 3,322 suspected cases of transfusion-associated virus infections were reported to the PEI: 1,902 HCV, 188 HIV and 1,232 possible HBV cases. According to Opinion 34 regarding look-back procedures (German Advisory Group Blood) and according to published operational procedure [5], only 50 out of 3,322 notifications (1.5%) have been confirmed.

19 HCV transmissions were confirmed before the implementation of HCV NAT testing during a 2-year period (1997 and 1998). On the basis of 11.40 million transfused blood components this corresponds to a reporting frequency of 1.67 cases per million units (table 2). After the implementation in 1999 over a period of 14 years and an equivalent of 83.16 million transfused blood compo-

nents, only one further HCV transmission was reported, corresponding to a highly significant difference (RRR 0.006, 95% CI 0.0002–0.0461; p < 0.0001).

Prior to the implementation of HIV NAT testing during a period of 7 years (1997–2003), four HIV transmissions were confirmed. This corresponds to 0.1 cases per million units (40.31 million transfused blood components). After the implementation in 2004, two further HIV transmissions occurred over a period of 9 years and an equivalent of 54.47 transfused blood components (table 3). No significant difference could be demonstrated between the first reporting rate 0.1 cases per million units versus 0.04 cases per million units (RRR 0.371, 95% CI 0.034–2.594; p = 0.412).

Between 1999 and 2005, prior to the implementation of anti-HBc donor testing, a total of 14 HBV transmissions were confirmed, corresponding to 0.35 cases per million units (40.55 million transfused blood components). After the implementation, four HBV transmissions occurred over a 7-year period and 42.7 million transfused blood components (table 4). A significant difference could be demonstrated between the reporting rate of 0.35 cases and 0.09 cases per million units (RRR 0.27, 95% CI 0.065–0.862; p = 0.0168).

Table 5. TTBI and fatalities after the administration of PC (apheresis and pooled PC) during a period of 15 years (prior and after implementation of shelf life reduction)

	Implementation of pre-donation sampling			Implementation of shelf life reduction		
	before	year of	after	before	year of	after
Period	1999–2002	2003	2004–2007	2004–2007	2008	2009–2013
Transfused PC $\times 10^6$	1.30	0.32	1.58	1.58	0.45	2.45
Confirmed TTBI-related fatalities	2	1	3	3	0	2
TTBI cases	18	5	18	18	3	13
Reporting rate: cases / 10^6 PC	13.85	15.63	11.39	11.39	6.66	5.31
1 TTBI per 0.X million PC	1:0.072	1:0.064	1:0.088	1:0.088	1:0.15	1:0.19
1 TTBI-related fatality per 0.X million PC	1:0.65	1:0.32	1:0.53	1:0.53		1:1.23
Confirmed TTBI cases	comparison 1999–2002 vs. 2004–2007: RRR 0.82 (95% CI 0.40–0.1.68); $p = 0.617$			comparison 2004–2007 vs. 2009–2013: RRR 0.0416 (95% CI 0.21–1.00); $p = 0.041$.		

Table 6. Immune-mediated TRALI after the administration of FFP during a period of 9 years (prior and after implementation of TRALI minimisation measures)^a

	Implementation of TRALI minimization measures		
	before	year of	after
Period	2005–2008	2009	2010–2013
Transfused FFP units $\times 10^6$	4.70	1.22	4.84
TRALI-related fatalities	14	0	0
Confirmed TRALI cases	50	5	2
Reporting rate: cases / 10^6 FFP units	10.64	4.09	0.41
1 case per X million units	1:0.094	1:0.22	1:2.42
One TRALI-related fatality per 0.X million units	1:0.34		
^a Comparison 2005–2008 vs. 2010–2013: RRR 0.039 (95% CI: 0.005–0.148); $p < 0.0001$.			

TTBI Reporting Rate

During the whole period of observation (1997–2013), a total of 333 suspected TTBI were reported; 105 cases could be confirmed based on the available laboratory data. 41 of these infections were caused by RBC concentrates, 59 by PC and 5 by FFP. 11 of 13 confirmed fatalities occurred between 1997 and 2007, and two between 2008 and 2013. Four fatalities occurred after the administration of RBC concentrates during the reporting period 1997–2000 and nine fatalities after the administration of PC (5 pooled and 4 apheresis PC). Most of these PC were applied at the end of the shelf life (4th or 5th day after manufacture). The last case with fatal outcome occurred in 2013 after administration of a pooled PC.

Within an observational period of 15 years, reporting frequencies of TTBI varied between 4.00 and 18.18 cases per million transfused PC, 0.8 and 0.3 cases per million transfused RBC concentrates, and between 0.6 and 0.0 cases per million transfused FFP units.

Before the implementation of pre-donation sampling (1999–2002), the reporting frequency for PC was 13.85 cases per million units; after the implementation (2004–2007) it decreased to 11.39 cases as shown in table 5. A comparison of these two periods did not demonstrate a statistical significance (RRR 0.82, 95% CI 0.40–0.1.676; $p = 0.617$). After the limitation of the shelf life for PC in 2008, the reporting frequency decreased from 11.39 cases per million units (2004–2007) to 5.31 cases per million units during a 5-year period (2009–2013). The comparison of both periods dem-

onstrates a statistically significant difference in reporting rates for TTBI (RRR 0.0416, 95% CI 0.21–1.00; $p = 0.041$).

TRALI Reporting Rate

Over the whole period (1997–2013), 841 suspected TRALI reactions were reported, and a total number of 203 cases were confirmed according to the ISBT criteria: 122 immune-mediated TRALI (60%) and 40 non-immune-mediated TRALI (20%) and 41 non-classified cases (20%).

20 of 21 cases of blood component-related fatal TRALI reactions occurred between 1997 and 2009. Three fatalities were caused by RBC concentrates, two by PC and 16 by FFP. In all cases with fatal outcome immune-mediated TRALI was confirmed. The last two cases with a fatal outcome occurred in 2009 and in 2011 after administration of PC. Leucocyte antibody testing revealed 1 donor with HLA class I and 1 with HNA-3a antibodies.

131 donors involved were tested positive for leucocyte antibodies: 90 FFP donors (69%), 29 RBC donors (22%) and 12 PC donors (9%). Only 5 male donors but 126 female donors were involved.

As shown in table 6, the TRALI-reporting frequency for FFP was 10.64 cases per million units during a 4-year period prior to the implementation of risk minimisation measures (2005–2008). After the implementation, the reporting rate decreased to 0.41 cases per million FFP units (2010–2013). A comparison of both periods demonstrates a statistically significance difference (RRR 0.039, 95% CI 0.005–0.148; p value < 0.0001).

Discussion

In evaluating the reduction of transfusion-related reactions, various factors must be considered that may influence reporting rates. The German Haemovigilance System as defined by the Medicinal Products Act came into force in 1997. No sufficient data are available for statistical analysis before that date. It is also obvious that reporting rates do not provide a complete picture of the frequency of transfusion reactions and therefore are not comparable with study data.

HCV NAT testing was implemented in 1999, HIV NAT testing in 2004 and anti-HBc donor testing in 2006. Since then no further TTVI risk minimisation measures have been added. An evaluation of each risk minimisation measure for virally transmitted infection was performed comparing adequate time periods. Regarding TTBI two measures were introduced, and for this reason, time periods before and after pre-donation sampling as well as before and after shelf life reduction of PC have been compared. An assessment of reported TRALI reactions on the basis of a standardised definition has been carried out since 2005 [5]. To evaluate the benefit of TRALI minimisation measures, we chose 2005–2008 as the time frame for the pre-implementation period and 2009–2013 for the post-implementation period.

On the basis of the German haemovigilance data, a significant reduction in HCV transmission could be confirmed after the introduction of HCV NAT testing. Regarding HBV transmission, the introduction of anti-HBc donor testing reduced the reporting rate to one third by an average of 1 transmission per year. To achieve this reduction, a high rate of unspecific positive test results and consequently a high number of donor-related look-back procedures have to be accepted. Because of the occurrence of two HIV transmissions in 2007 and 2010, no significant benefit was demonstrated for HIV NAT testing. In both cases with HIV-1 RNA false-negative test results nucleotide sequencing of the viral target region revealed new HIV-1 variants that mismatched with primers of mono-target assays. It could be assumed that dual-target assays would have been capable to detect new variants to a large extent. A prevention of these cases would have led to a measurable improvement, but on the basis of two HIV transmissions a period of 17 years (2005–2022) is needed to prove a significant difference. Therefore, the effect HIV NAT testing has to be discussed considering the low overall reporting rate of transfusion-related HIV infection. In addition to these reporting data, the rate of NAT-only-positive donations following introduction of NAT testing demonstrate that NAT testing considerably contributed to a risk minimisation regarding TTVI [9].

Other haemovigilance systems demonstrate comparable reporting rates. The Swissmedic haemovigilance report 2013 describes only single cases of TTVI in the last decade with currently estimated risks of 1:6.7 million donations for HCV, 1:4.1 million donations for HIV and 1:1.4 million donations for HBV [2]. According to the SHOT report 2013, only one single HCV and HIV transmission, but 10 HBV transmissions have been confirmed for blood components in the UK since 1997 [1]. Data of the SHOT

report lead to the assumption that one potentially infectious HIV transmission could be expected every 3 years due to negative serological test results during the window period [1]. It was also stated that far fewer HIV transmissions are observed in practice, partly because the estimate has wide uncertainty and the model does not incorporate pack non-use and recipient susceptibility to infection. Also under-ascertainment and underreporting has to be considered, for example due to recipients dying from an underlying medical condition before a chronic asymptomatic viral condition is identified, or, in the case of HBV, an asymptomatic acute infection.

Regarding TTBI, a minimal reduction of TTBI reporting rate from 13.8 to 11.4 cases per million PC was seen after the introduction of pre-donation sampling. The implementation of the shelf life reduction halved the reporting rate further to 5.3 per million units, corresponding with one TTBI case in 190,000 platelet units. A significant decrease in the reporting rate could only be demonstrated 5 years after implementation.

TTBI data of other haemovigilance systems are partly consistent with our data. The SHOT report 2009 confirmed a total of 22 TTBI during the last 10 years, representing a reporting frequency of 1 case in 117,000 platelet units [1]. After the implementation of bacterial screening testing, no further TTBI have been confirmed since 2009 as described in the UK (SHOT report 2013) [1]. In contrast, despite bacterial screening testing, the American Red Cross (ARC) published TTBI frequencies between 1:40,000 and 1:193,000 depending on the collecting procedure. The fatality rate was one in 500,000 platelet units [10]. Swissmedic described an estimated TTBI risk of 1:600,000 donations for the last decade [2]; after the introduction of pathogen inactivation procedure for all PC (2011), no further TTBI was confirmed [11].

To interpret the benefit of risk-reducing measures, the multifactorial aetiology of TTBI must be considered as already described [12]. The removal of the initial 10–40 ml of blood after venepuncture before drawing donors' blood has been shown to reduce the bacterial load introduced into manufactured blood components by 40–90% although no significant effect was demonstrated [13]. A comparable evaluation in Germany revealed a significant reduction of bacterial contamination compared to periods without pre-donation sampling for RBC concentrates and pooled PC [14], demonstrating that this measure is effective in reducing contamination of blood components with skin bacteria at the time of phlebotomy. On the other hand, limitations of the PC shelf life focus on the prevention of severe bacterial infections due to a high bacterial level after a longer incubation time, caused by unrecognised donor bacteraemia or insufficient skin disinfection, but will not be suitable to avoid infections with skin bacteria in immunosuppressed patients.

Additional measures may lead to a further decrease of TTBI. These could be more effective and reliable screening tests or adequate pathogen reduction procedures. To balance the benefits, risks and burden of these strategies, more data as well as scientific evaluations are needed [11, 15, 16].

After the exclusion of female donors with a history of pregnancy from FFP donation, only 2 immune-mediated TRALI that fulfilled consensus criteria during a 4-year period were reported. Since then, no TRALI case with fatal outcome was reported after FFP administration and 1 single case caused by a PC. Our data show that a significant reduction in immune-mediated TRALI was achieved by a defined risk minimisation measure. The testing of female donors also provides the opportunity to exclude only subjects with an increased risk and maintain for example important apheresis donors.

This is in accordance with haemovigilance data of the SHOT report. In 2003, the English National Blood Services introduced a 'male only plasma policy', which covers all high plasma components [3]. After the implementation of the safety measure, the overall risk of confirmed TRALI fell from 15.5 per million units (1999–2004) to 3.2 per million (2005–2006) in the UK [17]. The same effect was also demonstrated concerning TRALI-induced fatalities caused by FFP. A total of 9 deaths was reported by the SHOT programme in 2003 and, thereafter, fell to 1 in 2006 [17]. In the USA, the ARC implemented a 'male-predominant plasma strategy' comparable to the measures in the UK and Canada [18, 19]. Since November 2007, plasma collection for FFP was restricted to male-only donors, whereas platelet donations were not included. After the implementation of safety measures, the ARC demonstrated a decrease in 80% for TRALI cases involving only plasma transfusion (19.5 vs. 4.0 per million) and a reduction from 6 fatal cases in 2006 to zero in 2008 [20].

Since 2010, we confirmed 10 immune-mediated TRALI cases after administration of RBC concentrates (6 cases) and PC (4 cases). In accordance with the ISBT criteria, also 4 non-immune-mediated TRALI were seen. Based on these cases, the extension of TRALI safety measures has been discussed, but at present, the number of cases fulfilling consensus criteria is too limited to justify further steps.

On basis of current haemovigilance data we can conclude that serious transfusion-related reactions are rare complications. After implementation of risk minimisation measures, a low reporting rate was demonstrated for TTBI (1:0.19 million) and very low rates for immune-mediated TRALI (1:2.42 million) and TTVI (<1:10 million). Reporting rates for transfusion-related fatalities ranged between 1:1.23 million for TTBI and no reported case for immune-mediated TRALI. In comparison risk minimisation measures like introduction of safety standards and improved training resulted in a decrease of anaesthesia-related mortality from 6.4:10,000 in the 1940s to 0.4:100,000 at present [21].

In four of six implemented safety measures a significant benefit could be demonstrated on the basis of haemovigilance data. Although haemovigilance data showed little benefit of pre-donation sampling, a significant reduction of bacterial contamination for RBC concentrates and pooled PC was observed [14]. Also the effect of HIV NAT testing has to be considered as limited because of the very low reporting rates (1:10 million vs. 1:27 million units).

Risk minimisation measures should only be implemented on the basis of a careful risk analysis. The introduction of defined and product-specific measures allows an ongoing evaluation of risk reduction and, if necessary, a modification of initial measures.

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Disclosure Statement

The authors declare that they have no conflicts of interest relevant to the manuscript submitted.

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