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Blood Donation-Related Adverse Reactions: Results of an Online Survey among Donors in Germany (2018)

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Keywords

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Abstract

Introduction: According to German legislation, reports of suspected serious adverse reactions (AR) associated with the donation of blood and its components are continuously being evaluated by the Paul-Ehrlich-Institut. This survey aimed at providing a more complete picture of the AR associated with the donation of blood and blood components. ***Materials and Methods:*** Eligible donors had the opportunity to anonymously report all AR occurring during or after their last donation by completing an online questionnaire. Reported AR were classified according to the Standard for Surveillance of Complications Related to Blood Donation. Donors' self-assessment of AR seriousness was compared with the official severity classification as laid down by German legislation. Besides a descriptive statistical analysis, a multiple logistic analysis was performed to identify risk factors for AR. ***Results:*** A total of 8,138 data records were evaluated. Slightly more males (57.9%) participated in the survey and, except for donors aged ≥60 years, all age groups were equally represented. The majority of participants were whole blood donors (85.4%), repeat donors (97.2%), and stayed under observation in the blood establishment (BE) for more than 5 min (63.1%) after donation. Most participants did not report any reaction (72.5%), whereas 2,237 reported at least one AR (27.5%), 475 of whom underwent apheresis and 1,762 donated whole blood. Most AR occurred after leaving the BE (64.4%). Only a minority of participants required medical treatment (5.1%) or assessed the experienced AR as serious (3.9%). The most frequently reported donor AR were haematoma and other local reactions (57.6%). Vasovagal reactions without and with loss of consciousness were developed in 17 and 2% of the participants, respectively, whilst 7.6% experienced citrate reactions. New AR (i.e., allergic reactions and symptoms associated with iron deficiency) were reported as well. The occurrence of AR was linked to risk factors (i.e., female gender, young age, first-time donation, and thrombocytapheresis). ***Discussion:*** This survey yielded a more comprehensive AR spectrum, revealed a prolonged time to symptom onset, and identified risk factors for AR. This novel information could be implemented in an amended informed consent addressing common and rare AR.

Introduction

Serious adverse reaction (AR) in the European Blood Directive 2002/98/EC [1] is defined as "unintended response in donor or in patient associated with the collection or transfusion of blood or blood components that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity." In Germany, reporting of serious AR occurring in whole blood (WB) and in apheresis donors became mandatory in 2012 according to section 63i of the German Medicinal Products Act (MPA) [2, 3]. Although the number of reported serious donor AR increased significantly in 2015, with around 500 annual case reports between 2015 and 2018, more than 50% of all blood establishments (BE)

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have never reported serious donor AR since then [4]. Because BE are only obliged to report serious AR, a comprehensive overview of all AR, serious and non-serious, has not yet been undertaken. Furthermore, a differentiation between serious and non-serious donor AR seems difficult, because the existing definition of seriousness is the same for both blood recipients with underlying diseases and healthy blood donors.

While definitions, validated by the collaboration of the International Society of Blood Transfusion (ISBT) Working Party on Haemovigilance, the International Haemovigilance Network (IHN), and the American Association of Blood Banks (AABB) Donor Haemovigilance Working Group [5], have been standardised and facilitate the classification of donor AR [6], a clear-cut and donor-related specific definition distinguishing serious from non-serious AR would be desirable.

For the very first time in Germany, the online survey aimed: (i) to get a comprehensive overview of the frequency and type of donor AR occurring after donating blood or blood components reported directly by the donors, irrespective of seriousness and statutory reporting requirements; and (ii) to better understand how blood donors deal with unintended responses, allowing them to self-rate their experienced AR.

Materials and Methods

Questionnaire

The questionnaire was designed by scientists working at the haemovigilance department of the Paul-Ehrlich-Institut (PEI), the competent authority for blood safety surveillance in Germany. The questions regarding AR were based on the ISBT Standard for Surveillance of Complications Related to Blood Donation. As it was expected that donors in general might not be familiar with the medical vocabulary, these standards were paraphrased with language that is understandable to laymen. However, for the evaluation these laymen terms were assigned back to the corresponding ISBT standards. Likewise, the information given under "other reaction, please specify" was assigned to the ISBT standards.

In November 2017, a pilot study was conducted at one BE, in which a paper-based preliminary version of the questionnaire was applied to a small sample of the target donor population in a controlled setting. In the next step, the questionnaire was modified and ambiguous questions were eliminated. The final version of the questionnaire contained a total of 13 questions and was estimated to take approximately 3–5 min to complete (Fig. 1).

Initial questions were on gender, age group, and number of previous donations. Further questions related to the participant's last donation and concerned the donation type, year of last donation, experienced donor AR, time to symptom onset, requirement and type of medical treatment, and self-assessment of seriousness (self-evaluation without being influenced by the medical staff or by a written definition of seriousness). The final part of the questionnaire addressed the recurrence of donor AR, onsite postdonation observation time, and self-evaluation of the informed consent (IC) provided prior to donating. Furthermore, the participant was asked to assess the tolerability of previous donations in general.

Target Population

The target population comprised donors of blood or its components aged ≥18 years who had donated at least once. Individuals willing to give blood or blood components but who had never donated blood were excluded.

Anonymous Online Survey

In March 2018, the PEI contacted a total of 61 German BE parent organisations by email, 4 of which were private companies exclusively collecting plasma for fractionation, and the remaining 57 institutions were BE mainly manufacturing blood components for transfusion (6 Red Cross, 2 private, and 49 state and/or municipal organisations). All of them were invited to actively support an anonymous online survey among donors of WB and blood components.

In order to announce the survey to donors, information material (posters, flyers, and web links) was circulated among BE. All information materials were specifically designed to inform about and promote the survey.

The final questionnaire was implemented in a Content Management System (CMS) online survey tool (Government Site Builder, Informationstechnologiezentrum Bund/Materna, Germany, version 7). The anonymous online survey was accessible for participants from April 3 to September 30, 2018 via a website (www.pei.de/spendesicherheit).

Data Collection and Data Management

Data entered via the online tool were automatically stored in an anonymous way (personal data were not saved) in the FileMaker Pro relational database (Claris International Inc., Santa Clara, CA, USA, version 14.06). Data underwent plausibility checks and a cleansing process; invalid data records were excluded from further analysis. AR were classified according to the Standard for Surveillance of Complications Related to Blood Donation established by the Working Group on Donor Vigilance of the ISBT Working Party on Haemovigilance, the IHN, and the AABB Donor Haemovigilance Working Group [5].

Statistical Analysis

Within the scope of a descriptive statistical analysis, absolute and relative frequencies were calculated for qualitative data. For quantitative variables, the median, minimum, and maximum were computed. If applicable, analyses were stratified by gender, age group, donation frequency, donation type, and year. In addition, the subjective assessment of the donors about the seriousness of their reactions was compared with the classification of seriousness according to section 63i of the German MPA [2, 3].

Multiple logistic regression analysis was performed using the reporting of at least one AR (of an AR of special interest) as the dependent variable, and the variables gender, age group, donation frequency, and donation type as explanatory variables in order to identify factors independently associated with the reporting of at least one AR (of an AR of special interest). Only variables which were significantly associated with the reporting of AR (of special interest; $p < 0.05$) remained in the multiple logistic regression model. For the primary analysis, a backward variable selection method was used.

Sensitivity Analysis

In order to examine the influence of possible recall bias (systematic error that occurs when participants do not accurately remember previous events or experiences or omit details) on the results, the AR spectrum observed in 2018 and 2017 was compared with previous periods. Regarding the multiple logistic regression model, the analyses were repeated applying two other methods of variable selection (stepwise, forward).

Question	Answers	Question	Answers	Question	Answers
1. Gender?	○ Male	6. Adverse reaction experienced during or after last donation? *(multiple answers possible)*	○ Haematoma	10. Frequency of adverse reactions at previous donations?	○ Not applicable *(first-time donor)*
	○ Female		○ Pain in the punctured arm		○ Never
	○ Other		○ Paraesthesia		○ Once
2. Age group?	○ 18–29 years		○ Itching		○ 2 up to 5 times
	○ 30–45 years		○ Dizziness without syncope		○ More than 5 times
	○ 46–60 years		○ Dizziness with syncope	11. Tolerability of previous donations?	○ Not applicable *(first-time donor)*
	○ Older than 60 years		○ Citrate reaction		○ Very good
3. Donation frequency?	○ First-time donor		○ Other reaction, please specify		○ Good
	○ 2 up to 10 times		○ No reaction *(continue with question 10)*		○ Different
	○ 11 up to 20 times	7. Occurrence of reported adverse reaction? *(multiple answers possible)*	○ During donation		○ Rather bad
	○ More than 20 times		○ After donation in the blood establishment	12. Onsite postdonation observation time (last donation)?	○ Longer than 15 min
4. Donation type?	○ Whole blood		○ After leaving the blood establishment on the day of donating		○ Up to 15 min
	○ Plasmapheresis		○ In the first week after donating		○ Up to 5 min
	○ Thrombocytapheresis		○ Later		○ Not at all
	○ Other apheresis	8. Medical treatment required?	○ None	13. Assessment of informed consent?	○ Very good
5. Year oflast donation?	○ 2018		○ Yes, outpatient care in the blood establishment		○ Good
	○ 2017		○ Yes, outpatient care in the practice		○ Satisfying
	○ 2016		○ Yes, hospitalisation		○ Sufficient
	○ 2015	9. Assessment of seriousness?	○ Non-serious		○ Insufficient
	○ 2014		○ Serious		
	○ Prior to 2014				

Fig. 1. Anonymised questionnaire for donors of WB and blood components on AR during or after donation (translated into English).

Software

The statistical analysis was performed using the Statistical Analysis System (SAS Institute Inc., Cary, NC, USA, version 9.4).

Results

Participants

Of all the 61 BE parent organisations contacted, 59, with 169 blood facilities and some of them additionally having an unknown number of mobile collection teams, decided to participate and informed their donors about the survey using the informational material provided by the investigator. From an estimated number of 1 million individuals donating blood within 6 months (there are about 2 million donors of blood and plasma in Germany per year) [7], a total of 9,438 data records were collected during the 6-month survey (Fig. 2). Of these, 1,188 technical duplicates were excluded from further analysis, as were 20 of the remaining 8,250 data records because they were received after the data lock point and a further 92 because they were classified as incomplete (Fig. 3). Finally, 8,138 evaluable records were analysed in aggregated form only (Table 1).

Baseline Data

Overall, more males (57.9%) than females (41.9%) participated in the survey (other gender: 0.2%). In contrast, among first-time donors (n = 228), there were more women (n = 140) than men (n = 87), and in one data record other gender was documented (Table 1).

Apart from subjects aged older than 60 years (941 donors), the age distribution was well balanced among the predefined age groups 18–29 years (2,311 donors), 30–45 years (2,174 donors), and 46–60 years (2,712 donors; Table 1).

A minority of the participants were first-time donors (2.8%), whereas about half of the donors had donated more than 20 times before (53.0%; Table 1). The participants mainly donated WB (6,950 subjects), considerably

Table 1. Baseline results of the online survey among blood donors in Germany

Parameter and category (i)	Absolute frequency, n_i	Relative frequency, %
Total	8,138	100.0
Gender		
Male	4,711	57.9
Female	3,411	41.9
Other	16	0.2
Age group		
18–29 years	2,311	28.4
30–45 years	2,174	26.7
46–60 years	2,712	33.3
Older than 60 years	941	11.6
Donation frequency		
First-time donor[1]	228	2.8
2 up to 10 times	2,120	26.1
11 up to 20 times	1,479	18.2
More than 20 times	4,311	53.0
Donation type		
WB	6,950	85.4
Plasmapheresis	715	8.8
Thrombocytapheresis	454	5.6
Other apheresis	19	0.2
Year of last donation		
2018	6,777	83.3
2017	853	10.5
2016	155	1.9
2015	76	0.9
2014	53	0.7
Prior to 2014	224	2.8
Onsite postdonation observation time (last donation)		
Longer than 15 min	1,985	24.4
Up to 15 min	3,152	38.7
Up to 5 min	1,943	23.9
Not at all	1,058	13.0
Subjective assessment of IC		
Very good	4,000	49.2
Good	3,092	38.0
Satisfying	679	8.3
Sufficient	222	2.7
Insufficient	145	1.8
Tolerability of previous donations		
n.a. (first-time donor)	228	2.8
Very good	6,024	74.0
Good	1,610	19.8
Different	258	3.2
Rather bad	18	0.2
AR during or after last donation		
No reaction	5,901	72.5
Reaction	2,237	27.5

AR, adverse reaction; WB, whole blood; IC, informed consent.
[1] First-time donor: 87 males (38.2%), 140 females (61.4%), 1 other (0.4%).

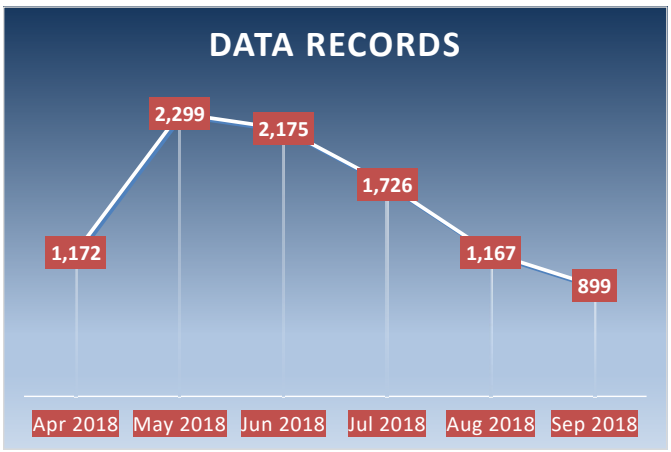

Fig. 2. Number of data records collected per month within the scope of the 6-month online survey.

fewer individuals underwent apheresis (1,188 subjects), and a majority had donated in 2018 (83.3%) and 2017 (10.5%; Table 1). An onsite postdonation observation time longer than 5 min was reported by 5,137 participants (63.1%), whereas 1,058 subjects (13.0%) left the BE immediately after donating without being monitored (Table 1).

Of all the participants, 87.2% classified the quality of the IC as "very good" or "good," 8.3% as "satisfying," 2.7% as "sufficient," and 1.8% as "insufficient" (Table 1). Apheresis donors (62.5%) more frequently gave very good ratings than WB donors (46.9%), and first-time donors (61%) more frequently gave very good ratings than repeat donors (48.8%), regardless of the number of previous donations (data not shown).

A majority of the participants classified the tolerability of previous donations as "very good" or "good" (93.8%; Table 1). Rating of general tolerability of previous donations did not differ across the donation types but depended on the donation frequency. Repeat donors with more than 20 donations more frequently classified the tolerability of previous donations as "very good" (data not shown).

Adverse Reactions

A majority of donors, 5,901 out of 8,138, did not report any AR (72.5%), among them 3,663 out of 4,711 men (77.7%) and 2,229 out of 3,411 females (65.4%). Regarding the donation frequency, 73.0% of all repeat donors (5,772 out of 7,910) and only 56.6% of all first-time donors (129 out of 228) did not experience any AR (data not shown).

A total of 2,237 donors reported at least one AR (27.5%; Table 1). The reported AR occurred at the time of donation in 445 (19.9%), after donation in 352 (15.7%), and

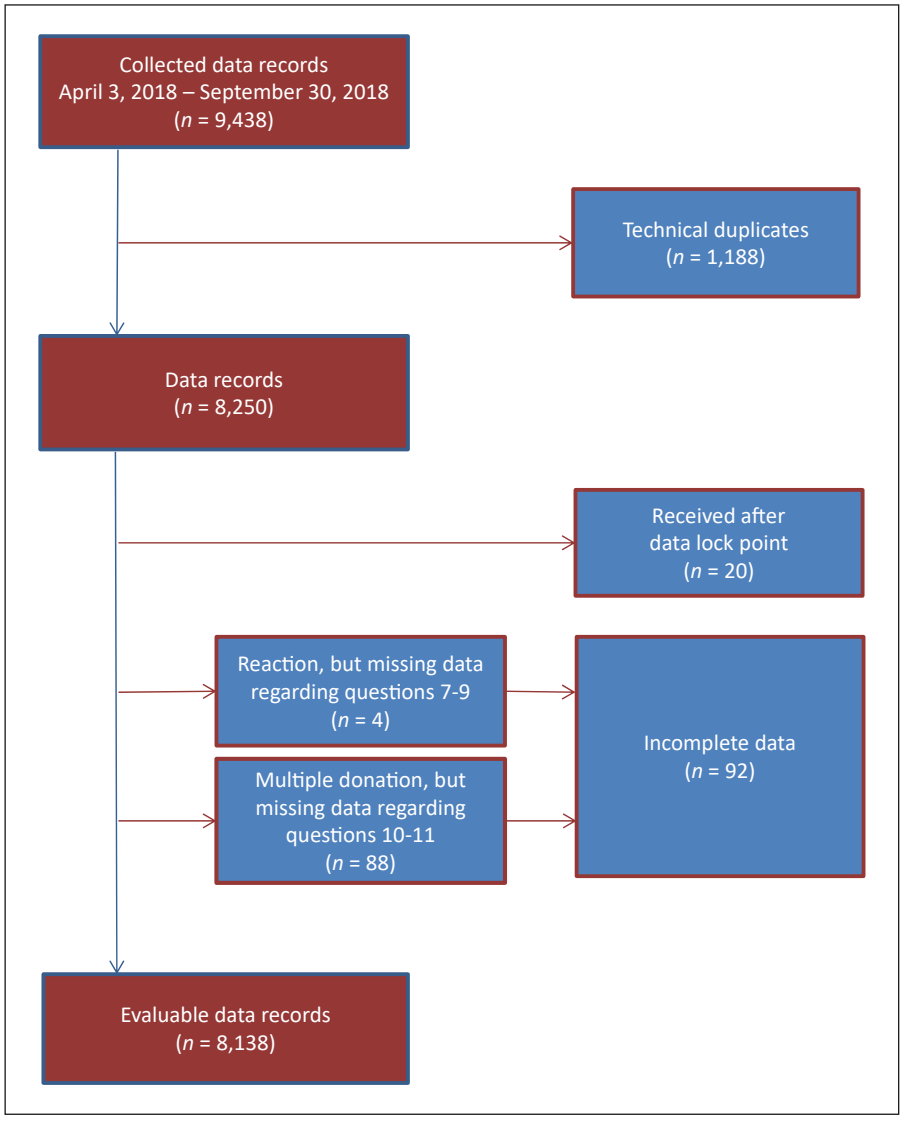

Fig. 3. Data processing flow chart.

after leaving the BE in 1,440 (64.4%) donors (Table 2). Interestingly, the onsite postdonation observation time was not correlated with the occurrence of an AR in the BE (Spearman correlation coefficient –0.02937; $p = 0.16$; data not shown). Moreover, repeat donors who had never experienced an AR during or after previous donations are probably those who left the BE without being monitored after donating.

A sample of 2,124 of the 2,237 donors who experienced at least one AR indicated that no medical treatment was required after the onset of the AR (94.9%), whereas 88 donors needed medical treatment in the BE (3.9%), 24 donors required treatment by a physician in an outpatient setting (1.1%), and 1 donor was hospitalised (0.04%; Table 2). Furthermore, 2,149 donors classified the AR as non-serious (96.1%) and 88 as serious (3.9%; Table 2). The 88 records with the assessment "serious" comprised all types of AR without a tendency to a certain kind of AR. Among donors with AR who classified the reaction as serious, 74 gave WB (84.1%) and 14 underwent apheresis (15.9%). Between the 88 donors who rated the AR as serious, 63 did not require medical treatment (71.6%), 12 were treated in the BE (13.6%), and 13 were physically examined in an outpatient setting (14.8%). The only patient who was hospitalised assessed the AR as non-serious (data not shown). Thus, the assessment of seriousness made by the participants of this survey was not in line with the classification of seriousness according to section 63i of the German MPA.

Irrespective of donation type and status, the 5 most frequently reported AR were: (i) haematoma with/without swelling at the puncture site; followed by (ii) pain in the punctured arm and/or erythema, swelling, limited mobility; (iii) dizziness with/without sweating, nausea, vomiting; (iv) citrate reaction characterised by metallic taste, tingling around the mouth, in fingers, in toes (only

Table 2. Reporting of AR

Parameter and category (i)	Absolute frequency, n_i	Relative frequency, %
Total	2,237	100.0
Occurrence of reported AR		
During donation	445	19.9
After donation in the BE	352	15.7
After leaving the BE on day of donating	888	39.7
In the first week after donating	487	21.8
Later	65	2.9
Medical treatment required		
None	2,124	94.9
Yes, outpatient care in the BE	88	3.9
Yes, outpatient care in the practice	24	1.1
Yes, hospitalisation	1	0.04
Subjective assessment of seriousness		
Non-serious	2,149	96.1
Serious	88	3.9
Frequency of AR at previous donations		
n.a. (first-time donor)	99	4.4
Never	382	17.1
Once	452	20.2
2 up to 5 times	841	37.6
More than 5 times	463	20.7

AR, adverse reaction; BE, blood establishment.

Table 3. Type and frequency of reported AR classified according to the Standard for Surveillance of Complications Related to Blood Donation (www.isbtweb.org/working-parties/haemovigilance)

Category and reported AR (i)	Absolute frequency, n_i	Relative frequency, %
Total	3,215[a]	100.0
A: Complications mainly with local symptoms		
A1: Complications mainly characterised by the occurrence of blood outside the vessels	1,083	33.7
A2: Complications mainly characterised by pain	763	23.7
A3: Localised infection/inflammation	7	0.2
B: Complications mainly with generalised symptoms: VVR		
B1: Without loss of consciousness	554	17.2
B2: With loss of consciousness on collection facility	37	1.2
B3: With loss of consciousness outside collection facility	26	0.8
C: Complications related to apheresis		
Citrate reaction	243	7.6
D: Allergic reactions		
D1: Allergy local	110	3.4
D2: Generalised allergic reaction (anaphylactic reaction)	15	0.5
E: Other serious complications related to blood donation		
Other serious complications related to blood donation	2	0.1
F: Other complications		
F1: Reactions associated with iron deficiency	224	7.0
F2: Other reactions (headache, diarrhoea, recurrent infections, impotence, dysgeusia...)	111	3.5
X: General health ameliorated		
General health ameliorated	14	0.4
Y: Reaction not further explained		
Reaction not further explained	26	0.8

AR, adverse reaction; VVR, vasovagal reaction.
[a] Some of the 2,237 donors reported more than 1 reaction.

Table 4. Multiple logistic regression analysis with the reporting of at least one AR as the dependent variable

Parameter and category vs. reference	Analysis of maximum likelihood estimates						Odds ratio estimates		
	DF	estimate	standard error	Wald χ^2	Pr > χ^2 *p* value	Exp (Est)	point estimate	95% Wald confidence limits	
Intercept	1	–2.0445	0.0964	450.0980	<0.0001	0.129			
Gender									
Other vs. male	1	0.8461	0.5444	2.4151	0.1202	2.331	2.331	0.802	6.775
Female vs. male	1	0.4940	0.0533	85.7798	<0.0001	1.639	1.639	1.476	1.819
Age group									
18–29 vs. older than 60 years	1	1.2119	0.1105	120.2985	<0.0001	3.360	3.360	2.706	4.172
30–45 vs. older than 60 years	1	0.5587	0.1076	26.9532	<0.0001	1.748	1.748	1.416	2.159
46–60 vs. older than 60 years	1	0.2275	0.1058	4.6287	0.0314	1.255	1.255	1.020	1.545
Donation frequency									
First time vs. more than 20 times	1	0.4613	0.1498	9.4821	0.0021	1.586	1.586	1.183	2.127
2–10 times vs. more than 20 times	1	0.3098	0.0707	19.2239	<0.0001	1.363	1.363	1.187	1.566
11–20 times vs. more than 20 times	1	0.0721	0.0757	0.9067	0.3410	1.075	1.075	0.927	1.247
Donation type									
Thrombocytapheresis vs. WB	1	1.2581	0.1043	145.5902	<0.0001	3.519	3.519	2.868	4.317
Plasmapheresis vs. WB	1	0.3039	0.0896	11.5046	0.0007	1.355	1.355	1.137	1.615
Other apheresis vs. WB	1	0.0860	0.5294	0.0264	0.8710	1.090	1.090	0.386	3.076

AR, adverse reaction; WB, whole blood; DF, degrees of freedom.

Table 5. Multiple logistic regression analysis with the reporting of dizziness with syncope as the dependent variable

Parameter and category vs. reference	Analysis of maximum likelihood estimates						Odds ratio estimates		
	DF	estimate	standard error	Wald χ^2	Pr > χ^2 *p* value	Exp (Est)	point estimate	95% Wald confidence limits	
Intercept	1	–7.1655	1.0101	50.3245	<0.0001	0.001			
Gender									
Female vs. male	1	0.8123	0.2766	8.6274	0.0033	2.253	2.253	1.310	3.874
Other vs. male	1	–10.1804	561.3	0.0003	0.9855	0.000	<0.001	<0.001	>999.999
Age group									
18–29 vs. older than 60 years	1	2.6748	1.0144	6.9535	0.0084	14.510	14.510	1.987	105.951
30–45 vs. older than 60 years	1	1.0208	1.0703	0.9097	0.3402	2.775	2.775	0.341	22.613
46–60 vs. older than 60 years	1	1.2742	1.0455	1.4853	0.2229	3.576	3.576	0.461	27.753

DF, degrees of freedom.

applicable for apheresis); and (v) paraesthesia in the punctured arm like numbness, tingling.

Contrasting with the mandatory annual reports, the AR of the online survey for the first time comprised allergic reactions and reactions like fatigue and exhaustion, possibly pointing to symptoms of an iron deficiency. Interestingly, euphoria and general health amelioration were also reported (Table 3).

Reporting of at least one AR was independently associated with gender, age group, donation frequency, and donation type: females, young individuals, first-time donors, and subjects undergoing thrombocytapheresis had an elevated odds for an AR (Table 4). Reporting of dizziness with syncope was independently associated with gender and age group: females and young donors had increased odds for dizziness with syncope (Table 5). Reporting of a citrate reaction was independently associated with gender, age group, and donation type: female gender, young age, and thrombocytapheresis were linked to an increased odds for citrate reaction (Table 6).

Sensitivity Analysis

The AR spectrum observed in 2017/2018 was comparable to the AR spectrum of previous periods.

Table 6. Multiple logistic regression analysis with the reporting of citrate reaction as the dependent variable (restricted to apheresis)

Parameter and category vs. reference	Analysis of maximum likelihood estimates						Odds ratio estimates		
	DF	estimate	standard error	Wald χ^2	Pr > χ^2 *p* value	Exp (Est)	point estimate	95% Wald confidence limits	
Intercept	1	−3.0476	0.3610	71.2861	<0.0001	0.047			
Gender									
Female vs. male	1	0.6884	0.1611	18.2643	<0.0001	1.991	1.991	1.452	2.730
Other vs. male	1	−10.6324	588.6	0.0003	0.9856	0.000	<0.001	<0.001	>999.999
Age group									
18–29 vs. older than 60 years	1	0.8621	0.3591	5.7627	0.0164	2.368	2.368	1.171	4.787
30–45 vs. older than 60 years	1	0.6461	0.3645	3.1422	0.0763	1.908	1.908	0.934	3.898
46–60 vs. older than 60 years	1	0.1833	0.3707	0.2446	0.6209	1.201	1.201	0.581	2.484
Donation type									
Thrombocytapheresis vs. plasmapheresis	1	1.5955	0.1635	95.1780	<0.0001	4.931	4.931	3.579	6.794
Other apheresis vs. plasmapheresis	1	0.0623	0.7697	0.0066	0.9355	1.064	1.064	0.235	4.811

DF, degrees of freedom.

Discussion

Collection of AR

As in other European countries, in Germany reporting of serious AR occurring during or after the donation of blood and its components is mandatory for BE. Non-serious AR do not have to be notified.

In Germany, from 2011 through 2014, on average 10.3 (range 1–24) serious donor AR per year were reported to the PEI. From 2015 through 2018, following a written reminder that reporting of serious donor AR is mandatory, on average 490.3 (range 531–444) serious donor AR per year were notified [4], corresponding to circa 0.1 serious donor AR per 1,000 donations in general. This corresponds to 0.13, 0.40, and 0.03 serious donor AR per 1,000 WB, thrombocytapheresis, and plasmapheresis donations, respectively.

In 2010, the French haemovigilance data reported 0.8 and 5.5 serious donor AR per 1,000 WB and thrombocytapheresis donations, respectively [8]. In the same year the Netherlands registered 5.5 AR per 1,000 donations, regardless of donation type [9].

These numbers support the notion that non-serious donor AR are observed at much higher rates. Moreover, the major difference between the French and German data regarding serious donor AR suggests that a standardised grading tool of severity is urgently needed.

Being aware of the fact that less than 50% of all BE in Germany reported serious donor AR between 2015 and 2018, it may be assumed that the number of serious donor AR that had occurred by far exceeded the number of those reported. This hypothesis was supported by a study conducted in 2013 in India where the rate of immediate AR observed from BE personnel increased more than 6-fold to 103.2 AR per 1,000 donors [10] when donors themselves were asked whether they had experienced any AR.

The present work represents the first online survey conducted in Germany that aims at collecting self-reported donor AR irrespective of seriousness. This information could not have been captured within the scope of spontaneous reporting according to the national law because only serious donor AR have to be notified.

Donor participation reached its peak in May 2018 and then steadily decreased until September 2018 despite renewed advertising on June 14, 2018 on the occasion of World Blood Donor Day. The reasons for the decline are unclear. The realisation of the survey strongly relied on the support offered by the participating BE and had no influence on the presentation and distribution of the informational material. It may be that after a while donors were no longer explicitly pointed to the survey by BE staff. There was sufficient informational material available and a shortage of supply can be excluded.

The participants' characteristics reflected very well the current donor population in Germany, with the majority being male, repeat, and WB donors in general, and more females among first-time donors [7]. In this survey, 27.5% of the participants reported at least one AR, a rate that is comparable to the AR rate of a similar online survey among Canadian blood donors [11] and is within the order of magnitude reported by the Indian survey [10].

Risk Factors

The presented findings are in line with previous studies demonstrating that younger age, first-time donation, female gender, and donation type (thrombocytapheresis) are associated with a higher risk of experiencing a donor AR [11–14]. Regarding vasovagal reactions (VVR) in

blood donors, younger age, WB donation [15], female gender [16, 17], as well as first-time donation [18] are routinely identified as independent risk factors for experiencing VVR. Further risk factors for VVR mostly identified on the univariate level include ethnicity with higher rates of VVR among white versus non-white donors [19, 20], lower body mass index (BMI)/weight versus higher BMI/weight [18], and a lower versus higher blood volume [18]. Neither ethnicity, weight, nor height was asked for as part of the survey.

Reasons for the higher AR rate among first-time donors and women could be the fact that first-time donors mainly included women having a lower blood volume and a lower body weight than men who, in contrast, represented the majority of repeat donors. Young women might decide to refrain from donating after experiencing any AR during or after the first donation, whereas men more often repeatedly give blood. The assumption that the experience of any AR may influence adherence to donation is supported by the finding of decreasing AR rates with an increasing number of donations and older age [11, 14].

Type and Time to Onset of AR

In hitherto published studies, the most frequently reported AR after WB and apheresis donation were local bruises and haematomas with and without swelling, fatigue, and VVR with and without syncope [12, 14]. The presented findings are in line with the published literature.

The spectrum of donor AR reported in the survey considerably differs from the distribution of serious donor AR captured by passive haemovigilance [4]. In the online survey, more than half of all AR were haematomas and other local reactions. In contrast, VVR with syncope represented more than 50% of all serious donor AR reported to PEI. As expected, the total number of AR collected in the survey was significantly higher as compared to the number of serious AR reported in the German national haemovigilance report. However, the distribution of AR by donation type was roughly comparable, showing the highest AR rate among cell apheresis donors.

The majority of participants experienced AR after leaving the BE, with several reactions occurring 1 week after donation or even later. Similar observations were made in an Indian survey among donors [10]. This may be due to the fact that the majority of AR reported were local reactions including nerve injury and inflammation. Depending on the severity of the vessel and tissue trauma this type of AR may not develop immediately but will rather occur hours or days after the donation. Thus, a prolonged postdonation observation time would not change the results.

The data obtained from this survey described the existence and time to onset of AR for the first time in Germany, because AR classified as "non-serious" are not notifiable according to section 63i of the German Medicinal Products Act (MPA) [2, 3]. Recording the frequency and time to onset of serious and non-serious donor AR is important for both donors and BE because it allows improving the IC with respect to AR and helps monitoring donors with increased risk.

Donor Self-Assessment of AR

Among the participants who experienced at least one AR, the majority assessed it as "non-serious," which is consistent with the finding that almost all participants tolerated previous donations well, irrespective of donation type (WB or apheresis donation).

The majority of participants, especially among repeat donors with reported previous AR, continued donating blood. However, a bad tolerability, especially among first-time donors, may of course contribute to non-adherence to blood donation.

Donor Self-Assessment of IC

Apheresis donors rated the quality of IC better than WB donors. This could be attributed to the fact that a more detailed IC is being used to instruct apheresis donors. Keeping this in mind, the currently used IC for WB donation could be amended accordingly, addressing both common and rare AR, thus making the donor aware of expected AR. Well-informed blood donors may, in fact, better deal with AR. In addition, an appropriate donor care after giving blood will create a trustful relationship between donors and BE.

Strengths

The self-reported AR were not "filtered" by medical staff so that authentic answers could be expected. This survey provides additional information that is complementary to the information received via the notifications according to legal requirements [2, 3].

Limitations

Recall bias may impact the results in cases where considerable time has passed between the last donation and participation in the survey, meaning that AR cannot be remembered properly. The results for the years 2017/2018 were, therefore, compared with those for the years before and were found to be very similar, indicating that recall bias was not an issue.

The majority of blood donors were laymen, who might describe the nature and seriousness of AR differently compared to medical personnel. These AR are reported and assessed in a subjective way, whereas notification (according to legal requirements) is done by healthcare pro-

fessionals who underwent medical training. This may give rise to information and reporting bias. On the other hand, this information complements the assessments and type of donor reactions reported by the BE.

Conclusion

Overall, the findings reveal a high safety level in the WB and apheresis donation in German BE. Self-reported AR revealed a low rate of serious donor AR and a very low rate of reactions requiring medical treatment. Furthermore, the quality of IC was generally rated positively.

This survey yielded a more comprehensive AR spectrum, revealed that reactions most frequently occurred after the donors left the BE, and identified risk factors for AR within the analysed donor population. This novel information could be implemented in an amended IC addressing common and rare AR and increasing the awareness for donors with increased risk for AR.

Considering the marked differences in published ratios of serious donor AR, the need for a harmonized severity grading tool becomes evident [21]. However, it is not to be expected that a prolonged postdonation observation time would reduce the number of late occurring AR and thus improve the donor experience in general.

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Statement of Ethics

The online survey was conducted in an anonymous way without saving any personal data so that the highest standard of privacy was guaranteed. An approval by the local Ethics Committee was not required. The authors declare that ethical principles and anonymisation were obeyed. The research was conducted in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.O. and M.He.: research idea; M.He., K.P., D.O., B.K.-S., and M.B.F.: study design; K.P., M.Ho., and S.O.: data acquisition; M. Ho., K.P., and S.O.: data management; D.O. and S.O.: statistical analysis; S.O., M.He., M.B.F., B.K.-S., and D.O.: data interpretation; S.O., M.He., and D.O.: manuscript draft; S.O., K.P., M.Ho., M.He., M.B.F., B.K.-S., and D.O.: manuscript review; M.He. and D.O.: manuscript finalisation; M.He., D.O., M.B.F., and B.K.-S.: supervision.

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