



EUROPEAN COMMISSION

DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation

B4 – Medical products: quality, safety, innovation

SUMMARY OF THE 2016 ANNUAL REPORTING OF SERIOUS ADVERSE REACTIONS AND EVENTS FOR BLOOD AND BLOOD COMPONENTS (DATA COLLECTED FROM 01/01/2015 TO 31/12/2015)

1. EXECUTIVE SUMMARY

Blood transfusion is an essential medical procedure supporting many different healthcare specialities across the European Union (EU), with millions of EU citizens receiving donated blood and blood components every year. However, the use of any substance of human origin carries some risk, notably the possible transmission of diseases from the donor. These risks can be controlled and minimised by the application of comprehensive safety and quality measures such as are laid down in EU legislation. Despite these measures, rare adverse outcomes are detected and, in line with the legislation¹, these must be reported and monitored at a national and EU level through vigilance and surveillance programmes.

Since 2008, in line with obligations defined in the legislation, the EU Member States and Iceland, Liechtenstein and Norway have submitted to the European Commission (hereinafter referred as the Commission) annual vigilance reports on the notification of serious adverse reactions (SAR) which occur in recipients of blood and blood components and serious adverse events (SAE) which occur in the chain from donation to clinical application.²

The Commission works with national competent authorities to verify the consistency and clarity of the information submitted on SARE (serious adverse reactions and events) and to improve the data collection procedure. The completeness and comparability of the data collected in the blood field has improved over time. The SARE exercise has also facilitated the development and consolidation of the Member States' national vigilance programmes.

This report summarises the data submitted by the Member States during 2016, for the year 2015, and assesses the data in the light of the information submitted in the previous years.

Some key results of the 2016 reporting exercise are the following:

- Overall, 31 countries (28 EU Member States, Iceland, Liechtenstein, and Norway) reported in the SARE annual exercise. Of these, 24 countries indicated receiving complete data from

¹ Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events.

² Article 8 of Directive 2005/61/EC provides that Member States shall submit to the Commission an annual report, by 30 June of the following year, on the notification of serious adverse reactions and events (SARE) received by the competent authority using the formats in Part D of Annex II and C of Annex III.

their reporting establishments³. This represents an increase compared to the previous exercise, showing the efforts that parties involved are making each year to improve the accuracy and completeness of reported data.

- 25.3 million units of blood or blood components, were reported by 31 countries as being issued for transfusion and/or transfused⁴. Partial data reported by 21 countries indicated that 4.6 million patients were transfused.
- Concerning SAR in recipients, there were 1,349 cases reported for 2015 with imputability level 2 or 3 (likely or certain to have been caused by the transfusion), which are the focus of further analysis in this report. The total number of SAR has slightly decreased compared with previous exercises. Anaphylaxis, febrile non-haemolytic transfusion reaction (FNHTR) and transfusion associated circulatory overload (TACO) appear to be the most frequent serious adverse reactions in recipients.
- The results also show that there were 25 deaths likely or certainly resulting from blood transfusions in 2015. Compared with previous exercises this number has slightly decreased. It is noted that the majority of deaths were not directly attributable to the quality and safety of blood components, but rather to clinical practice or to unforeseeable reactions.
- Concerning SAE, which amounted to 2,338 cases for 2015, the reported figures have decreased compared to the previous years. Most of the SAE occurred due to human error (68.7%). This fact emphasises the importance of root-cause analysis to determine the best measures to avoid the repetition of serious adverse events. SAE reporting rates vary considerably between countries.

The reports submitted by the countries included information not only on recipients but also donors for whom 7,769 reactions were reported on a voluntary basis (18 countries reported). It is important to collect these data and to further assess the underlying causes in order to better protect those citizens who volunteer to donate blood, and thus, make transfusion possible.

Before publishing the summary report, the Commission presented the data contained in this report at the meetings of the Competent Authorities for blood and blood components in 2017. This gave the opportunity to the reporting countries to interact and share experience and knowledge on haemovigilance, hence supporting the development of their national systems and improving the safety of blood transfusion.

2. DATA COLLECTION METHODOLOGY

This document provides a summary report of the data collected during 2015 (from 1st January to 31st December) and submitted to the Commission in 2016 by the EU Member States and Iceland,

³ Article 1 of Directive 2005/61/EC defines a “reporting establishment” as “the blood establishment, the hospital blood bank or facilities where transfusion takes place that reports serious adverse reactions and/or serious adverse events to the competent authority”.

⁴ For 3 countries, only the units reported as transfused were submitted. It is evident that the number of units transfused must also have been issued prior to transfusion.

Liechtenstein and Norway. It also includes a comparison with the data from previous years and draws general conclusions. The Commission provided the following tools to the participating authorities to promote a standardised approach to data reporting:

- 1) An electronic reporting template to be sent to a DG SANTE hosted data base. The electronic reporting template used in 2016 (for 2015 data) was version 2.5.5.
- 2) The Common Approach document for definition of reportable serious adverse events and reactions ('the Common Approach") attached to the electronic reporting template. The document provides guidance to Member States and is not legally binding. First published in 2008, the Common Approach has been regularly updated to clarify points of ambiguity and inconsistency. This has in turn resulted in a gradual increase of the quality and accuracy of the data collected from the Member States. In 2016, version 5.2 of the Common Approach document was available to those countries reporting 2015 SARE data.

In December of 2016 a service contract agreement was signed between the Commission and the Council of Europe/ European Directorate for the Quality of Medicines and Healthcare (EDQM) to carry out the verification and analysis of the SARE exercise 2016. Since the beginning of 2017 the EDQM has therefore contacted reporting countries when needed in order to clarify and verify the accuracy of the data, and has performed a detailed analysis of the information presented in this report.

3. MAIN FINDINGS OF THE 2015 DATA COLLECTION

3.1 General comments

For the 2016 exercise (data reported in 2015), the PDF reporting template was unchanged. A revised version of the Common Approach document had been developed by the Commission, together with the Haemovigilance Working Group. This new version updated Annex II by splitting activity step definitions and examples of SAE specifications.

Country reports were received from all 28 EU Member States, Iceland, Liechtenstein and Norway, comprising aggregated data from 3,427 reporting facilities. Some countries have not provided complete data on all denominators (i.e. blood units issued, blood units transfused and number of recipients), raising questions about the availability and accuracy of the data. Despite this, denominator data have improved overall in comparison with previous exercises.

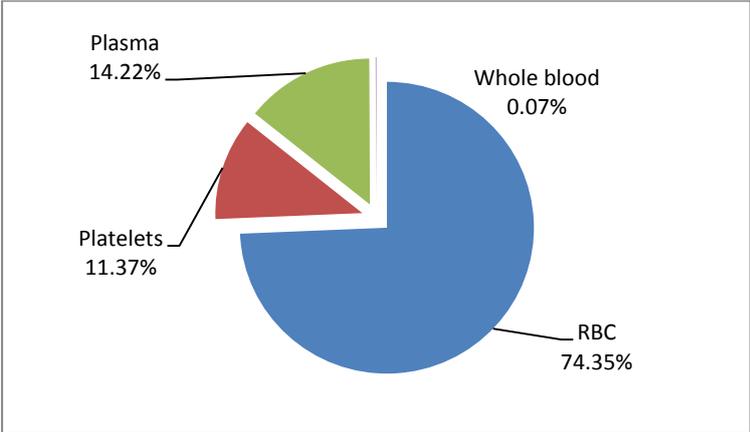
Concerning data completeness, 24 countries submitted complete data, 7 countries achieved 80-98% of data completeness and 1 country did not report this figure. Although data quality has continued to improve, the data presented here are considered partial and still do not represent the entire picture. Conclusions should, therefore, be interpreted with caution.

The data were presented at the June 2017 meeting of the competent authorities for blood and blood components. Additionally, clarification and verification of the data between the EDQM, the Commission and Member States was carried out on different occasions on a bi-lateral basis.

3.2. Denominators

All Member States, Iceland, Liechtenstein and Norway submitted reports, thereby complying with the annual report submission established by Article 8 of Directive 2005/61/EC.

As regards the **units of blood components issued**, 28 countries (AT, BE, BG, CY, CZ, DE, EE, EL, FI, FR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MT, NL, PL, PT, RO, SE, SI, SK and UK) provided data. The remaining three countries (DK, ES and NO) did not give the number of units issued, but did provide the number of units transfused. As all units transfused must have first been issued, their numbers for units transfused have been included in the total number of units reported issued. A total number of 25,324,888 units of blood and blood components were reported as issued in 2015. Figure 1 shows the breakdown of units issued by component type (including the transfused data from DK, ES and NO).

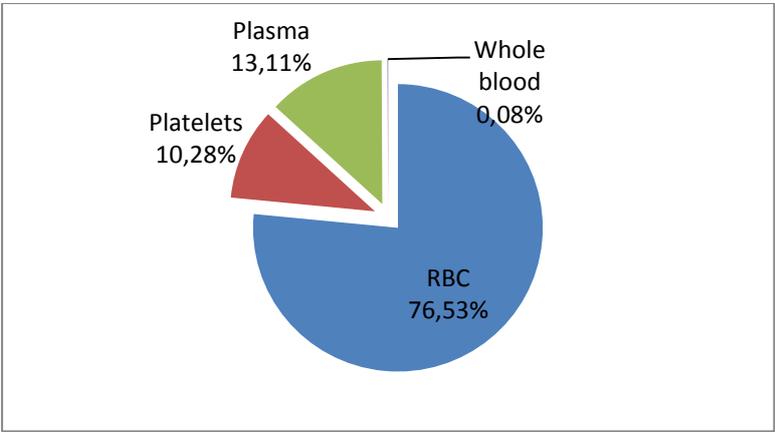


Component type	Units issued
Red Blood Cells	18,827,934
Platelets ⁵	2,878,632
Plasma	3,600,941
Whole blood	17,381
Total	25,324,888

Figure 1: Units issued⁶ (per blood component); data 2015.

Twenty-nine countries (all but BE, LI, SE) also provided the total number of whole blood collections, amounting to 18,580,777 and the number of apheresis collections, amounting to 5,506,122.

Concerning the **units of blood components transfused**, there were 21,443,125 units reported as transfused by EU and EEA countries. It should be noted that this is not the total number of units transfused, as only 26 countries (AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FR, HR, IS, IE, IT, LI, LT, LV, MT, NO, NL, PT, RO, SE, SK and UK) reported this figure for at least one blood component. The data for units transfused per blood component, is shown in Figure 2.

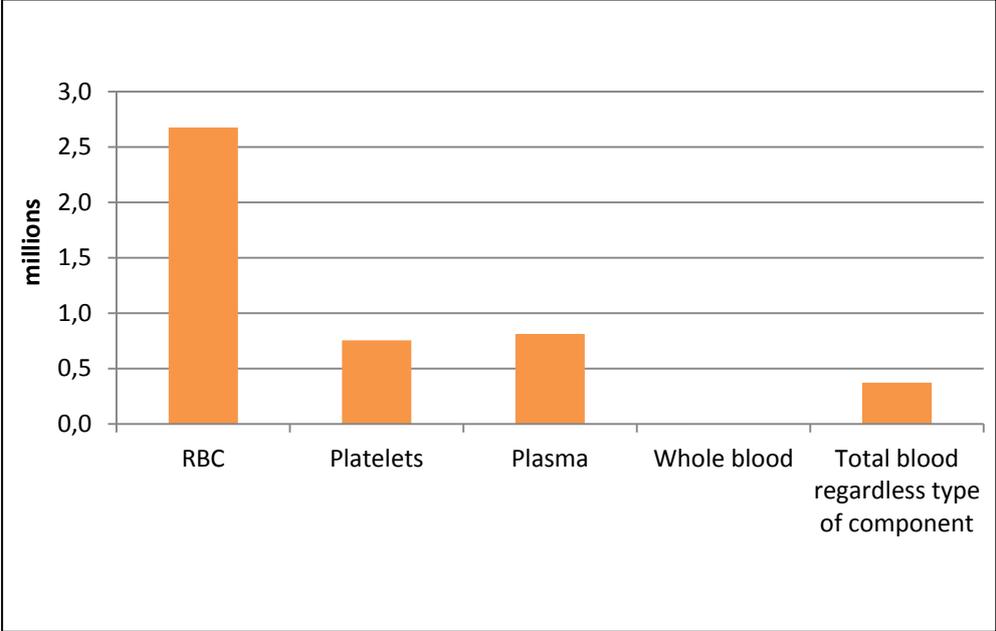


Component type	Units transfused
Red Blood Cells	16,410,868
Platelets ⁵	2,204,991
Plasma	2,810,377
Whole blood	16,889
Total	21,443,125

Figure 2. Units transfused (per blood component); data 2015.

⁵ Note that one platelet unit is normally prepared from several donations.
⁶ Including data from units transfused from DK, ES and NO.

Regarding **recipients transfused**, there were 4,619,930 patients transfused in 2015 according to the reports. These are figures provided by 17 countries (AT, BE, CY, CZ, DK, ES, FR, IS, IE, IT, HR, LI, MT, NL, PT, SE, and UK) which provided the number of recipients transfused by blood component type and 4 countries (BG, EE, LT and RO) which provided the total number of recipients transfused regardless of the type of component. The breakdown of the transfused recipients is shown in Figures 3 and 4.



Component type	Recipients transfused
Red Blood Cells	2,676,374
Platelets	754,921
Plasma	812,701
Whole blood	2,982
Total blood regardless type of component ⁸	372,952
Total	4,619,930

Figure 3. Recipients transfused (per blood component); data 2015⁸.

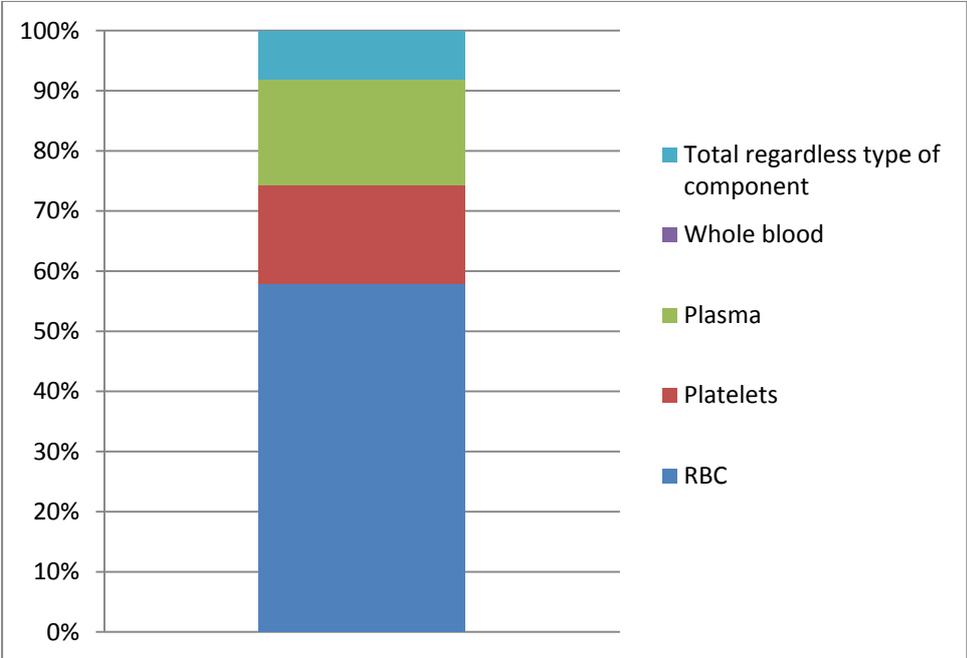


Figure 4. Total percentage of recipients transfused by type of component; data 2015⁷.

⁷ Four countries were not able to provide the number of recipients transfused per type of component, but provided the total of patients transfused regardless the type of component.

3.3. Serious Adverse Reactions

3.3.1. Information by country

In 2015, a total of 2,587 SAR with imputability of 1 to 3 were reported in the exercise. Eight countries (EE, ES, IT, LI, LV, LU, RO, and SE) did not report any SAR of imputability level 1.

Directive 2005/61/EC provides that reporting establishments notify to the competent authority all relevant information about serious adverse reactions of imputability level 2 or 3⁸. Further analysis of SAR in this report relates only to the reporting of SAR at imputability levels 2 and 3. During 2015, a total of 1,349 SAR at imputability level 2 or 3 were reported. Of those, 25 resulted in death.

For the 26 countries that provided data for the number of SAR and units transfused per blood components, there were 15,896 units transfused per SAR.

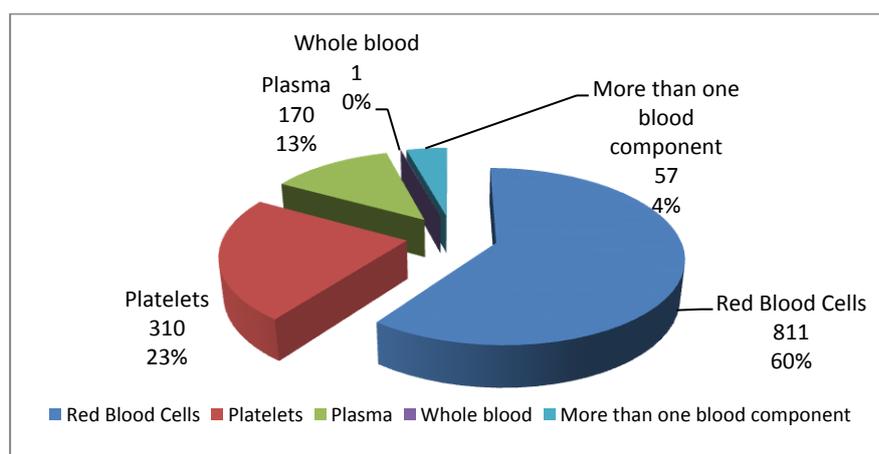
These figures should also be interpreted with caution as many reports are still partial and differences between countries do not necessarily indicate a safer system. In fact, a higher number of SAR reported may indicate a more reliable and accurate reporting system, and a lower number of SAR may indicate underreporting.

3.3.2. Information by blood component

Of the 1,349 SAR of level 2- 3 reported:

- 811 SAR were related to **red blood cells**
- 310 SAR were related to **platelets**
- 170 SAR were related to **plasma**
- 1 SAR was related to **whole blood**
- 57 SAR were related to **more than one blood component**.

Figure and table 4 shows the percentage of SAR and number of units transfused per blood component.



Component type	Units transfused per SAR
Red Blood Cells	20,235
Platelets	7,113
Plasma	16,532
Whole blood	16,889

Figure 4. Percentage of SAR per blood component and units transfused per SAR.

3.3.3. Information by category of SAR

⁸ Where it is likely or certain that the reaction is attributable to the blood or blood component. Article 5, para 3a of Directive 2005/61/EC.

The 1,349 SAR (level 2 - 3) reported were classified as follows:

- Anaphylaxis/ hypersensitivity: 453 cases
- Febrile non-haemolytic transfusion reaction (FNHTR): 357 cases
- Transfusion associated circulatory overload (TACO): 185 cases
- Immunological haemolysis: 172 cases, of which
 - 78 cases due to ABO incompatibility and
 - 78 cases due to other alloantibodies
 - 16 Delayed haemolytic transfusion reaction
- Transfusion associated dyspnoea (TAD): 53 cases
- Transfusion related acute lung injury (TRALI): 48 cases
- Transfusion transmitted infections: 34 cases, of which
 - 17 bacterial infection, and
 - 17 viral infection of which 9 were hepatitis E, 3 hepatitis C, 2 HIV, 2 hepatitis B, and one Cytomegalovirus
- Hypotension: 11 cases
- Non-immunological haemolysis: 7 cases
- Post transfusion purpura: 5 cases
- Hypertension: 4 cases
- Circulatory disorders (other than circulatory overload): 1 case
- Other: 19

The percentage of SARs per category is shown in Figure 5.

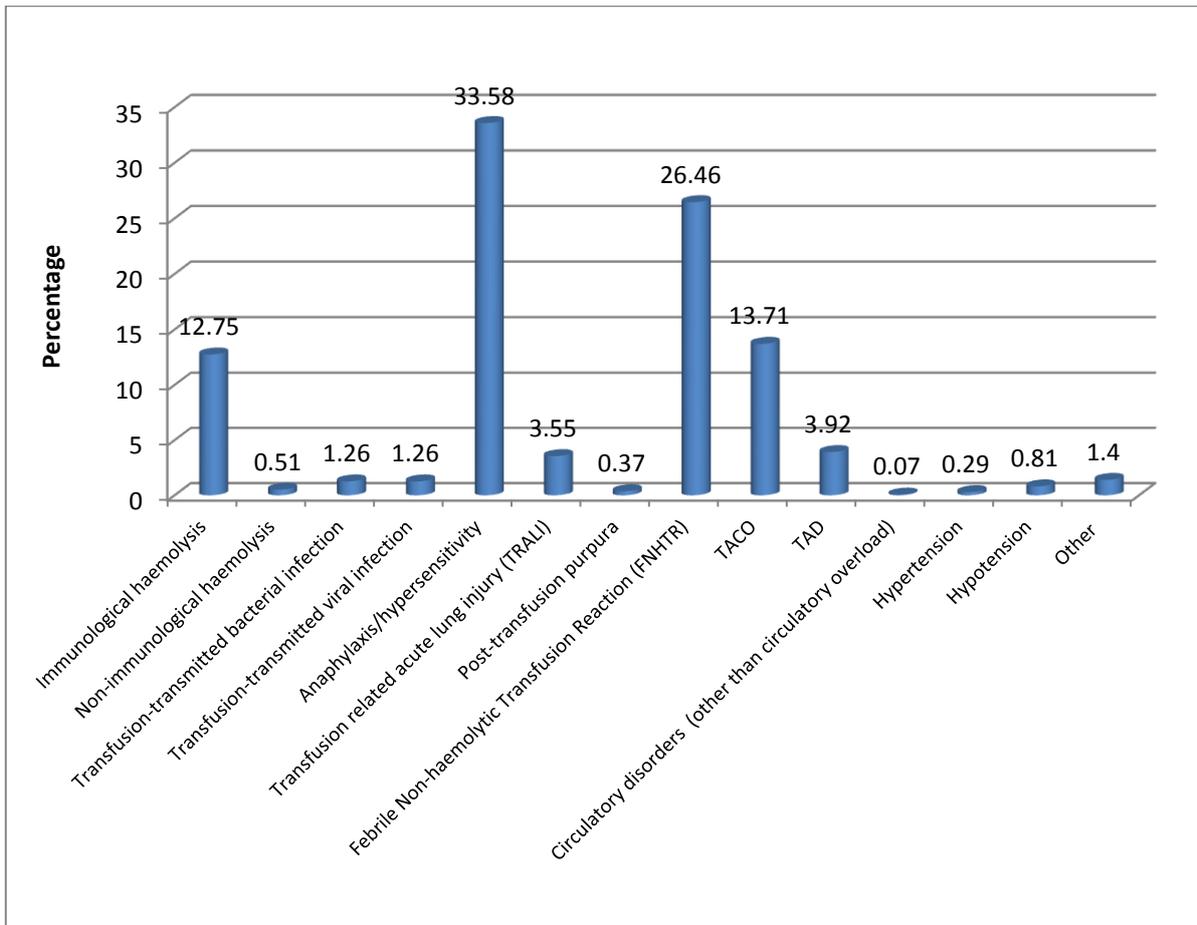


Figure 5. Percentage of SARs per category; data 2015.

3.3.4. Recipient deaths

Over the 1,349 cases of SAR reported, there were 25 deaths, as follows:

- 10 were associated to immunological haemolysis (5 due to ABO incompatibility associated to red blood cells transfusion, 3 delayed haemolytic transfusion reaction following red blood cells transfusion and 2 due to other alloantibodies following red blood cell transfusion). This number represents 40% of all reported deaths.
- 8 were associated with TACO (7 following red blood cells transfusion and 1 following platelet transfusion). This number represents 32% of all reported deaths.
- 5 were associated with TRALI (2 following red blood cells transfusion, 1 following plasma transfusion, 1 following platelets transfusion, and 1 patient transfused with multiple components). This number represents 20% of all reported deaths.
- 1 was associated with bacterial transmission, following platelet transfusion. This number represents 4% of all reported deaths.
- 1 was reported under the “other” category, following the transfusion of red blood cells. This number represents 4% of all reported deaths.

The United States Food and Drug Administration (FDA) publishes an annual summary of “Fatalities reported to FDA following blood collection and transfusion”⁹. During 2015, there were 41 transfusion-related fatalities reported to the FDA. The statistics provided in the report allow some broad comparisons to be made with the annual vigilance reports on SARE submitted by EU and EEA countries to the Commission. For example, in the US in this period, TRALI and TACO caused the highest number of reported fatalities, followed by contamination, haemolytic transfusion reactions and anaphylaxis. In Europe, the information submitted in the SARE reporting exercise for 2016 (data from 2015) shows that the highest number of deaths related to the transfusion of blood and blood components was due to immunological haemolysis, followed by TACO, TRALI and transmission of bacterial infection.

3.3.5. SAR in donors

A majority of Member States submit data on SAR in donors on a voluntary basis. From those, a total of 7,769 SAR in donors were reported for 2015.

A subset of countries also provided additional information to the Commission on SAR in donors. Based on these reports, it can be seen that many of the reactions in donors were related to blood vessel and nerve injuries, vasovagal episodes, or cardiovascular reactions. Within those voluntarily reported SAR in donors, one death within 7 days of donation was included, even though its imputability was not clearly related to the act of blood donation. However, given the fact that donors should be protected from untoward responses resulted from an altruist donation, it was considered important to include this information in the summary.

Considerable variability between countries in the reporting of SAR in donors is evident, with one country reporting almost 60% of the total¹⁰. In addition, it should be noted that, contrary to SAR = in recipients, Member States are not requested to report the imputability level of SAR in donors.

3.4. Serious Adverse Events

3.4.1. Information by country

SAE were reported by 24 countries; the total number of SAE reported for 2015 was 2,338. It should be noted that seven countries (HU, IS, LI, LT, LU, MT and SK) reported that in 2015 there had been no reportable SAE.

It is worth noting that the number of SAE reported varied substantially between reporting countries, both in terms of rates and the criteria for inclusion. For example, one country submitted 33% of all SAE whereas 4 countries reported just one SAE each. This suggests that further improvements should be made to the reporting criteria, with the collaboration of the Competent Authorities, to achieve a greater comparability of data.

⁹ Annual summary for 2015: “Fatalities reported to FDA following blood collection and transfusion” <https://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM518148.pdf>

¹⁰ It should be noted that there are no legally binding requirement to report the denominator and therefore no clear criteria for reporting.

As regards the denominator for SAE, the total number of units processed, 27 countries (all but BE, HU, LI and NO) reported a total of 25, 777, 859 units processed during 2015.

3.4.2. Information by type of SAE

Overall, of the 2,338 SAE reported, incidents were linked to the following activity steps:

- **Whole blood collection:** 449 SAE (19.2%)
- **Apheresis collection:** 43 SAE (1.8%)
- **Testing of donations:** 149 SAE (6.4%)
- **Processing:** 124 SAE (5.3%)
- **Storage:** 276 SAE (11.8%)
- **Distribution:** 328 SAE (14.0%)
- **Materials:** 17 SAE (0.7%)
- **Other activity steps:** 952 SAE (40,7% of reported SAE)

This data is presented in Figure 6.

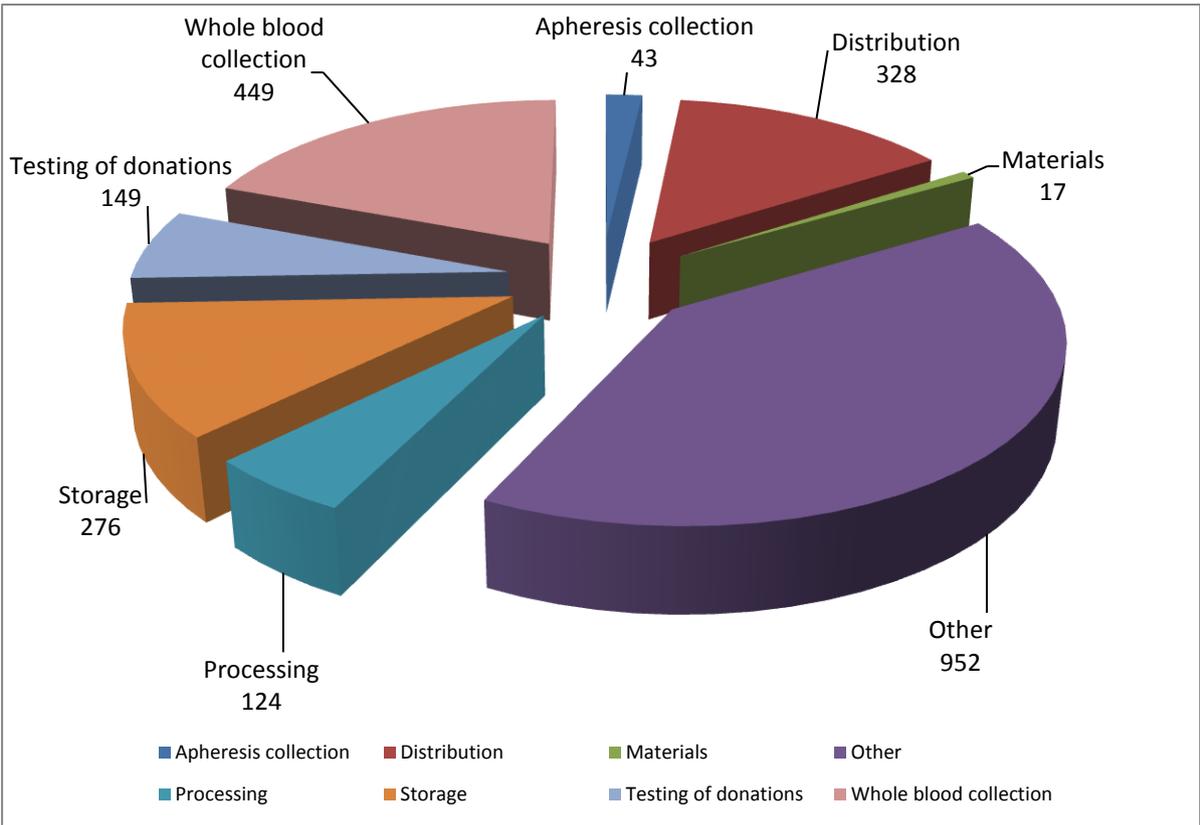


Figure 6. Serious adverse events per activity step; data 2015.

3.4.3. Information by specification of SAE

The 2,338 SAEs were attributed to one of the following specifications:

- **Human Error:** 1,606 SAE (68.7%)

- **Equipment failure:** 130 SAE (5.6%)
- **Product defect:** 151 SAE (6.5%)
- **Other:** 451 SAE (19.3%)

The data is shown in Figure 7.

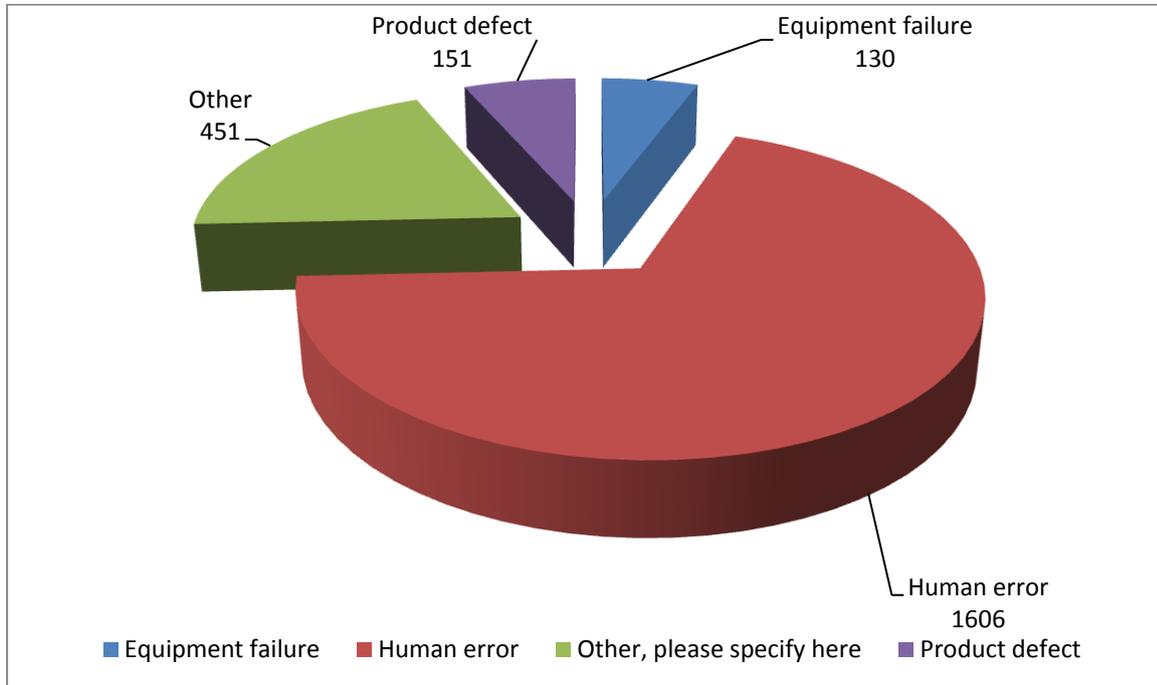


Figure 7. Serious adverse events per specification; data 2015.

Most of the SAE (68,7%) were reported within the category of “Human error” without any further detail. To facilitate improvement through learning from vigilance , consideration will be given to gathering more information in future exercises.

4. Comparison of SARE reporting 2011-2016

The table below (table 1) gives an overview of SARE reporting for 2011 - 2016 (data from 2010 to 2015). In general, the numbers of denominators have fluctuated from year to year: 23 – 25 million units issued, 12 – 22 million units transfused (has slightly increased in this exercise) and 2 – 4.6 million recipients transfused (also an increase in this exercise) which is only partly explained by the number of countries reporting.

The number of SAR (at imputability level 2 or 3) reported has increased from 2011 to 2014, but the number of deaths has remained relatively stable (around 20). For SAEs, the numbers reported are much lower than in previous years, which is probably the result of improved reporting by establishments and better training and education of staff involved in the process.

	2011		2012		2013		2014		2015		2016	
	Countries reporting	Number										
Units issued	26	22,817,166	29	24,821,809	27	25,129,344	27	24,043,766	27	25,717,028	26	25,324,888
Units transfused	19	16,718,258	17	12,311,691	20	13,351,948	22	16,564,817	25	21,425,047	25	21,443,125
Recipients transfused	11	2,298,304	16	2,964,839	19	3,595,155	20	3,216,938	18	4,190,835	21	4,619,930
SAR (1-3)	30	2,449	30	3,133	30	3,519	30	2,831	30	2,441	31	2,587
SAR (2-3)	30	1,259	30	1,574	30	1,831	30	1,739	30	1,410	31	1,349
SAR death (2-3)	30	20	30	14	30	22	28	22	30	27	31	25
SAE	28	16,360	25	4,113	28	2,953	30	2,972	30	4,460	24	2,338
SAR in donors					18	2,494	23	2,470	20	3,723	23	7,769

Table 1. Overview of the 2011-2016 SARE reporting exercises (2010-2015 data)

5. Conclusions

In the 2016 SARE annual reporting exercise, all countries involved submitted reports. Complete data was provided by 77% of the reporting countries (i.e. 24 out of 31). This represents an improvement in reporting compared to the previous years and the European Commission and Member States continue to work to improve data collection and to assist those countries which have difficulties in collecting reliable data.

The *number of SAR* in recipients (imputability level 2 - 3) reported for 2015 was 1,349. Anaphylaxis, febrile non-haemolytic transfusion reaction, immunological haemolysis and TACO appear to be the most frequent SAR. This figure has slightly decreased in comparison with previous years. However, considering that the data reported is partial, year-on-year comparisons should be interpreted with caution.

The results also show that the *number of deaths* likely or certain to have resulted from blood transfusion in 2015 totalled 25. This number has slightly decreased in comparison with the previous exercise, but remains relatively stable compared with previous years. However, it should be noted that of the 25 deaths reported, the majority were not attributable to the quality and safety of the blood component, but rather to clinical practice or to unforeseen reactions including immunological haemolysis, transfusion associated circulatory death and transfusion related acute lung injury.

For the *number of SAE*, the reported figures have decreased compared with the previous exercises. This is due to general improvements in data collection, which have resulted in only 'genuinely serious' adverse events being reported. It should be noted, however, that on an individual Member State basis a higher number of SAE reported may indicate a more reliable and accurate reporting system whereas a lower number may indicate under-reporting.

The large number of SAE reported as being caused by human error highlights the importance of root-cause analysis to determine the ultimate cause of serious adverse events.

Reporting on SAE revealed that there is a need to further clarify and improve collection of SAE data overall to ensure that the reporting criteria are consistently applied. The Joint Action VISTART¹¹ which includes a work package dedicated to vigilance reporting for blood, tissues and cells is concluding in 2017 and its inputs may contribute to improving the implementation of vigilance requirements and data collection.

In January 2017, a Vigilance Expert Sub-group (a sub-group to the Competent Authorities on Substances of Human Origin Expert Group, CASoHO E01718) was established by the Commission, in agreement with the Expert group, with agreed terms of reference that include supporting the development and improvement of the SARE reporting system. The future work of the sub-group should help to improve and harmonize the exercise and support the development of national SoHO vigilance systems. The work of the expert sub-group will also be important as the outcomes may contribute to the ongoing evaluation of the legal frameworks on blood, tissues and cells¹².

The voluntary *reporting on donors*, introduced in 2012 and undertaken by a majority of countries in this reporting exercise, highlights a significant increase in reported donor reactions. Overall, the number of SAR for 2015 was 7,769; this figure has increased substantially in comparison to previous years. Performing this exercise has allowed Member States to increase awareness of the importance of monitoring the safety and quality of care of those persons who make transfusion medicine possible. The availability of this data gives the opportunity for further assessment of the underlying reasons for donor reactions and for the implementation of preventive measures to reduce them.

Overall, the available data indicate that reporting is consistent with known effects and expected trends, with no new safety concerns regarding blood and blood components identified from national monitoring programmes.

At the European level the exercise has allowed Member States to share experience and knowledge on haemovigilance, supporting the development of their national systems. Individual countries should continue to use this exercise to evaluate the safety of their national blood sectors and to identify where quality issues occur and need to be addressed in order to improve the safety and quality of blood and blood components across the EU.

¹¹ Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation is a Joint Action co-funded by the European Union.

¹² https://ec.europa.eu/health/blood_tissues_organ/policy/evaluation_en