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SUMMARY OF THE 2015 ANNUAL REPORTING OF SERIOUS ADVERSE EVENTS AND REACTIONS (SARE) FOR BLOOD AND BLOOD COMPONENTS (DATA COLLECTED FROM 01/01/2014 TO 31/12/2014)

Contents

1. INTRODUCTION

Blood transfusion is a critical pillar supporting many different healthcare specialities across the European Union, with millions of patients 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 infectious diseases from the donor. These risks can be controlled and minimised by the application of comprehensive safety and quality measures; such measures are laid down in EU legislation. Despite these measures, rare adverse outcomes are detected and, in line with the legislation, these must be reported and monitored at a national and EU level through vigilance and surveillance programmes.

Since 2008, the EU Member States and Liechtenstein and Norway have submitted to 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, in line with obligations defined in the legislation.[1]

The Commission works with national competent authorities to verify the consistency and clarity of the submitted information 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 sector has improved over time. The exercise has also facilitated the development of the Member State national vigilance programmes.

This report summarises the data submitted by the Member States during 2015, for the year 2014, and assesses the data in the light of the information submitted in the previous years.

Some key results of the 2015 reporting exercise were the following:

- Overall, 30 countries (28 EU member states, Liechtenstein and Norway) reported in the SARE annual exercise. 20 countries indicated receiving complete data from their reporting establishments[2]. This is an improvement compared to the previous years.

- Almost *26 million units* of blood or blood components were reported by 30 countries as being issued for transfusion and/or transfused. Partial data indicated that well over *4 million patients were transfused* (4.3 million recipients reported by 18 countries).

- Concerning *SAR in recipients*, there were 1410 cases reported for 2014 with imputability level 2-3 (likely or certainly to have been caused by the transfusion) which have been the focus of further analysis in this report. Anaphylaxis, immunological haemolysis and transfusion associated circulatory overload appear to be the most frequent serious adverse reactions. Compared to 2012 and 2013, the number of SAR decreased[3].

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[1] 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.

[2] 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.'

[3] There were 1410 SAR cases (imputability level 2-3) reported for 2014, 1739 – for 2013 and 1831 – for 2012.

- The results also show that there were 27 *deaths* likely or certainly resulting from blood transfusions in 2014. Compared to previous years this number increased by 20%[4]. It is important to note that the majority of deaths were not directly attributable to the quality and safety of the blood component, but rather to clinical practice or to unforeseeable reactions.

- Concerning *SAE*, which amounted to 4460 cases for 2014, the reported figures have increased compared to the previous years[5]. The largest number of SAE occurred due to human error (55%); this highlights the importance of root cause analysis to determine the best measures to avoid serious adverse events. The increase is more likely to be associated with better reporting than with less safe practice. SAE reporting rates vary considerably between reporting countries.

The reports submitted by the countries included information not only on recipients but also *donors* for whom 3723 reactions were reported. It is important to collect these data and to further assess the underlying causes, in order to better protect those citizens who make transfusion medicine possible.

The 2015 SARE exercise, including the data analysis undertaken by the Commission, was presented to the Blood and Blood Components Competent Authorities in 2015 and 2016 and subsequent interactions allowed Member States to share experience and knowledge on haemovigilance, supporting the development of their national systems and improving the safety of blood transfusion.

The summary reports of 2011-2014 were published by the Commission and thus made accessible for the general public[6].

2. DATA COLLECTION METHODOLOGY

This document provides a summary report of the data collected during 2014 by the Member States and Liechtenstein and Norway (from 1st January to 31st of December) and submitted to the Commission in 2015, including comparison with the data from the previous years and drawing general conclusions. The Commission provided the following tools to the participating authorities in order to promote a standardised approach to data reporting:

1) An electronic reporting template to be sent to a DG SANTE hosted database. The template used in 2015 (for 2014 data) was version 2.5.1.

2) A 'common approach' document which, although not legally binding, provides guidance to Member States when filling out the electronic reporting template as required by Directive 2005/61/EC. First published in 2008, the Common Approach document has been regularly updated to clarify points of ambiguity and inconsistency. This has in turn resulted in a gradual

[4] There were 27 deaths (imputability level 2-3) reported for 2014, 22 deaths – for 2013 and 22 deaths – for 2012.

[5] There were 4,460 SAE cases reported for 2014, 2,972 – for 2013 and 2,953 for 2012.

[6] http://ec.europa.eu/health/blood_tissues_organs/docs/blood_sare_2014_en.pdf

http://ec.europa.eu/health/blood_tissues_organs/docs/blood_sare_2013_en.pdf

http://ec.europa.eu/health/blood_tissues_organs/docs/blood_sare_2012_en.pdf

http://ec.europa.eu/health/blood_tissues_organs/docs/blood_sare_2011_en.pdf

increase of the quality of the data collected from the Member States. In 2015, version 5.1 of the Common Approach document was available to those reporting SARE 2014 data.

3. MAIN FINDINGS OF THE 2014 DATA COLLECTION

3.1. General comments

For the 2015 exercise (data reported in 2014), the reporting template was not changed. A revised version of the 'Common approach for definition of reportable serious adverse events and reactions' was developed by the Commission, together with the Haemovigilance Working Group.

Responses were received from all 28 EU Member States, Liechtenstein and Norway, comprising aggregated data from 3,968 reporting facilities. Not all countries provided complete date on all denominators (i.e. blood units issued, blood units transfused and number of recipients), although denominator data improved in comparison with the previous year.

The data was presented at the November 2015 and the May 2016 meetings of the Competent Authorities on Blood and Blood Components. These meetings were followed by clarification and verification correspondence between the Commission and individual countries.

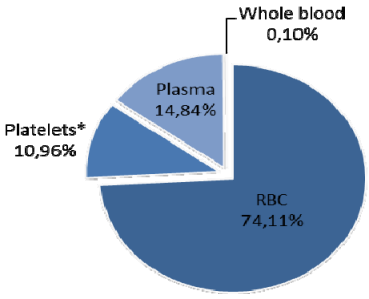
Although data completeness has continuously improved (20 countries reported receiving complete data from their reporting establishments), the data presented here still does not represent the entire situation (a further 8 countries received at least 80% of the expected data, one country less than 60% and one did not report this figure) and conclusions should therefore be drawn with caution.

3.2. Denominators

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

As regards the ***units of blood components issued***, 26 Member States (AT, BE, BG, CY, CZ, DE, EE, EL, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SE, SI, SK, UK) and Liechtenstein provided data. The remaining three countries (DK, ES and NO) did not provide the number of units issued but did provide the number transfused. As all units transfused must have been issued, their numbers for units transfused have been added to the total number of reported units issued to give a total number of 25,717,028 units of blood and blood components issued for transfusion in 2014. Figure 1 shows the breakdown of units issued by component type (including the transfused data from DK, ES and NO).

Figure 1: Units issued (per blood component)

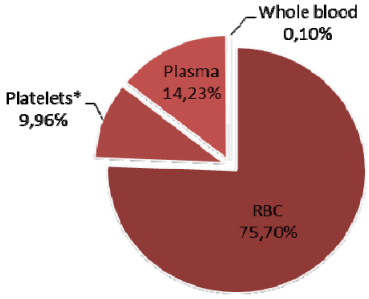


Component	Units Issued (mio units)
Red blood cells	19.06
Platelets[7]	2.82
Plasma	3.81
Whole blood	0.02
Total	**25.72**

All reporting countries also provided the total number of whole blood collections made during the year, amounting to 19,817,598, and 29 (all but SE) provided the number of apheresis collections, amounting to 5,460,831.

Concerning the ***units of blood components transfused***, there were 21,425,047 units reported as transfused by facilities in EU and EEA countries. It should be noted that this is not the total number of units transfused, as only 25 countries (AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FR, HR, IE, IT, LI, LU, LT, MT, NL, NO, PT, RO, SE, SK and UK) reported this figure for at least one blood component. Figure 2 shows the breakdown of transfused units per blood component.

Figure 2: Units transfused (per blood component)



Component	Units Transfused (mio)
Red blood cells	16.22
Platelets[8]	2.13
Plasma	3.05
Whole blood	0.02
Total	**21.42**

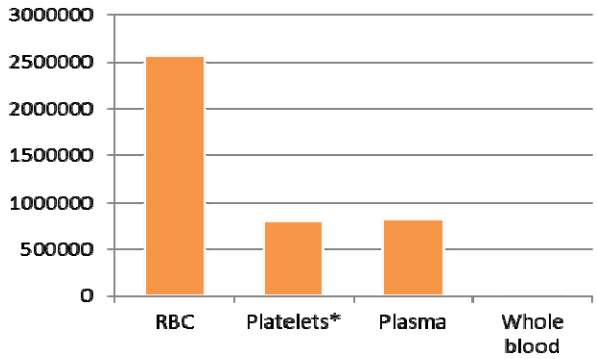
[7] Note that one platelet unit is normally prepared from several donations.

[8] idem

Estimate: as the data provided for the units transfused is partial, an attempt was made to estimate the total transfused units for all the countries. To undertake the estimation, the following approach was taken. Looking only at those countries that provided complete data for both units issued and units transfused in 2012-2014, it can be seen that there is a stable ratio of 92 %. Applying this factor to the total number of units known to have been issued gives a more realistic estimate of 23.7 million units transfused in the 30 countries.[9]

Regarding the ***recipients transfused***, there were 4,312,868 patients transfused in 2014 according to the reports. These are partial figures provided by 18 countries (AT, BE, BG, CZ, DK, EE, FR, HR, IE, IT, LI, LT, MT, NL, NO, PT, SE and UK). There were 16 countries which provided the number of recipients transfused by blood component type. Figure 3 shows the breakdown of the transfused recipients.

Figure 3: Recipients transfused (per blood component)



Component	Recipients Transfused (mio)
Red blood cells	2.56
Platelets	0.80
Plasma	0.81
Whole blood	0.02

*Estimate**:*** as above, the data provided for the patients transfused is partial. Therefore, an attempt was made to estimate the total number of transfused recipients in the reporting countries. Looking only at countries that provided both units transfused and patients transfused in 2012-2014, it can be seen that, on average, a transfused patient received 4.3 units. Applying this factor to the total estimate of units transfused in 2014, above, gives a more realistic total estimate of 5.6 million recipients of blood and blood components in the 30 countries during 2014, if all transfusions were reported by all countries.[10]

3.3. Serious Adverse Reactions (SAR)

3.3.1. Information by country

In 2014, a total of 2,441 SAR with imputability of 1 to 3 were reported in this exercise. Six countries (EE, ES, HR, IT, LV 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 3 (i.e. where

[9] This estimate should be interpreted cautiously, given the variations in reporting completeness.

[10] Another approach used to estimate the total number of transfused recipients (i.e. considering size of the population of the countries that have not reported the number of transfused recipients) gave an estimate of 5.9 million.

it is likely or certain that the reaction is attributable to the blood or blood component)[11]. Further analysis of SAR in this report relates only to the reporting of SAR at imputability levels 2 and 3. During 2014, a total of 1410 SAR at imputability level 2-3 were reported. Of these, 27 resulted in death.

For the 22 countries that provided data for the number of SAR and units transfused per blood components, there were 6.6 SAR per 100,000 units transfused and 15,195 units transfused per SAR.

Two countries (LU and RO) did not report any SAR attributed to blood and blood components in 2014 and four others (BG, CY, LI and LU) did not report any of level 2-3. 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 under-reporting.

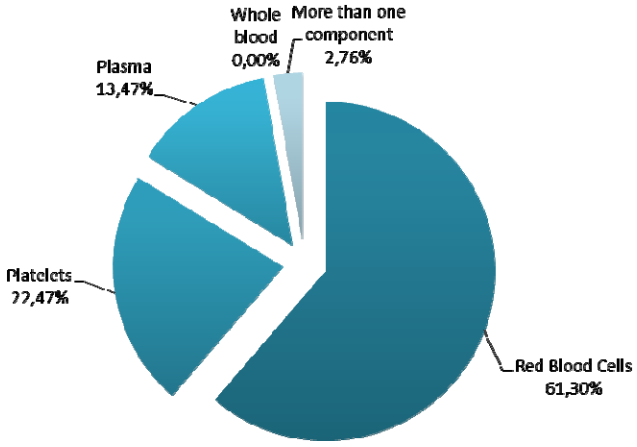
3.3.2. Information by blood component

Of the 1,410 level 2-3 SAR reported:

- 865 SAR were related to **red blood cells**,
- 316 SAR were related to **platelets**,
- 190 SAR were related to **plasma**,
- 0 SAR was related to **whole blood, and**
- 39 SAR were related to **more than one blood component.**

Figure 4 shows the number of units transfused of each component per SAR for the 22 countries that reported per unit transfused figures.

Figure 4: Percentage of SAR per blood component and units transfused per SAR[12]



Component	Units transfused per SAR
Red blood cells	18,751
Platelets	6,751
Plasma	16,050

[11] Cf. Article 5, para 3a of Directive 2005/61/EC.

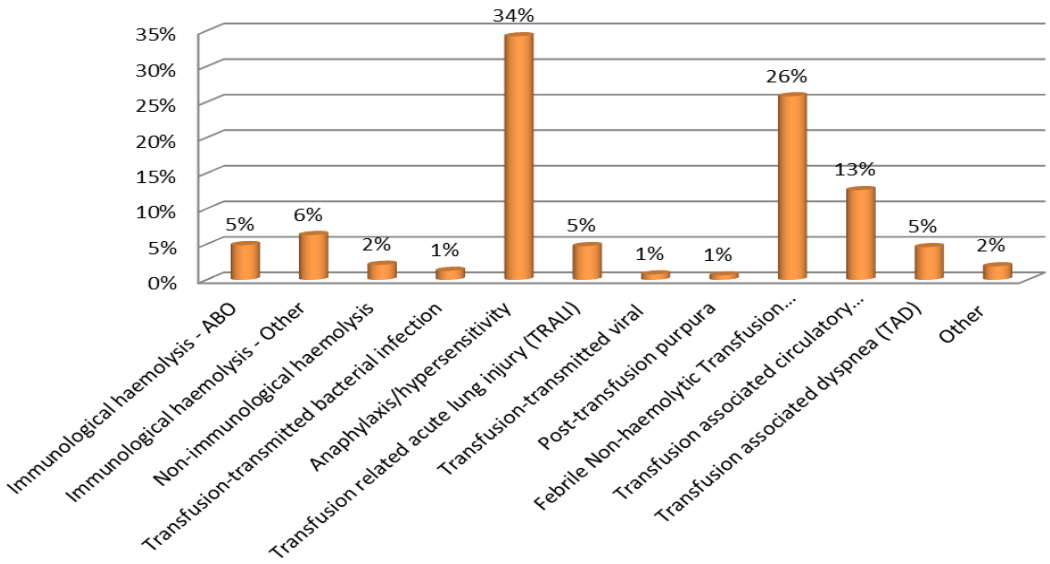
[12] For those countries which report units transfused and SAR for at least three blood components.

3.3.3. Information by category of SAR

The 1,410 SAR (level 2-3) reported were classified as follows:

- Anaphylaxis/hypersensitivity: 483 cases;
- Febrile non-haemolytic transfusion reactions (FNHTR) 364 cases;
- Transfusion associated circulatory overload (TACO): 178 cases;
- Immunological haemolysis: 158 cases, of which
    - 69 cases due to ABO antibody and
    - 89 cases due to other allo-antibodies;
- Transfusion related acute lung injury (TRALI): 67 cases;
- Transfusion associated dyspnea (TAD): 65 cases;
- Non-immunological haemolysis: 30 cases;
- Transfusion transmitted infections: 29 cases, of which:
    - 18 cases of bacterial transmission and
    - 11 cases of viral transmission of which 9 were hepatitis E, one was hepatitis B and one was Epstein Barr virus;
- Post transfusion purpura: 9 cases;
- Other SAR: 27 cases.

Figure 5: Percentage of SARs per category



3.3.4. Recipient Deaths

Among the 1,410 cases of SAR reported, there were 27 deaths as follows:

- 7 were associated with immunological haemolysis (4 due to ABO and associated with red blood cell transfusion, 1 due to ABO in a patient that received multiple components and 2 due to other antibodies following red blood cell transfusion); (26% of all reported deaths).

- 6 were associated with TACO (5 following red blood cell transfusion and 1 in a patient that was transfused with multiple components); (22% of all reported deaths).

- 4 were associated with TRALI (2 following red blood cell transfusion, 1 following platelet transfusion and 1 in a patient that was transfused with multiple components); (15% of all reported deaths).

- 4 were associated with bacterial transmission, following platelet transfusion in 3 cases and red blood cells transfusion in one; (15% of all reported deaths).

- 1 was associated with the transmission of hepatitis E by platelet transfusion; (4% of all reported deaths).

- 1 was associated with non-immunological haemolysis after red blood cell transfusion; (4% of all reported deaths).

- 1 was associated with an anaphylactic reaction following platelet transfusion; (4% of all reported deaths).

- 1 was associated with post-transfusion purpura in a patient that was transfused with multiple components; (4% of all reported deaths).

- 2 were reported under the 'other' category, both following platelet transfusion; (7% of all reported deaths).

The United States Food and Drug Administration (FDA) published an annual summary of 'Fatalities reported to FDA following blood collection and transfusion"[13]. During 2014, there were 56 reported transfusion-related fatalities reported to FDA. The annual report reveals that some broad comparisons can be made with the annual vigilance reports on SAR submitted by the EU and EEA countries to the Commission. For example, in the US, TRALI caused the highest number of reported fatalities, followed by TACO and haemolytic transfusion reactions; microbial infections and anaphylactic reactions accounted for a relatively small number of reported fatalities. In Europe, according to the information submitted in the SARE reporting exercise, the highest number of transfusion-related deaths was due to immunological haemolysis, followed by TACO, TRALI and transfusion-transmitted bacterial infection. The number of reported transfusion related deaths attributable to anaphylaxis was comparably small in both jurisdictions.

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[13] Annual summary for 2014: 'Fatalities reported to FDA following blood collection and transfusion" http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM459461.pdf

3.3.5 SAR in donors

Twenty two countries (AT, BE, BG, CY, CZ, DE, DK, EE, FI, FR, HR, IE, IT, LU, MT, NL, PL, PT, RO, SE, SI, and UK) reported a total of 3,723 SAR in donors (on a voluntary basis).

A subset of countries also provided descriptive information to the European 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 injuries, nerve injuries, vasovagal episodes, or cardiovascular reactions.

3.4. Serious Adverse Events (SAE)

3.4.1. Information by country

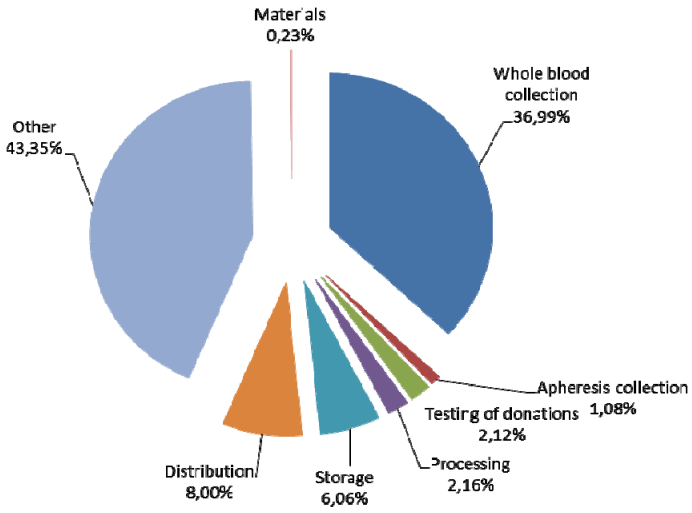
SAE were reported by the 28 Member States, Liechtenstein and Norway. The total number of SAE reported for 2014 was 4,460. It should be noted that five countries (HU, LI, LT, MT and SK) reported that there had been no reportable SAE in 2014.

3.4.2. Information by type of SAE

From the total 4,460 SAE reported, information was provided for 4,436 cases which linked the SAE with an activity step.

- Whole blood collection: 1,641,
- Apheresis collection: 48,
- Testing of donations: 94,
- Processing: 96,
- Storage: 269,
- Distribution: 355,
- Materials: 10 and
- Other activity steps: 1,923 events. This category includes 'compatibility testing', 'transport', ‘IT system errors’ and ‘microbial safety'.

Figure 6: Percentage of SAE by activity step

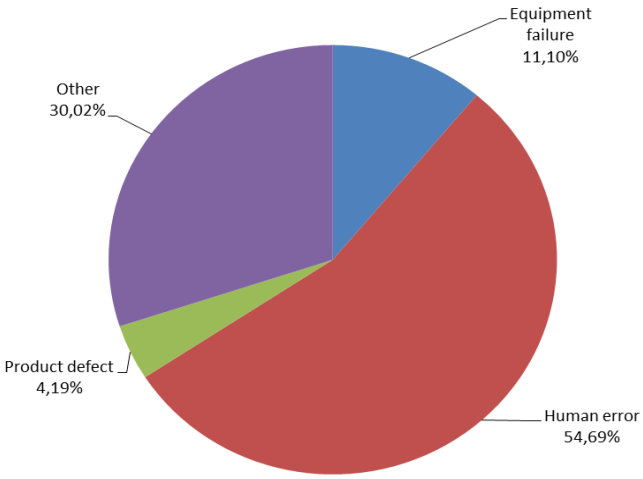


3.4.3. Information by Specification of SAE

The 4,460 SAEs were attributed to the following specifications:

- Human Error: 2,439
- Equipment failure: 495
- Product defect: 187
- Other: 1,339, including 'organisational errors' or unclassified SAE.

Figure 7: Percentage of SAE per specification



1,013 SAE were reported by one Member State in relation to damage to blood units during collection, processing and storage. Another Member State reported 1,386 SAE that occurred

during whole blood collection, including 1,316 related to high whole blood volume collected, 26 related to donors that were not compliant with inclusion criteria but were accepted, 20 related to incorrect labelling of blood donation bags and/or blood sampling intended for laboratory testing and 6 related to errors in recording and management of post information. SAE reporting varied very significantly between reporting countries, both in terms rates and criteria for case inclusion, suggesting that, with the collaboration of the Competent Authorities, further improvements should be made to the reporting criteria for greater comparability of data.

4. SARE REPORTING 2011-2015

The table below gives an overview of SARE reporting for the last five years (data from 2010 to 2014). As we can see, the number reporting denominators has not changed over the past years (although in 2015 fewer reported units issued compared to the previous years). In general, the numbers for denominators have fluctuated between years (23-26 million units issued, 12-21 million units transfused and 2-4 million recipients transfused), which is partly explained by the number of countries reporting.

The number of SAR reported in 2015 has slightly decreased compared to previous year (2,441 vs 2,831 at imputability level 1-3 and 1,410 vs 1,739 at imputability level 2-3). The number of deaths reported in 2015 increased compared to previous years (27 deaths vs to 22). For SAEs, the numbers reported in 2015 are considerably higher compared to last year (4,460 vs 2,972). There was also a significant increase in reported donor reactions (3,723 in 2014 vs 2,470 in 2013).

Table 1: Overview of the 2011 to 2015 SARE reporting exercises[14]

	2011		2012		2013		2014		2015	
	Countries reporting	Number	Countries reporting	Number	Countries reporting	Number	Countries reporting	Number	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**
Units transfused	19	16,718,258	17	12,311,691	20	13,351,948	22	16,564,817	**25**	**21,425,047**
Recipients transfused	11	2,298,304	16	2,964,839	19	3,595,155	20	3,216,938	**18**	**4,190,835**
SAR (1-3)	30	2,449	30	3,133	30	3,519	30	2,831	**30**	**2,441**
SAR (2-3)	30	1,259	30	1,574	30	1,831	30	1,739	**30**	**1,410**
SAR death	30	20	30	14	30	22	28	22	**30**	**27**
SAE	28	16,360	25	4,113	28	2,953	30	2,972	**30**	**4,460**
SAR in donors					18	2,494	23	2,470	**20**	**3,723**

[14] 2010-2014 data

5. CONCLUSIONS

In the SARE 2015 annual reporting exercise, all countries submitted reports. Complete data was provided by 67% of the reporting countries (i.e. 20 out of 30). This is an improvement compared to the previous years. The European Commission and Member States are continuously working to improve data collection and assist those countries which have difficulties in collecting reliable data.

The *number of SAR* in recipients (imputability level 2-3) reported for 2014 was 1,410. Anaphylaxis, febrile non-haemolytic transfusion reactions and transfusion associated circulatory overload appear to be the most frequent serious adverse reactions. Compared to 2012 and 2013, the number of SAR decreased (cf. 1,410 in 2014, 1,831 in 2012 and 1,739 in 2013). However, considering that the data reported is partial, year on year comparisons should be interpreted with caution. In relation to the number of units of blood components transfused in the EU (6.6 SAR per 100,000 units transfused), this number is considered low.

The results also show that the *number of deaths* likely to be, or certainly, resulting from blood transfusion in 2014 amounted to 27. Compared to the previous years, this number has slightly increased (cf. 27 deaths in 2014, 22 deaths in 2013 and 22 deaths in 2012). It is, however, important to note that of the 27 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 overload and transfusion related acute lung injury.

For *SAE*, the reported figures have also increased compared to the last years (cf. 4460 in 2014, 2,972 in 2013, 2,953 in 2012). The largest number of SAE reported for 2014 was due to human error and the process step most associated with SAEs was whole blood collection. Reporting on SAE revealed that there is a need to further clarify and improve the collection of SAE data overall to ensure that the reporting criteria are consistently applied. A Joint Action, VISTART[15] which includes a work-package dedicated to vigilance reporting for blood, tissues and cells is expected to provide inputs for improving the implementation of vigilance requirements and data collection.

The voluntary *reporting on donors*, added in 2012 and undertaken by a majority of countries in the last reporting exercise (i.e. 20 countries for 2014), highlights a significant increase in reported donor reactions. The number reported for 2014 increased by more than 50% compared to 2013 (3,723 for 2014 vs 2,470 for 2013). In recent years, awareness has grown of the importance of monitoring safety and quality of care for persons who make transfusion medicine possible. It is valuable to have these data which might enable further assessment of the underlying reasons for donor reactions and the implementation of measures to reduce them.

[15] Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation is a Joint Action co-funded by the European Union. The Joint Action started 10 October 2015; its duration is 36 months; website: https://vistart-ja.eu/

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 identify where quality issues occur and should be addressed to improve the safety and quality of blood transfusion across the EU.