Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2015

I. Background

As mentioned in the previous annual summaries of fatalities reported to the Food and Drug Administration (FDA), the blood supply is safer today than at any time in history. Due to advances in donor screening, improved testing, automated data systems, and changes in transfusion medicine practices, the risks associated with blood transfusion remain low. Overall, the number of transfusion-associated fatalities reported to the FDA remains small in comparison to the total number of transfusions. In 2013, for example, there were approximately 19 million blood components transfused.[1] During the proximate period of Fiscal Year (FY) 2011, there were 58 reported transfusion-associated fatalities, with subsequent reports of 65 in 2012, and 59 in 2013, 56 in 2014, and 41 in 2015.[2]

Although blood donations are generally safe, we also include information on the infrequent reports of donation-associated fatalities submitted to the agency. The number of donation-associated fatalities reported to the FDA also remains small in comparison to the total number of donations. In 2013, there were approximately 14 million whole blood and apheresis red blood cell donations[1], and in 2014, 32.6 million source plasma donations made in the U.S.[3] Over the combined five-year reporting period (FY2011 – FY2015), there were 45 reported donation-associated fatalities (associated with a variety of donated product)[2], with only one conclusively linked to the donation.[4]

FDA's Center for Biologics Evaluation and Research (CBER) is distributing this summary of fatality reports received by the FDA to make public the data received in FY2015 (October 1, 2014, through September 30, 2015), to provide the combined data received over the last five fiscal years, and to compare the FY2015 summary to the fatality reports received in the previous four fiscal years.[5] Throughout this report we note changes over time, but the reader should interpret these changes cautiously, given the small numbers of reports and inherent variations in reporting accuracy. The significance of shifts in numbers derived from small populations may appear to be greater than they really are.

Refer to Title 21, Code of Federal Regulations 606.170(b) for fatality reporting requirements. For information regarding the notification process, see our web page, Notification Process for Transfusion Related Fatalities and Donation Related Deaths, http://www.fda.gov/biologicsbloodvaccines/safetyavailability/reportaproblem/transfusiondonationfatalities/default.htm. For further information, see our *Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion*, September 2003.[6]

[1] Chung, K.-W., Basavaraju, S. V., Mu, Y., van Santen, K. L., Haass, K. A., Henry, R., Berger, J. and Kuehnert, M. J. (2016), Declining blood collection and utilization in the United States. Transfusion. doi: 10.1111/trf.13644.

[2] The reported numbers do not include those where the association was conclusively ruled out.

[3] Plasma Protein Therapeutics Association at http://pptaglobal.org/plasma/plasma-collection

[4] http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM459461.pdf

[5] The FY2005 - FY2010 data are not discussed in this report, but are available at: http://www.fda.gov/biologicsbloodvaccines/safetyavailability/reportaproblem/transfusiondonationfatalities/default.htm.

[6] Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion, September, 2003. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074947.htm.

If you have questions concerning this summary, you may contact us using any of the three following options:

1. Email us at fatalities2@fda.hhs.gov,
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II. Changes in Our Evaluation Approach:

In support of the FDA's international harmonization efforts and to provide consistency between US government agencies (http://www.fda.gov/aboutfda/reportsmanualsforms/reports/ucm298576.htm), we have modified our approach to the review and classification of fatality reports. The annual report for FY2015 aligns with the case definitions and imputability criteria used by the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network,[7] (http://www.cdc.gov/nhsn/PDFs/Biovigilance/BV-HV-protocol-current.pdf), the International Society of Blood Transfusion (ISBT) in collaboration with the International Haemovigilance Network (IHN) and the AABB Donor Haemovigilance Working Group[8] (https://www.aabb.org/research/hemovigilance/Documents/Donor-Standard-Definitions.pdf), the British Serious Hazards of Transfusion (SHOT)[9] , and the Hemovigilance activity report of the French National Agency for Medicines and Health Products Safety (ANSM)[10] .

In previous years, we classified fatalities in one of three categories: *transfusion/donation-related, not ruled out, or not related*. For cases beginning FY2015, fatalities previously classified either as *transfusion/donation-related*, or *not ruled out* are assigned a level of causation (imputability), specifically *definite/certain, probable/likely, possible, doubtful/unlikely/improbable*, and *not determined/assessable/evaluable*. Fatalities previously defined as *not transfusion/donation related* continue to be classified as *ruled out/excluded*. (Table 1)
Our review process continues to include a team of CBER medical officers who conduct a detailed review of the documentation submitted by the reporting facilities and obtained by FDA investigators to assess the relationship, if any, between the blood donation or transfusion and the fatality. Our new classification approach allows the review team an increased level of flexibility for an effective review, and consistent case classifications. These changes add clarity, and allow comparability with other domestic and international hemovigilance systems.

[7] Center for Disease Control and Prevention National Healthcare Safety Network, Biovigilance Component, Hemovigilance.
[8] International Society of Blood Transfusion Working Party on Haemovigilance in collaboration with the International Haemovigilance Network and the AABB Donor Haemovigilance Working Group, Standard for Surveillance of Complications Related to Blood Donation, December 2014.
[9] Annual Serious Hazards of Transfusion Report, 2014.
[10] French National Agency for Medicine and Health Product Safety (ANSM), 2013 Hemovigilance Activity Report.

Table 1: Imputability Definitions[7,8] FY 2015

Imputability	Definition
Definite/Certain	Conclusive evidence beyond reasonable doubt for attributing the fatality to the transfusion/donation
Probable/Likely	Evidence clearly in favor of the transfusion/donation as the cause of the fatality
Possible	Evidence is indeterminate for attributing the fatality to the transfusion/donation or alternative cause
Doubtful/Unlikely/Improbable	Evidence in favor of attributing the fatality to an alternative cause, but transfusion/donation cannot be excluded.
Ruled Out/Excluded	Conclusive evidence beyond reasonable doubt for attributing the fatality to cause other than transfusion/donation
Not Determined/Assessable/Evaluable	Insufficient information/relationship unknown

III. Results

During FY2015, we received a total of 62 fatality reports. Of these reports, 42 were associated with transfusion recipient fatalities, and 20 were fatalities associated with donation.

Of the 42 transfusion-associated fatality reports, we concluded:

a) 37 (88%) of the fatalities were classified as either *definite/certain, probably/likely,* or *possible.*
b) Four (10%) of the fatalities were classified as either *doubtful/unlikely/improbable,* or *not determined/assessable/evaluable.*
c) One (2%) of the fatalities was classified as *ruled out/excluded.*

Of the 20 donation-associated fatality reports, we concluded:

a) One (5%) of the fatalities was classified as *possible*.
b) 14 (70%) of the fatalities were classified as either *doubtful/unlikely/improbable,* or *not determined/assessable/evaluable*.
c) Five (25%) of the fatalities were classified as *ruled out/excluded.*

We summarize the results of our review in Table 2.

Table 2: Fatality Complication Breakdown by Imputability FY2015

CATEGORY	Definite/ Certain	Probable/ Likely	Possible	Doubtful/ Unlikely/ Improbable	Ruled Out/ Excluded	Not Determined/ Assessable/ Evaluable	TOTAL
Transfusion							
Allergy/Anaphylaxis	2	-	-	-	-	-	**2**
Contamination (Bacterial)	3	-	2	-	-	-	**5**
HTR (ABO)	2	-	-	-	-	-	**2**
HTR (non-ABO)	2	1	1	1	-	-	**5**
Hypotensive Reaction[18]	-	1	-	1	-	-	**2**
TACO	3	6	2	-	-	1	**12**
TRALI	5	N/A*	7	1	1	-	**14**
Donation							
Donor Fatality	-	-	1	12	5	2	**20**

*Definitions based on the Canadian Consensus Conference Panel on TRALI.[22,23]

For the purpose of comparison with previous fiscal years, we have included FY2015 imputabilities of *definite/certain, probable/likely,* and *possible* transfusion fatalities in the tables and figures for sections A through D of this document, which would most accurately compare with fatalities classified in previous years as *transfusion-related*. Section E and F presents the transfusion fatalities classified as *doubtful/unlikely/improbable,* or *not determined/assessable/evaluable,* which would most accurately compare with fatalities classified in previous years as *transfusion not ruled out.* Section G presents the transfusion fatality reports classified as *ruled out/excluded,* which would compare with fatalities classified in previous years as *not transfusion related*. Section H presents the reported fatalities associated with donation.

A. Overall Comparison of Transfusion-Associated Fatalities Reported from FY2011 through FY2015

In combined Fiscal Years 2011 through 2015, Transfusion Related Acute Lung Injury (TRALI)[11] caused the highest number of reported fatalities (38%), followed by Transfusion Associated Circulatory Overload (TACO) (24%) and hemolytic transfusion reactions (HTR) due to non-ABO (14%) and ABO (7.5%) incompatibilities. Microbial contamination (10%), anaphylaxis reactions (5%), and hypotensive reactions (1%) each accounted for a relatively smaller number of reported fatalities (Table 3).
While the number of fatalities attributed to TACO has varied, TACO was the second leading cause of transfusion-associated fatalities over the 5-year reporting period. The National Heart Lung and Blood Institute (NHLBI) Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) is focused on transfusion and reducing its risks, and current research includes a Phase 2 study titled *Severe Transfusion Reactions Including Pulmonary Edema (STRIPE),* which focuses on strategies that will prevent or reduce complications related to TACO and other transfusion complications.[12,13]

[11] http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/ucm110327.htm
[12] https://reds-iii.rti.org/REDSProgram.aspx.

The number of reported transfusion-associated deaths attributable to anaphylaxis[14, 15, 16, 17, 18, 19] has remained small over the last five fiscal years. We find few anaphylactic reactions attributable to IgA deficiency as seen in the cases reported for FY2011 through FY2015 where one of the eight cases reported a slightly low IgA level; normal IgA levels conclusively ruled out six cases, and IgA was not measured in the remaining case. Anaphylactic reactions may also be associated with haptoglobin-deficient patients with serum haptoglobin antibodies.[20] However, of the two anaphylaxis cases in FY2015, one haptoglobin level was reported as normal, and no haptoglobin was measured in the second case.

The number of reported transfusion- associated deaths attributable to hypotensive reactions[21] has also remained small over the last five fiscal years, with one case in FY2014 and one in FY2015. Since hypotension may be an element of the clinical presentation for other types of transfusion reactions, recognizing it as the primary cause can be challenging. In both of the reported cases there was no supportive evidence to conclude that hypotension was secondary to another condition.

[13] Kleinman S, Busch MP, Murphy EL et al. The National Heart, Lung, and Blood Institute Recipient Epidemiology and Donor Evaluation Study (REDS-III): a research program striving to improve blood donor and transfusion recipient outcomes. Transfusion. 2014 Mar;54(3 Pt 2):942-55.

[14] Lindsted G, Larsen R, Kriegaard M, et al. Transfusion-Associated Anaphylaxis during anaesthesia and surgery – a retrospective study. Vox Sanguinis 2014;107(2):158-65.

[15] Hirayama F. Current Understanding of allergic transfusion reactions: incidence, pathogenesis, laboratory tests, prevention and treatment. British Journal of Haematology 2013;160:434-444.

[16] Savage W, Tobian A, Savage J, et al. Scratching the surface of allergic transfusion reactions. Transfusion 2013;53:1361-1371.

[17] Sandler SG1, Eder AF, Goldman M, Winters JL. The entity of immunoglobulin A-related anaphylactic transfusion reactions is not evidence based. Transfusion. 2015 Jan;55(1):199-204.

[18] Savage WJ, Tobian AA, Savage J, et al. Transfusion and component characteristics are not associated with allergic transfusion reactions to apheresis platelets. Transfusion 2015;55:296-300.

[19] Sandler SG1, Eder AF, Goldman M, Winters JL. The entity of immunoglobulin A-related anaphylactic transfusion reactions is not evidence based. Transfusion. 2015 Jan;55(1):199-204.

[20] Shimada E, Tadokoro K, Watanabe Y, et al. Anaphylactic transfusion reactions in haptoglobin-deficient patients with IgE and IgG haptoglobin antibodies. Transfusion 2002;42:766-773.

[21] http://www.captodayonline.com/tuning-in-to-hypotensive-transfusion-reactions/

Table 3: Transfusion-Associated Fatalities by Complication, FY2011 – FY2015

Complication	FY11 No.	FY11 %	FY12 No.	FY12 %	FY13 No.	FY13 %	FY14 No.	FY14 %	FY15 No.	FY15 %	Total No.	Total %
Anaphylaxis	2	7%	2	5%	-	0%	2	7%	2	5%	**8**	**5%**
Contamination	4	13%	3	8%	5	13%	1	3%	5	14%	**18**	**10%**
HTR (ABO)	3	10%	3	8%	1	3%	4	13%	2	5%	**13**	**7.5%**
HTR (non-ABO)	6	20%	5	13%	5	13%	4	13%	4	11%	**24**	**14%**
Hypotensive Reaction	-	0%	-	0%	-	0%	1	3%	1	3%	**2**	**1%**
TACO	4	13%	8	21%	13	34%	5	17%	11	30%	**41**	**24%**
TRALI*	10	33%	17	45%	14	37%	13	43%	12	32%	**66**	**38%**
Other	1**	3%	-	0%	-	0%	-	3%	-	0%	**1**	**.5%**

Note: FY15 denotes an imputability of *Definite/Certain*, *Probable/Likely*, or *Possible*
*FY11-FY14 numbers include both *TRALI* and *Possible TRALI* cases [22,23]
**Other: GVHD (Graft vs. Host Disease)

B. Transfusion Related Acute Lung Injury (TRALI)

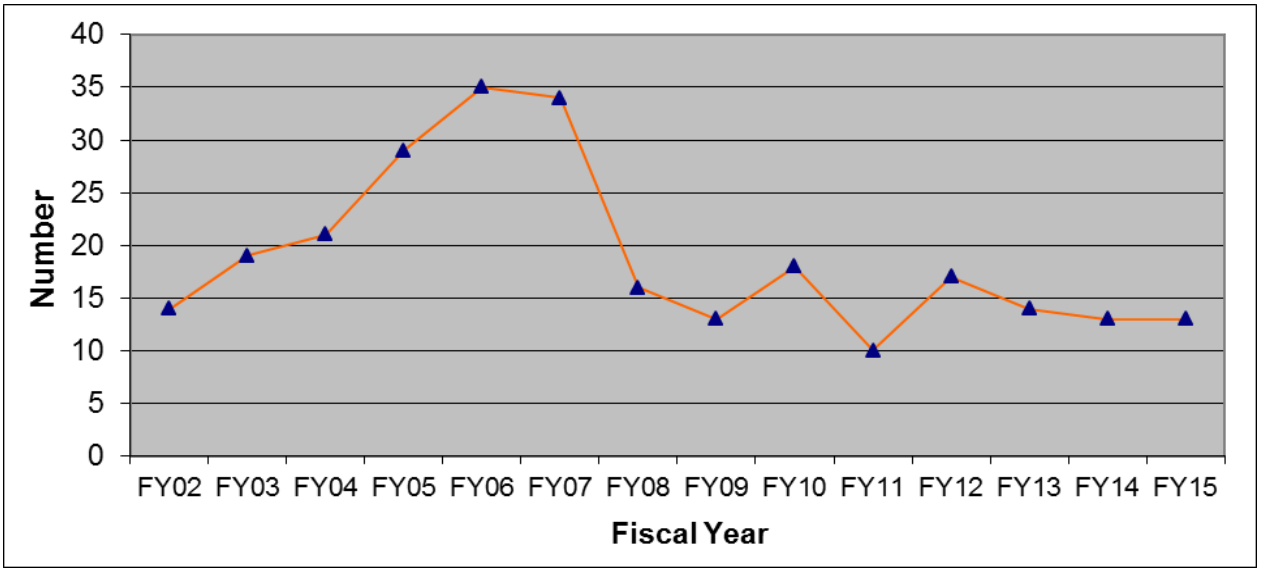
In FY2015, five of the reported TRALI cases were classified as *definite/certain* TRALI, and seven cases were classified as *possible* TRALI. In two cases, reporters who obtained patient testing were able to match donor antibodies with recipient cognate antigens. In the first case, HLA Class I and II antibodies matched the recipient cognate antigens. In the second case, HLA Class II antibodies matched recipient cognate antigens. Our limited data do not elucidate the role of particular donor antibodies or donor gender in the etiology of the TRALI reactions.

TRALI represented 38% of transfusion-associated fatalities reported to CBER over the last five fiscal years, and 32% in FY2015 (Table 3). Figure 2 shows a steady rise in TRALI cases between FY02 and FY07, and an abrupt decline to a fairly consistent plateau over the last seven fiscal years. Red blood cells continue to be the most frequently implicated product since 2012. (Figure 3)

Although this complication of transfusion continues to be one of the leading causes of transfusion-associated fatalities reported to the FDA, the voluntary measures taken by the transfusion community to reduce the risk of TRALI have coincided with a reduction in the number of TRALI deaths. Current literature describes the results of continued international efforts to reduce the use of high-volume plasma products for transfusion prepared from female donors, and other strategies to reduce the incidence of TRALI. [24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37]

[22] Goldman M, Webert KE, Arnold DM, et al. Proceedings of a consensus conference: towards an understanding of TRALI. Transfus Med Rev 2005;19:2-31.
[23] Kleinman S, Caulfield T, Chan P, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 2004;44:1774-1789.
[24] Muller MCA, Juffermans NP. Transfusion-related acute lung injury: a preventable syndrome? Expert Rev. Hematol. 2012;5(1):97-106.
[25] Wiersum-Osselton JC, Middleburg RA, Beckers EAM, et al. Male-only fresh frozen plasma for transfusion-related acute lung injury prevention: before-and-after comparative cohort study. Transfusion 2011;51:1278-1283.
[26] Schmidt AE, Adamski J. Pathology Consultation on Transfusion-Related Acute Lung Injury. Am J Clin Pathol 2012;138:498-503
[27] Saidenberg E, Petraszko T, et al. Transfusion-Related Acute Lung Injury (TRALI): A Canadian Blood Services Research and Development Symposium. Transfusion Medicine Reviews 2010;24:305-324.
[28] Arinsburg SA, Skerrett DL, Karp JK, et al. Conversion to low transfusion-related acute lung injury (TRALI)-risk plasma

Figure 1: TRALI Cases FY2002 - FY2015



significantly reduces TRALI. Transfusion 2012;52:946-952.

[29] Reesink HW, Lee J, Keller A, et al. Measures to prevent transfusion-related acute lung injury (TRALI). Vox Sanguinis 2012;103:231-259.

[30] Toy P, Ognjen G, Bacchetti P, et al. Transfusion-related lung injury: incidence and risk factors. Blood 2012;119:1757-1767.

[31] Eder A, Herron Jr R, Strupp A, et al. Effective reduction of transfusion-related lung injury risk with male-predominant plasma strategy in the American Red Cross (2006-2008). Transfusion 2010;50:1732-1742.

[32] Clifford L, Singh A, Wilson G, et al. Electronic health record surveillance algorithms facilitate the detection of transfusion-related pulmonary complications. Transfusion 2013;53:1205-1216.

[33] Association Bulletin #14-02 – TRALI Risk Mitigation for Plasma and Whole Blood for Allogeneic Transfusion. http://www.aabb.org/resources/publications/bulletins/Pages/abwhatsnew.aspx.

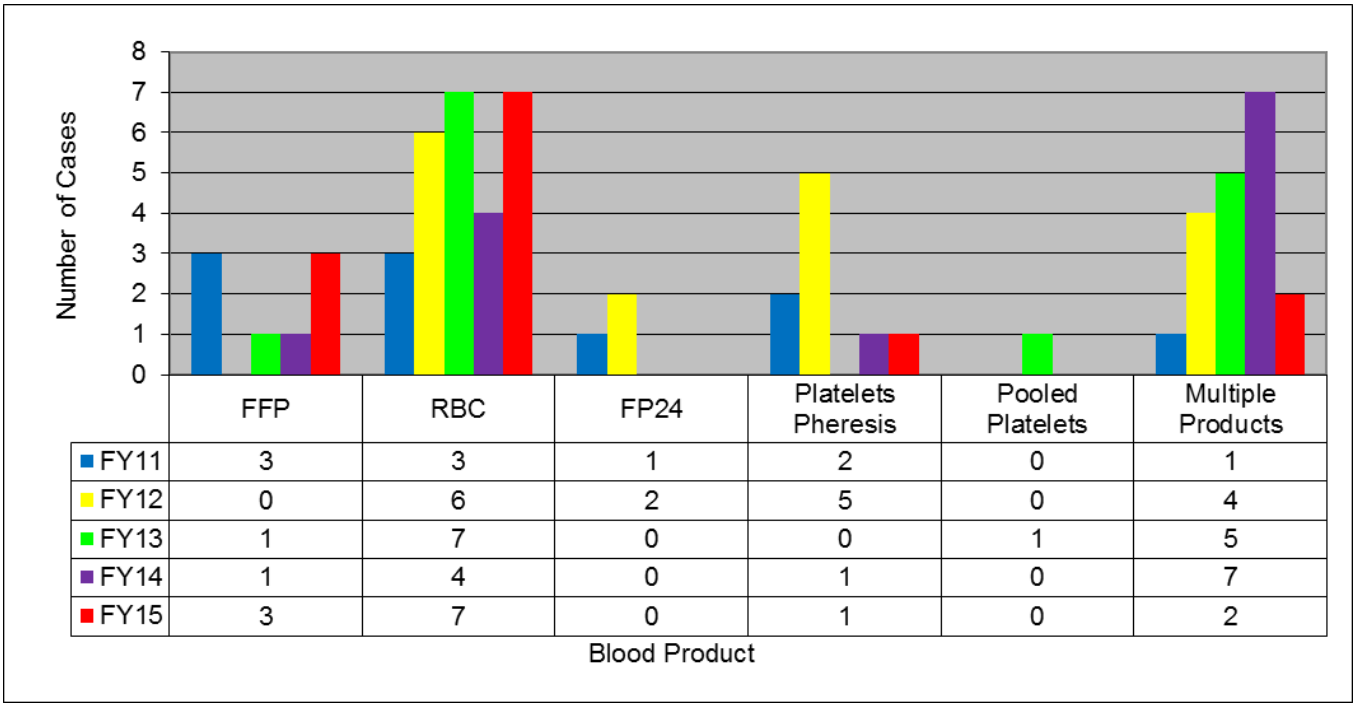
[34] Menis M, Anderson SA, Forshee FA, et al. Transfusion-related acute lung injury and potential risk factors among the inpatient US elderly as recorded in Medicare claims data, during 2007 through 2011. Transfusion 2014;54:2182-2193.

[35] Silliman CC, Kelher MR, Khan SY, et al. Experimental prestorage filtration removes antibodies and decreases lipids in RBC supernatants mitigating TRALI in vivo. Blood 2014;123:3488-3495.

[36] Popovsky MA. Transfusion-related acute lung injury: three decades of progress but miles to go before we sleep. Transfusion 2015;55:930-934.

[37] Peters AL, Van Stein D, Vlaar AP. Antibody-mediated transfusion-related acute lung injury; from discovery to prevention. British Journal of Haematology 2015. DOI 10.1111/bjh.13459.

Figure 2: Reports of TRALI Cases by Implicated Blood Product FY2011 – FY2015



	FFP	RBC	FP24	Platelets Pheresis	Pooled Platelets	Multiple Products
FY11	3	3	1	2	0	1
FY12	0	6	2	5	0	4
FY13	1	7	0	0	1	5
FY14	1	4	0	1	0	7
FY15	3	7	0	1	0	2

FFP – Fresh Frozen Plasma
RBC – Red Blood Cells
FP24 – Plasma Frozen within 24 hours

C. Hemolytic Transfusion Reactions (HTR)

In FY2015, there were two reported ABO hemolytic transfusion fatalities (5% of confirmed transfusion-associated fatalities), and four non-ABO hemolytic transfusion fatalities (11% of confirmed transfusion-associated fatalities). (Table 3)

The two reports of fatal hemolytic transfusion reactions which were found to be related to ABO-incompatible transfusions include an error in patient identification at the time of specimen collection, and a case of ABO-incompatible apheresis platelets.[38]

1. HTR (ABO) – *Definite/Certain.*
   A group A RBC unit was transfused to a patient who initially typed as AB Pos. When a subsequent sample was collected, it was determined the patient's correct type was B Pos. There was a failure to properly identify the patient prior to collection, resulting in a case of wrong blood in tube (WBIT).
2. HTR (ABO) – *Definite/Certain.*
   A group A apheresis platelet was transfused to a group B patient. A hemolytic transfusion reaction was observed, and a high titer of anti-B (1:2048) was subsequently identified.

The four reports of non-ABO fatal hemolytic transfusion reactions include one case of hyperhemolysis syndrome, and three cases of emergently released red blood cells to recipients with one or more antibodies. In the latter three cases, the institution's emergency release procedures were followed appropriately.

[38] Fontaine MJ, Mills AM, et al. How we treat: risk mitigation for ABO-incompatible plasma in plateletpheresis products.

1. HTR (non-ABO) – *Definite/Certain*
   A hypotensive patient with a 5.1 g/dL hemoglobin and clinical concern for GI bleed was emergently transfused two units of red blood cells. The patient had multiple known antibodies (anti-E, anti-K, anti-Jk^a, anti-M, anti-Co^b, and possible anti-Cw), however phenotypically compatible units were not immediately available. Of the two units emergently transfused, one unit was subsequently determined to be positive for M, and the second unit was positive for Jk^a.

2. HTR (non-ABO) – *Definite/Certain*
   A sickle cell patient was transfused with units that were crossmatch- compatible and phenotypically matched for antigens corresponding to known antibodies. Following a hemolytic reaction, the history and clinical course of this patient supported a diagnosis of acute hyperhemolysis syndrome. No new red cell antibodies were identified.

3. HTR (non-ABO) – *Probable/Likely*
   A patient with a 4.4 g/dL hemoglobin was emergently transfused a unit of red blood cells. It was subsequently discovered during follow-up type and screen testing that the patient presented with anti-c, anti-E, anti-K, and positive direct antiglobulin test (DAT). The transfused unit was subsequently determined to be c positive (E and K antigen negative) and crossmatch-incompatible. The patient presented with multiple serious co-morbidities and her condition was likely exacerbated by the transfusion of incompatible blood.

4. HTR (non-ABO) – *Possible*
   A cardiac patient with a 4.9 g/dL hemoglobin and history of transfusion received two emergently released units, which were later found to be incompatible. Multiple antibodies were identified including anti-C, anti-E, anti-S, anti-Jk^b, anti-Fy^a, and anti-Fy^b. Although, the transfusion reaction investigation was consistent with a delayed hemolytic transfusion reaction, the patient died following a subsequent surgical procedure with post-surgical complications. The evidence was indeterminate for attributing the fatality to the transfusion or post-surgical complications.

Reviewing data from previous years, the number of hemolytic transfusion reactions has remained low, particularly with ABO HTRs, where the error is most frequently preventable misidentification of the patient or the patient's sample. There were two reported ABO hemolytic transfusions (5%) that were confirmed to be fatal in FY2015, compared to four (13%) in FY2014. The number of non-ABO hemolytic transfusion reactions represents a count unchanged with four cases in both FY2014 and FY2015 (Table 3). These cases are comparatively less preventable as seen in FY2015, where all cases were transfusions due to emergent need, and antibody history was not always known. There has been an overall downward trend in the total number of reported fatalities due to HTRs (both ABO and non-ABO) since FY2002, and numbers have stabilized in recent years (Figure 4).

Table 4: Hemolytic Transfusion Reactions by Implicated Antibody, FY2011 – FY2015

Antibody	FY11 No.	FY12 No.	FY13 No.	FY14 No.	FY15 No.	Total No.
ABO	3	3	1	4	2	**13**
Multiple Antibodies*	1	2	1	-	2	**6**
Other**	2	-	-	2	1	**5**
K	1	1	2	-	-	**4**
Jk^a	-	-	1	1	-	**2**
Jk^b	-	1	1	-	-	**2**
c	1	-	-	-	1	**2**
C	-	-	-	1	-	**1**
Fy^a	1	-	-	-	-	**1**
Js^b	-	1	-	-	-	**1**
Total	**9**	**8**	**6**	**8**	**6**	**37**

*Multiple Antibodies:

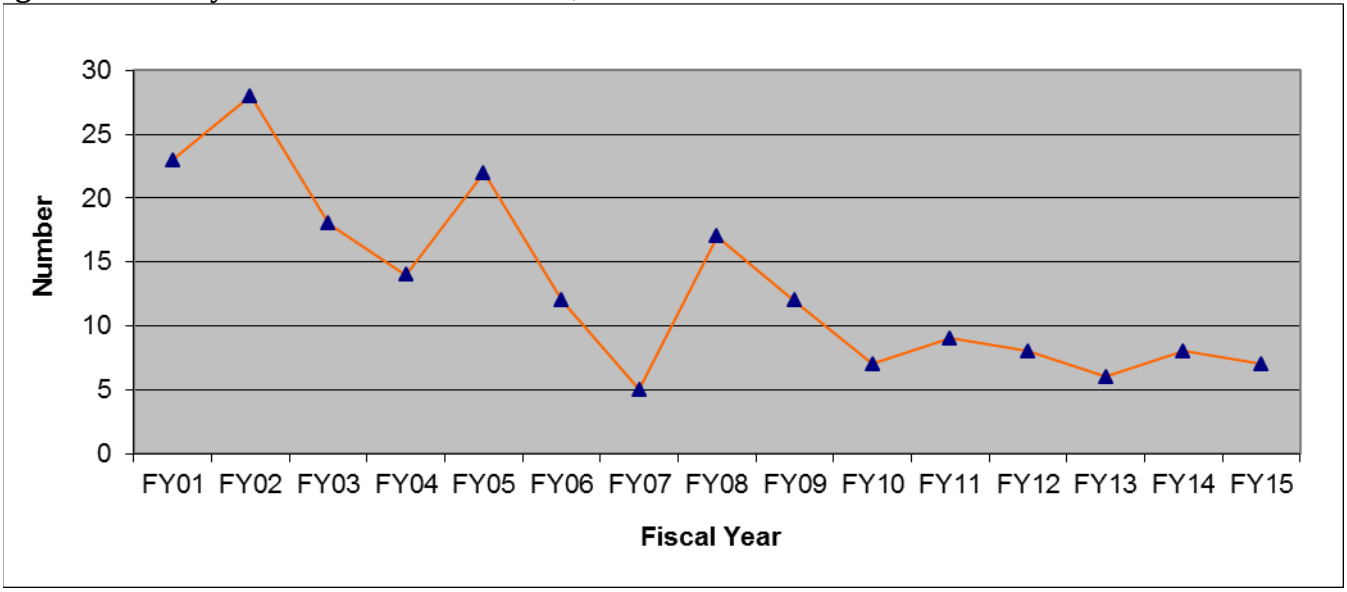
FY2011: anti-Jk^a+c+E+M (warm reacting).
FY2012: antibody combinations include: S+E; C+K.
FY2013: anti-c+E
FY2015: antibody combinations include: E+K+Jk^a+M+Co^b+Cw**;** C+E+S+Jk^b+Fy^a+Fy^b

**Other:

FY2011: Includes one report of an unidentified antibody and one report of Hyperhemolysis Syndrome[39, 40]
FY2014: Includes one report of Hyperhemolysis Syndrome in which no new or additional antibody was identified
FY2015: Includes one report of Hyperhemolysis Syndrome in which no new or additional antibody was identified

[39] Win N, New H, et al. Hyperhemolysis Syndrome in sickle cell disease: case report (recurrent episode) and literature review. Transfusion 2008;48:1231-1238.
[40] Santos B, Portugal R, et al. Hyperhemolysis Syndrome in patients with sickle cell anemia: report of three cases. Transfusion. 2015 Jun;55(6 Pt 2):1394-8.

Figure 3: Hemolytic Transfusion Reactions, FY2001 – FY2015



D. Microbial Contamination

In FY2015 there were five reported fatalities, all attributed to bacterial contamination (Table 5). Three of the FY2015 cases involve transfusion of apheresis platelets which were contaminated with *Staphylococcus aureus* (Figure 5). One case involved transfusion of both parts of an apheresis platelet which was contaminated with coagulase-negative staphylococci and one case involved a red cell unit which was contaminated with *Enterococcus faecium* (Table 5, Figure 5).

Table 5: Contamination breakdown for FY2015

Product	Organism	Imputability
Apheresis platelets	*Staphylococcus aureus*	Definite/Certain
Apheresis platelets	*Staphylococcus aureus*	Definite/Certain
Apheresis platelets	*Staphylococcus aureus*	Possible
Apheresis platelets	Coagulase-negative staphylococci	Definite/Certain
Red Blood Cells	*Enterococcus faecium*	Possible

1. Contamination (*Staphylococcus aureus*) - *Definite/Certain* (two cases)
   In each case, the patient received an apheresis platelet product and *Staphylococcus aureus* was identified in both the product and in the patient. No other sources for the contamination were identified, and the patient was not infected with *Staphylococcus aureus* prior to transfusion.

2. Contamination (Coagulase-negative staphylococci) - *Definite/Certain*
   A patient received an apheresis platelet product and coagulase-negative staphylococci were identified in both the product and in the patient. No other sources for the contamination were identified, and the patient was not infected with coagulase-negative staphylococci prior to transfusion.

3. Contamination (*Staphylococcus aureus*) – *Possible*
   A patient received an apheresis platelet product and *Staphylococcus aureus* was identified in an associated product. There were no post-transfusion cultures performed on the patient or the platelet bag, however sepsis was reported as immediate cause of death.

4. Contamination (*Enterococcus faecium*) – *Possible*
   A patient received an apheresis platelet transfusion and was febrile prior to start of transfusion. *Enterococcus faecium* was cultured from the product; however, no organism was isolated from the patient's blood cultures. The patient was also diagnosed with a rectal perforation.

Reviewing data from the last five years, *Staphylococcus aureus* accounted for the greatest number of the reported deaths due to contamination (5/18), and *Babesia microti* accounted for the second highest number of fatalities (3/18), although there were no transfusion-transmitted cases of Babesia reported as fatalities in FY14 or FY15 (Table 6). Recent articles provide additional information about transfusion transmitted *Babesia.* [41, 42, 43]

Figure 5 shows the microorganisms implicated by product. *Babesia microti* infections were associated with three of the five RBC transfusions. The two *Serratia marcescens* infections were associated with transfusion of pooled platelets, and the 10 deaths associated with transfusion of apheresis platelets were distributed among seven organisms (Figure 5). Recent articles provide additional information about bacterial contamination of platelet products.[44, 45, 46, 47]

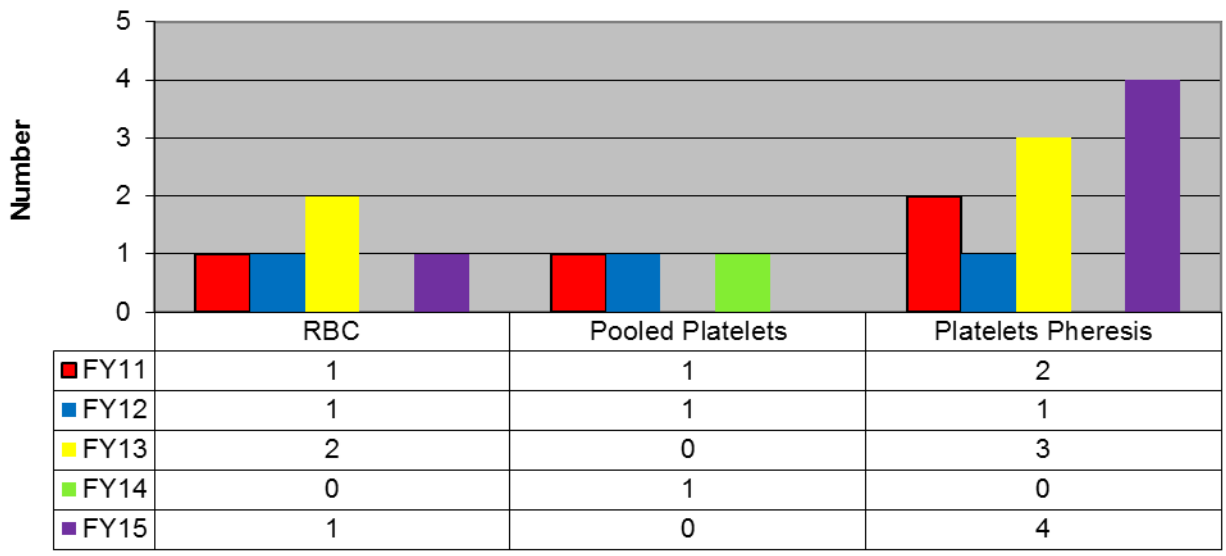
Figure 6 shows the trend of contamination (bacterial) associated with apheresis platelets from FY 2002 to FY2015. These data show that the number of bacterial infections has been trending downward, as the highest number of infections was seen in FY2002, when eight were identified. Bacterial contamination of platelet components remains a public health concern which FDA has addressed in a recently published Draft Guidance on controlling the risk of bacterial contamination to enhance the safety and availability of platelets for transfusion.[48]

[41] Johnson ST, Van Tassell ER, et al. Babesia microti real-time polymerase chain reaction testing of Connecticut blood donors: potential implications for screening algorithms. Transfusion 2013;53:2644-2649.
[42] Young C, Chawla A, et al. Preventing transfusion-transmitted babesiosis: preliminary experience of the first laboratory-based blood donor screening program. Transfusion 2012;52:1523-1529.
[43] Simon M, Leff J, Pandya A, et al. Cost-effectiveness of blood donor screening for *Babesia microti* in endemic regions of the United States. Transfusion 2014;54:889-899.
[44] Rollins MD, Molofsky AB, Nambiar A, et al. Two Septic transfusion reactions presenting as transfusion-related acute lung injury from a split plateletpheresis unit. Crit Care Med 2012;40:2488-2491.
[45] Palavecino EL, Yomtovian RA, Jacobs MR. Bacterial contamination of platelets. Transfus Apher Sci 2010;42:71-82.
[46] Eder AF, Kennedy JM, Dy BA, et al. American Red Cross Regional Blood Centers: Limiting and detecting bacterial contamination of apheresis platelets: inlet-line diversion and increased culture volume improve safety. Transfusion 2009;49:1554-1563.
[47] Benjamin R. Bacterial contamination. ISBT Science series 2014;9:37-43
[48] http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM425952.pdf

Table 6: Contamination by Implicated Organism, FY2011 - FY2015

Organism	FY11	FY12	FY13	FY14	FY15	TOTAL
Staphylococcus aureus	1	1	-	-	3	**5**
Babesia microti	1	1	1	-	-	**3**
Serratia marcescens	-	1	-	1	-	**2**
Staphylococcus epidermidis	-	-	1	-	-	**1**
Coagulase-negative staphylococci	-	-	-	-	1	**1**
Klebsiella pneumoniae	1	-	-	-	-	**1**
Morganella morganii	1	-	-	-	-	**1**
Pseudomonas fluorescens	-	-	1	-	-	**1**
Acinetobacter species	-	-	1	-	-	**1**
Enterococcus faecium	-	-	-	-	1	**1**
West Nile virus	-	-	1	-	-	**1**
TOTAL	**4**	**3**	**5**	**1**	**5**	**18**

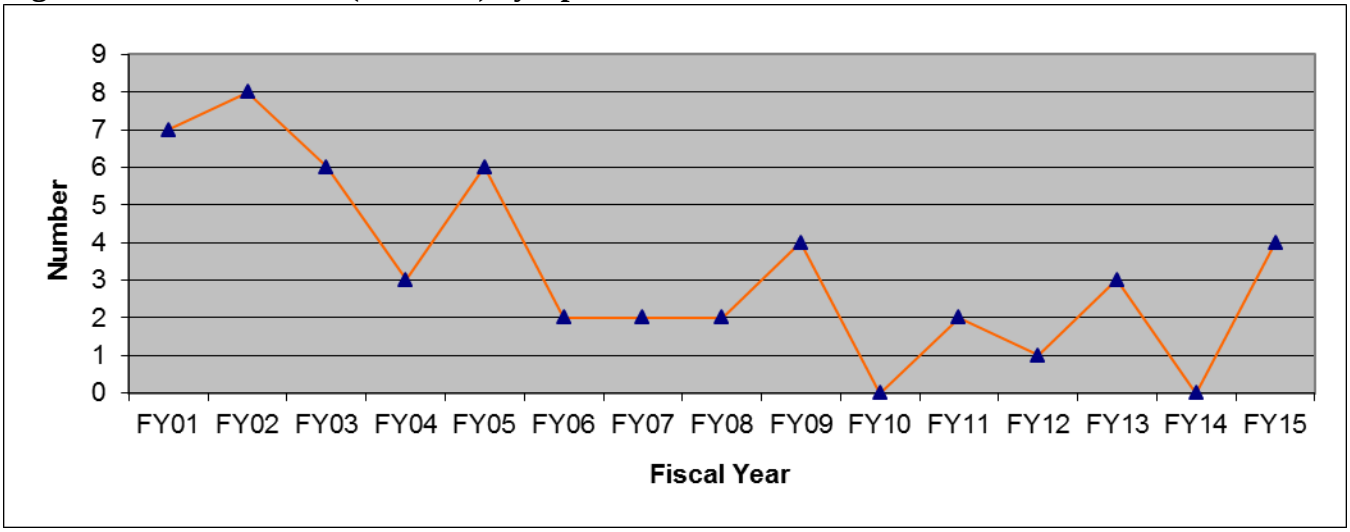
Figure 4: Contamination by Implicated Blood Product FY2011 – FY2015



	RBC	Pooled Platelets	Platelets Pheresis
FY11	1	1	2
FY12	1	1	1
FY13	2	0	3
FY14	0	1	0
FY15	1	0	4

Red Blood Cells microorganisms: *B. microti (3), P. fluorescens (1), E. faecium (1)*
Pooled Platelets microorganisms: *S. aureus (1), S. Marcescens (2)*
Platelets Pheresis microorganisms: *S. aureus (4), S. epidermidis (1),* coagulase-negative staphylococci *(1), M. morganii (1), K. pneumoniae (1),* West Nile virus *(1), Acinetobacter sp. (1)*

Figure 5: Contamination (bacterial) by Apheresis Platelets, FY2001 – FY2015



E. Transfusion Doubtful/Unlikely/Improbable

We classified three (7%) of the 42 reported transfusion fatalities in FY2015 as *doubtful/unlikely/improbable,* including one HTR (non-ABO), one Hypotensive Reaction, and one case of TRALI. Although the transfusion could not be excluded, the evidence in each of these cases was in favor of attributing the fatality to the patient's underlying medical condition(s). Thus, we did not include these reported fatalities in the analysis in Sections III.A through III.D.

F. Transfusion Not Determined/Assessable/Evaluable

We classified one (2%) of the 42 reported transfusion fatalities in FY2015 as *not determined/assessable/evaluable*. In this case, the patient had several underlying conditions, and there was insufficient information submitted to determine the extent of the relation. Thus, this reported fatality was also not included in the analysis in Sections III.A through III.D.

G. Transfusion Ruled Out/Excluded

We classified one (2%) of the 42 reported transfusion fatalities in FY2015 as *ruled out/excluded*. Our medical reviewers concluded that, while there was a temporal relationship between transfusion and subsequent death of the recipient, there was conclusive evidence beyond a reasonable doubt for attributing the fatality to a cause (underlying condition) other than transfusion. Thus, we did not include these reported fatalities in the analysis in Sections III.A through III.D.

H. Donation Fatalities

The process of blood donation is generally safe and determining that a causal link exists between a donation and the fatality remains uncommon among reported donation fatalities. For FY2015, there were no donation fatalities classified as *definite/certain*, or *probable/likely.* There was one (5%) fatality classified as *possible*, 12 (60%) fatalities classified as *doubtful/unlikely/improbable,* five (25%) fatalities classified as *ruled out/excluded,* and two (10%) fatalities classified as *not determined/assessable/evaluable*. (Table 7)

Donation – *Possible*

There was one fatality following a Source Plasma donation where the evidence was indeterminate for attributing the complication to the donation or an alternative cause (e.g., underlying medical condition).

Donation – *Doubtful/Unlikely/Improbable*

There were a total of 12 fatalities following 10 Source Plasma donations, one Whole Blood donation, and one Apheresis Platelet donation in which the relationship between the donation and subsequent death of the donor was classified as *doubtful/unlikely/improbable.* In these cases the evidence was in favor of attributing the death to a cause other than the donation (e.g., underlying medical condition), but the donation could not be excluded.

Donation – *Ruled Out/Excluded*

There were a total of five fatalities following four Source Plasma donations, and one Whole Blood donation in which the donations were classified as *ruled out/excluded*. In these cases, there was clear evidence beyond a reasonable doubt for attributing the fatality to causes other than donation (e.g., drug overdoses, or underlying medical conditions).

Donation – *Not Determined/Assessable/Evaluable*

There were two fatalities following Source Plasma donations in which the relationship between the donation and subsequent death of the donor was classified as *not determined/assessable/evaluable*. In these cases, either insufficient evidence was available to determine whether a causal relationship existed, or the report appeared to contain incomplete or discrepant information surrounding the donor's death.

Table 7: Donation Fatalities with Imputability by Product FY2015

	Definite/ Certain	Probable/ Likely	Possible	Doubtful/ Unlikely/ Improbable	Ruled Out/ Excluded	Not Determined/ Assessable/ Evaluable	TOTAL
Source Plasma	-	-	1	10	4	2	**17**
Whole Blood	-	-	-	1	1	-	**2**
Apheresis Platelets	-	-	-	1	-	-	**1**
Apheresis Red Cells	-	-	-	-	-	-	**-**
Total	**-**	**-**	**1**	**12**	**5**	**2**	**20**

The changes in our review and classification process presented a challenge in terms of comparing FY2015 donation fatalities with previous years. In the majority of cases from FY2011 to FY2014, it was concluded that the donation could not be definitively ruled out as the cause of the donor's death. In these cases, the most common conclusion was *donation not ruled out*. Thorough medical review determined that the available evidence did not definitively rule out the donation being implicated in the donor's death, nor did the available evidence support a causal relationship between the donation and the donor's death. For FY2015, the cases classified as *doubtful/unlikely/improbable*, and *not determined/assessable/evaluable* would most accurately compare to the *donation not ruled out* cases from previous years. (Table 8)

Table 8: Donation "Not Ruled Out" by Product FY2011- FY2015

Donated Product	FY11	FY12	FY13	FY14	FY15	TOTAL
Source Plasma	6	9	4	4	12	**35**
Whole Blood	1	2	1	1	1	**6**
Apheresis Platelets	-	-	-	1	1	**2**
Apheresis Red Blood Cells	1	-	-	-	-	**1**
Total	**8**	**11**	**5**	**6**	**14**	**44**

(FY2015 numbers include *doubtful/unlikely/improbable* and *not determined/assessable/evaluable*)

Finally, donation fatalities definitively ruled out as being implicated in the donor's death are markedly less frequent than the combination of cases classified as *donation not ruled out*, *doubtful/unlikely/improbable*, and *not determined/assessable/evaluable* in FY2011 to FY2015. These reported donation fatality cases have been classified in years past as *donation ruled out*. For FY2015, the cases classified as *ruled out/excluded* would equally compare categorically to *donation ruled out* cases from previous years. (Table 9)

Table 9: Donation "Ruled Out" by Product FY2011-FY2015

Donated Product	FY11	FY12	FY13	FY14	FY15	TOTAL
Source Plasma	1	3	1	2	4	**11**
Whole Blood	1	-	1	-	1	**3**
Apheresis Platelets	-	-	-	-	-	**-**
Apheresis Red Blood Cells	-	-	-	-	-	**-**
Total	**2**	**3**	**2**	**2**	**5**	**14**