Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2011

I. Background

As previously mentioned in the annual summary of fatalities reported to the FDA in Fiscal Years (FY) 2005 through FY2010, 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 continue to decrease. Overall, the number of transfusion related fatalities reported to the FDA remains small in comparison to the total number of transfusions. In 2008, for example, there were approximately 24 million blood components transfused.[1] During the proximate period of FY2008, there were 54 reported transfusion related and potentially[2] transfusion related fatalities, with subsequent reports of 66 in FY2009, 64 in FY2010, and 58 in FY2011.

CBER is distributing this summary of transfusion fatality reports received by the FDA to make public the data received in FY2011, to provide the combined data received over the last five fiscal years, and to compare the FY2011 report to the fatality reports received in the previous four fiscal years.[3] We also include information on the infrequent reports of post-donation fatalities. 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 Sections 606.170(b) and 640.73 of Title 21, Code of Federal Regulations (21 CFR 606.170(b) and 21 CFR 640.73), 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.[4]

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[1] Report of the US Department of Health and Human Services. The 2009 national blood collection and utilization survey report. Washington, DC: US Department of Health and Human Services, Office of the Assistant Secretary of Health, 2011.

[2] Transfusion could not be ruled out as the cause of the fatality.

[3] The FY2005/FY2006 data are not discussed in this report, but are available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM129521.pdf

[4] 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.

A team of CBER medical officers reviews 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 reported fatality.

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,
2. Call us at 301-827-6220, or
3. Write us at:
   FDA/Center for Biologics Evaluation and Research
   Office of Compliance and Biologics Quality
   Division of Inspections and Surveillance (HFM-650)
   1401 Rockville Pike, Suite 200 North
   Rockville, Maryland 20852-1448

II. Results

During FY2011 (October 1, 2010, through September 30, 2011), we received a total of 79 fatality reports. Of these reports, 69 were transfusion recipient fatalities and 10 were post-donation fatalities.

Of the 69 transfusion recipient fatality reports, we concluded:

a) 30 (43%) of the fatalities were transfusion-related,
b) 28 (41%) of the fatalities were cases in which transfusion could not be ruled out as the cause of the fatality,
c) 11 (16%) of the fatalities were unrelated to the transfusion.

We summarize the results of our review in the following sections. Sections A through D of this document present the transfusion-related fatalities. Sections E and F and Table 4 present the fatality reports which were unrelated to the transfusion, or in which we could not rule out the transfusion as the cause of death. Section G presents the post-donation fatality reports.

A. Overall Comparison of Transfusion-Related Fatalities Reported from FY2007 through FY2011

In combined Fiscal Years 2007 through 2011, Transfusion Related Acute Lung Injury (TRALI) caused the highest number of reported fatalities (43%), followed by hemolytic transfusion reactions (total of 23%) due to non-ABO (13%) and ABO (10%) incompatibilities. Complications of Transfusion Associated Circulatory Overload (TACO), microbial infection, and anaphylactic reactions each accounted for a smaller number of reported fatalities (Table 1 and Figure 1). Over the last three fiscal years, the number of fatal TACO reports has decreased, from 12 (27%) in FY2009, to 8 (20%) in FY2010, and 4 (13%) in FY2011. Recent articles provide additional information about TACO. [5,6,7] The number of reported transfusion related deaths attributable to anaphylaxis[8,9] has remained small over the last five fiscal years; with the exception of one FY2010 case, in which IgA levels were not measured, patient IgA deficiency was ruled out in 11 of the 12 cumulatively reported cases. In another FY2010 case, a haptoglobin deficiency was possibly implicated in the patient's anaphylactic reaction.

Table 1: Transfusion-Related Fatalities by Complication, FY2007 through FY2011

Complication	FY07	FY07	FY08	FY08	FY09	FY09	FY10	FY10	FY11	FY11	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
TRALI*	34	65%	16	35%	13	30%	18	45%	10	33%	91	43%
HTR (non-ABO)	2	4%	7	15%	8	18%	5	13%	6	20%	28	13%
HTR (ABO)	3	6%	10	22%	4	9%	2	5%	3	10%	22	10%
Microbial Infection	6	12%	7	15%	5	11%	2	5%	4	13%	24	11%
TACO	5	10%	3	7%	12	27%	8	20%	4	13%	32	15%
Anaphylaxis	2	4%	3	7%	1	2%	4	10%	2	7%	12	6%
Other	0	0%	0	0%	1**	2%	1**	3%	1**	3%	3	1%
Totals	52	100%	46	100%	44	100%	40	100%	30	100%	212	100%

*These numbers include both "TRALI" and "possible TRALI" cases[10,11]

**Other:

FY2009: Hypotensive Reaction[12]
FY2010: Graft vs. Host Disease (GVHD)
FY2011: GVHD

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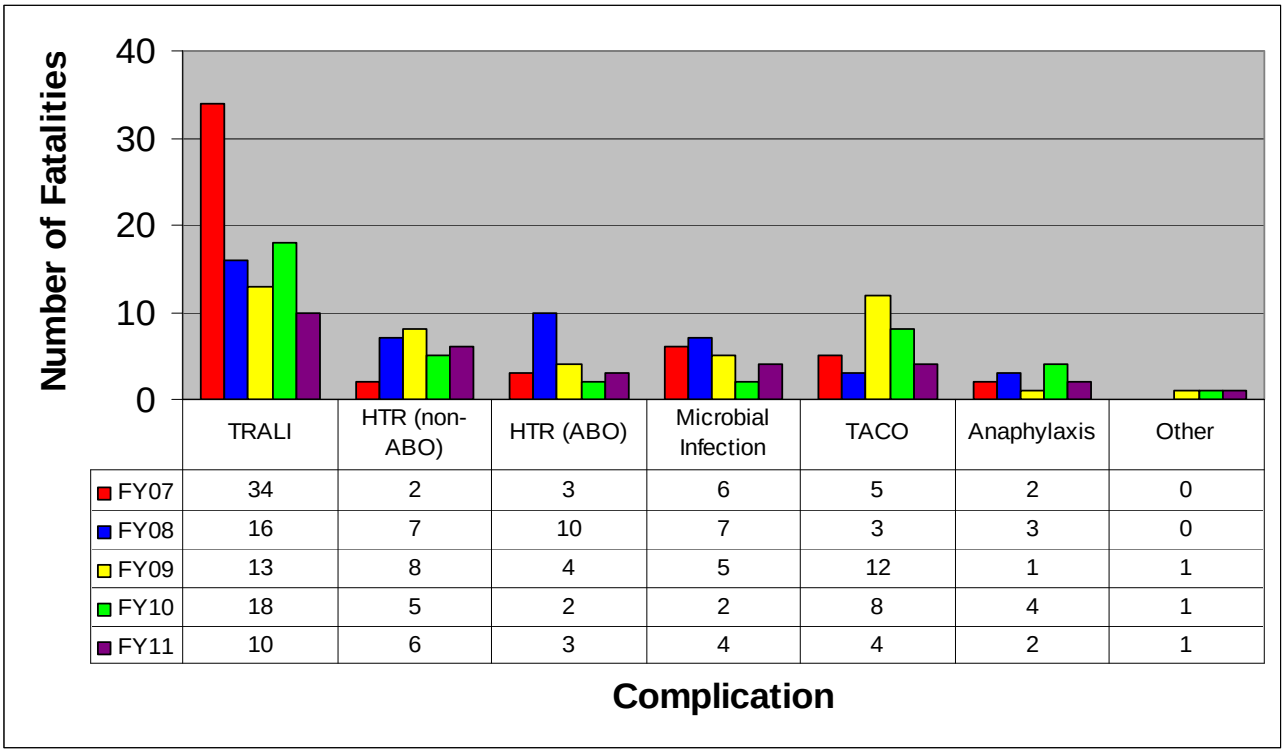
[5] Popovsky MA. Transfusion associated circulatory overload: the plot thickens. Transfusion 2009;49:2-4.
[6] Narick C, Triulzi J, Yazer M. Transfusion-associated circulatory overload after plasma transfusion. Transfusion 2012;52:160-165.
[7] Tobian A, Sokoll L, Tisch D, et al. N-terminal pro-brain natriuretic peptide is a useful diagnostic marker for transfusion-associated circulatory overload. Transfusion 2008;48:1143-1150.
[8] Nara A, Aki T, et al. Death due to blood transfusion-induced anaphylactic shock: A case report. Legal Medicine 2010:12:148-150.
[9] Shimada E, Odagiri M, Chaiwong K, et al. Detection of Hp^{del} among Thais, a deleted allele of the haptoglobin gene that causes congenital haptoglobin deficiency. Transfusion 2007;47:2315-2321.
[10] 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.
[11] 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.
[12] Centers for Disease Control and Prevention. The National Healthcare Safety Network (NHSN) Biovigilance Component protocol. 2009:17.

Figure 1: Transfusion-Related Fatalities by Complication, FY2007 through FY2011



	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY07	34	2	3	6	5	2	0
FY08	16	7	10	7	3	3	0
FY09	13	8	4	5	12	1	1
FY10	18	5	2	2	8	4	1
FY11	10	6	3	4	4	2	1

B. Transfusion Related Acute Lung Injury (TRALI)

While TRALI represented 43% of confirmed transfusion related fatalities reported to CBER over the last five fiscal years, there was a decrease in TRALI fatalities, from 18 (45% of confirmed transfusion related fatalities) in FY2010, to 10 (33%) in FY2011, and an overall decrease in TRALI fatalities over the reporting period. In FY2007, TRALI accounted for 65% of confirmed transfusion related fatalities, compared to 33% in FY2011 (Table 1).

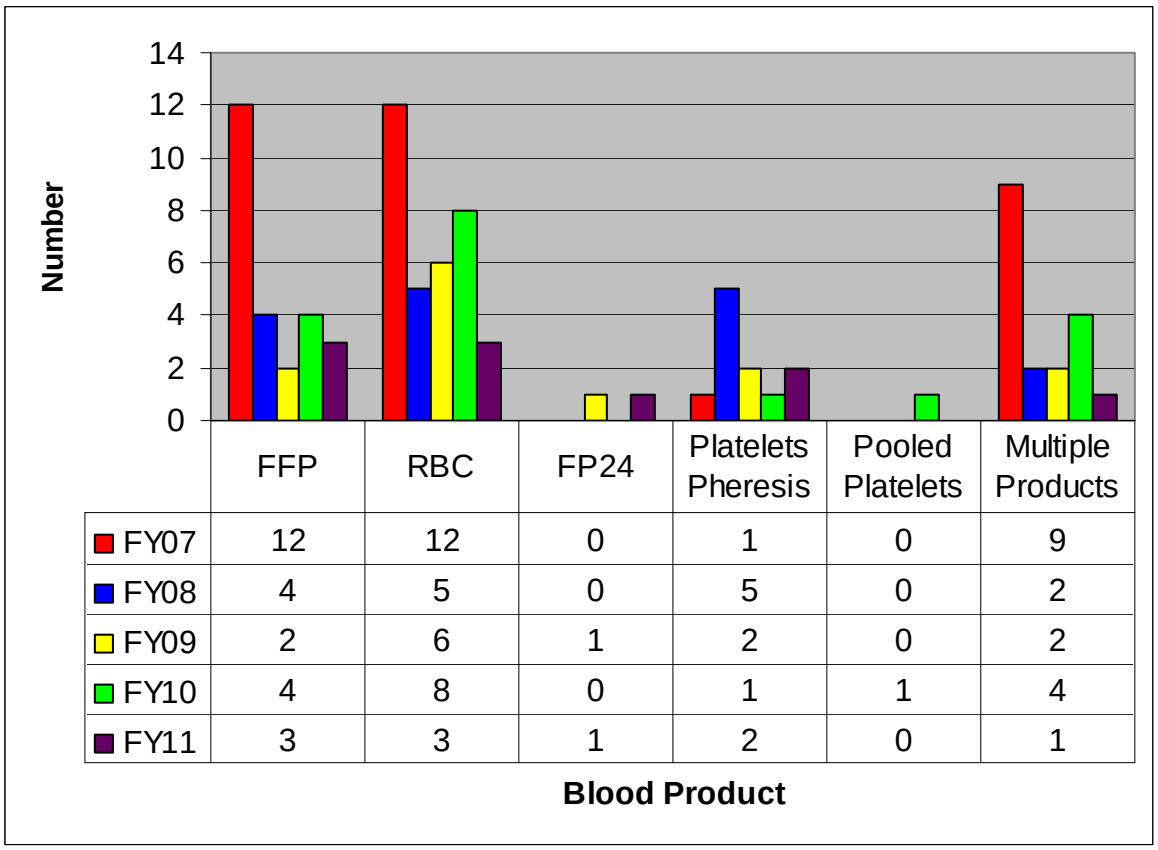
In FY2011, the 10 TRALI cases were temporally associated with products from 24 donors. HLA/HNA antibody test results were available for 21 of these donors. Donor genders were identified for 22 of the donors, which included 11 males and 11 females. Our limited data do not elucidate the role of particular donor antibodies or donor gender.

In five cases, reporters who included patient testing data were able to match donor antibodies with recipient cognate antigens; however, there were no antigen/antibody combinations that appeared more frequently than others.

Although the transfusion community has taken voluntary measures to reduce the risk of TRALI, this complication of transfusion continues to be one of the leading causes of transfusion-related fatalities reported to the FDA. However, the number of TRALI cases associated with plasma products continues to decrease (Figure 2). Current literature describes the results of continued

international efforts to reduce the use of plasma for transfusion prepared from female donors, and other strategies to reduce the incidence of TRALI.[13,14,15,16,17,18,19,20]

Figure 2: Reports of TRALI Cases by Implicated Blood Product, FY2007 through FY2011



	FFP	RBC	FP24	Platelets Pheresis	Pooled Platelets	Multiple Products
FY07	12	12	0	1	0	9
FY08	4	5	0	5	0	2
FY09	2	6	1	2	0	2
FY10	4	8	0	1	1	4
FY11	3	3	1	2	0	1

[13] Middleburg RA, van Stein D, Zupanska B, et al. Female donors and transfusion-related acute lung injury. A case-referent study from the International TRALI Unisex Research Group. Transfusion 2010;50:2447-2454.
[14] 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.
[15] Shaz BH, Stowell SR, Hillyer CC. Transfusion-related acute lung injury: from bedside to bench and back. Blood 2011;117:1463-1471.
[16] 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.
[17] Arinsburg SA, Skerrett DL, Karp JK, et al. (2011), Conversion to low transfusion-related acute lung injury (TRALI)-risk plasma significantly reduces TRALI. Transfusion. doi: 10.1111/j.1537-2995.2011.03403.x.
[18] Lucas G, Win N, Calvert A, et al. (2011), Reducing the incidence of TRALI in the UK: the results of screening for donor leukocyte antibodies and the development of national guidelines. Vox Sanguinis. doi: 10.1111/j.1423-0410.2011.01570.x
[19] Toy P, Ognjen G, Bacchetti P, et al. Transfusion-related lung injury: incidence and risk factors. Blood 2012;119:1757-1767.
[20] 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.

C. Hemolytic Transfusion Reactions

In FY2011, the number of reported fatal hemolytic transfusion reactions increased from 7 (18%) in FY2010 to 9 (30%) of confirmed transfusion related fatalities. There were increases in both ABO hemolytic reactions - from 2 (5%) in FY2010, to 3 (10%) in FY2011, and non-ABO hemolytic reactions – from 5 (13%) in FY2010, to 6 (20%) in FY2011 (Figure 1 and Table 1). Despite these recently observed increases, a downward trend in the total number of reported fatalities due to hemolytic transfusion reactions has continued since FY2001 (Figure 3).

Table 2: Hemolytic Transfusion Reactions by Implicated Antibody, FY2007 through FY2011

	FY07	FY07	FY08	FY08	FY09	FY09	FY10	FY10	FY11	FY11	Total	Total
Antibody	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
ABO	3	60%	10	59%	4	33%	2	29%	3	33%	22	44%
Multiple Antibodies*	1	20%	1	6%	2	17%	3	43%	1	11%	8	16%
Other**	0	0%	0	0%	2	17%	0	0%	2	22%	4	8%
Fy^a	0	0%	2	12%	1	8%	0	0%	1	11%	4	8%
Jk^b	0	0%	2	12%	0	0%	1	14%	0	0%	3	6%
Kell	0	0%	2	12%	0	0%	0	0%	1	11%	3	6%
Jk^a	1	20%	0	0%	2	17%	0	0%	0	0%	3	6%
c	0	0%	0	0%	0	0%	0	0%	1	11%	1	2%
Js^b	0	0%	0	0%	1	8%	0	0%	0	0%	1	2%
Co^a	0	0%	0	0%	0	0%	1	14%	0	0%	1	2%
Totals	5	100%	17	100%	12	100%	7	100%	9	100%	50	100%

*Multiple Antibodies:

FY2007: anti-M+C

FY2008: anti-C+K+Fy^b+S+N+V+Js^a+Go^a+warm autoantibody.

FY2009: antibody combinations included E+Jk^b, S+Jk^a+Jk^b+K+Fy^a+Fy^b+V+C+N+HTLA

FY2010: antibody combinations included D+C+K+S, Jk^b+FY^a+C+E+K+Le^a+Le^b, c+E+Jk^b+K+Le^a+panagglutinin+cold agglutinin

FY2011: anti- Jk^a +c+E+M (warm reacting)

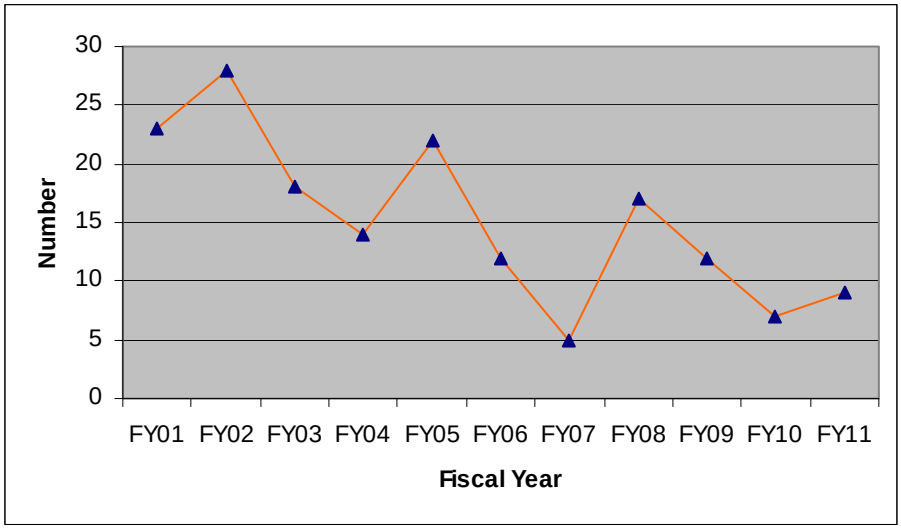
**Other:

FY2009: Includes one report of an unidentified warm autoantibody and one report of Hyperhemolysis Syndrome. Information about this syndrome has been published.[21]

FY2011: Includes one report of Hyperhemolysis Syndrome, and one report of an unidentified antibody..

[21]Win N, New H, et al. Hyperhemolysis Syndrome in sickle cell disease: case report (recurrent episode) and literature review. Transfusion 2008;48:1231-1238.

Figure 3: Hemolytic Transfusion Reactions, FY2001 through FY2011



In FY2011, there were three reports of fatal hemolytic transfusion reactions due to ABO-incompatible transfusions:

Two of these fatalities were attributed to errors:

- In one case, correctly labeled red blood cells (RBC's) were issued in separate coolers for two patients. Failure to properly identify one patient resulted in transfusion of an incompatible group A RBC to the group O recipient.
- The second case occurred after initiation of a massive transfusion protocol for a trauma patient whose blood group was unknown. The container released to the emergency room (ER) inadvertently included both group O and group A RBC units. The patient was later determined to be group O.

The remaining case illustrates the potential risk associated with ABO-incompatible plasma in plateletpheresis products, when donor ABO antibodies in the transfusion product are incompatible with the patient's red blood cells and are present in sufficiently high titers to cause *in vivo* hemolysis. This case involved transfusion from a donor with a high-titer anti-A.[22] Over the last five years there has been one other fatality due to transfusion of apheresis platelets with a high-titer blood group antibody, an anti-B (FY2008). In both cases, the recipients' blood groups had recently changed following ABO-mismatched hematopoietic stem cell transplants.

In FY2011, there were six reports of non-ABO fatal hemolytic transfusion reactions:

Two of the six cases were attributed to errors in the lab:

- In one case, an anti-K was correctly identified; however, an error in pulling segments for K typing and compatibility testing resulted in the transfusion of an incompatible, K positive unit.
- In a second case, a positive antibody screen misread as negative resulted in transfusion of an incompatible Fy^a positive unit. The immediate spin compatibility test did not detect the incompatibility.
- The remaining four cases illustrate difficult compatibility issues without clear answers, including three patients with complex RBC antibody presentations which worsened following transfusion, and one case of delayed hemolytic transfusion reaction/hyperhemolysis syndrome in a sickle cell patient.

D. Microbial Infection

In FY2011, there were four reported fatalities attributed to microbial infection, compared to two in FY2010. *Babesia microti,* associated with a transfusion of Red Blood Cells, was implicated in

[22] Fontaine MJ, Mills AM, et al. How we treat: risk mitigation for ABO-incompatible plasma in plateletpheresis products. Transfusion. doi: 10.1111/j.1537-2995.2012.03596.x.

one of these fatalities, and *S. aureus*, *K. pneumoniae*, and *M. morganii* were implicated, one case each, in platelet transfusion fatalities. Apheresis Platelets were associated with the *K. pneumoniae* and *M. morganii* infections, and the *S. aureus* infection was associated with a unit of Pooled Platelets (Figure 4).

Babesia accounts for 42% (10/24) of reported deaths due to microbial infection over the previous five fiscal years, followed by *Staphylococcus aureus*, which accounts for 21% (5/24) (Table 3).

Recent articles provide additional information about transfusion transmitted *Babesia*.[23,24]

During the five-year reporting period, all of the implicated bacteria associated with fatal microbial infections were facultative anaerobes.

Figure 5 shows a downward trend in the number of bacterial infections associated with Apheresis Platelets since FY2001.

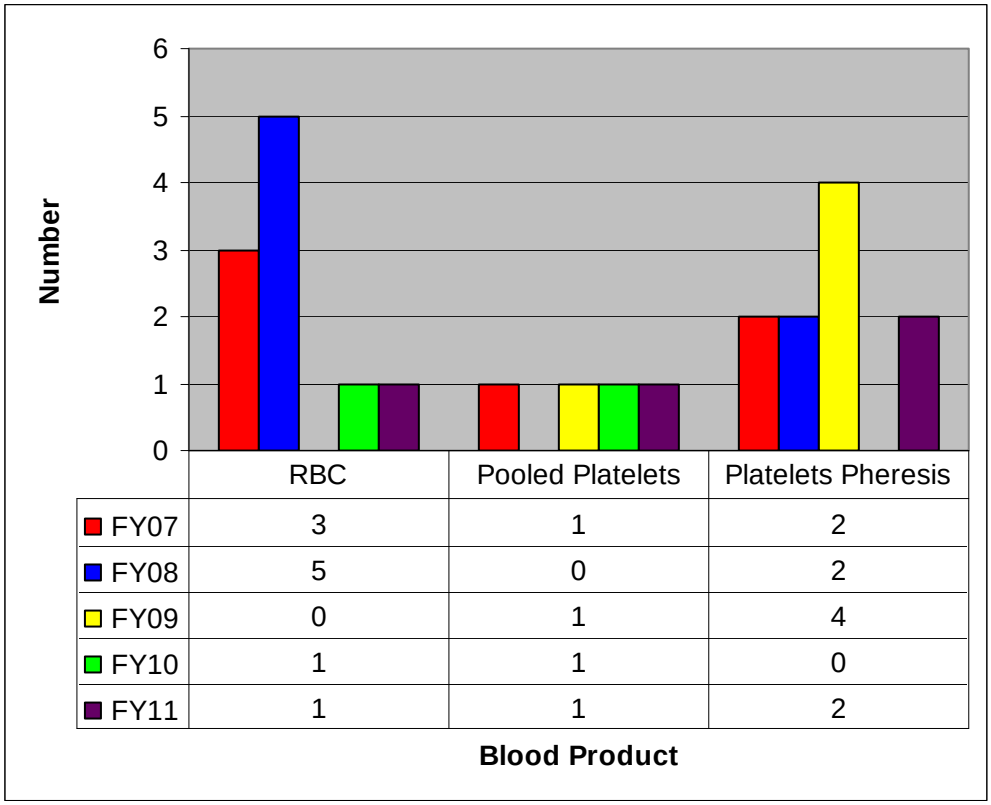
Table 3: Microbial Infection by Implicated Organism, FY2007 through FY2011

Organism	FY07	FY07	FY08	FY08	FY09	FY09	FY10	FY10	FY11	FY11	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
*Babesia**	3	50%	5	71%	0	0%	1	50%	1	25%	10	42%
Staphylococcus aureus	1	17%	1	14%	2	40%	0	0%	1	25%	5	21%
Escherichia coli	0	0%	0	0%	0	0%	1	50%	0	0%	1	4%
Staphylococcus epidermidis	0	0%	1	14%	0	0%	0	0%	0	0%	1	4%
Morganella morganii	0	0%	0	0%	0	0%	0	0%	1	25%	1	4%
Streptococcus dysgalactiae (Group C)	1	17%	0	0%	0	0%	0	0%	0	0%	1	4%
Klebsiella oxytoca	1	17%	0	0%	0	0%	0	0%	0	0%	1	4%
Streptococcus viridans	0	0%	0	0%	1	20%	0	0%	0	0%	1	4%
Streptococcus pneumoniae	0	0%	0	0%	1	20%	0	0%	0	0%	1	4%
Staphylococcus warneri	0	0%	0	0%	1	20%	0	0%	0	0%	1	4%
Klebsiella pneumoniae	0	0	0	0	0	0	0	0	1	25%	1	4%
Total	6	100%	7	100%	5	100%	2	100%	4	100%	24	100%

*Nine *Babesia microti* and one probable *Babesia MO-1* species

[23] Gubernot DM, Nakhasi HL, Mied PA, et al. Transfusion-transmitted babesiosis in the United States: summary of a workshop. Transfusion 2009;49:2759-2771.
[24] Tonetti L, Eder AE, Dy B, et al. Transfusion-transmitted *Babesia Microti* identified through hemovigilance. Transfusion 2009;49:2557-2563.

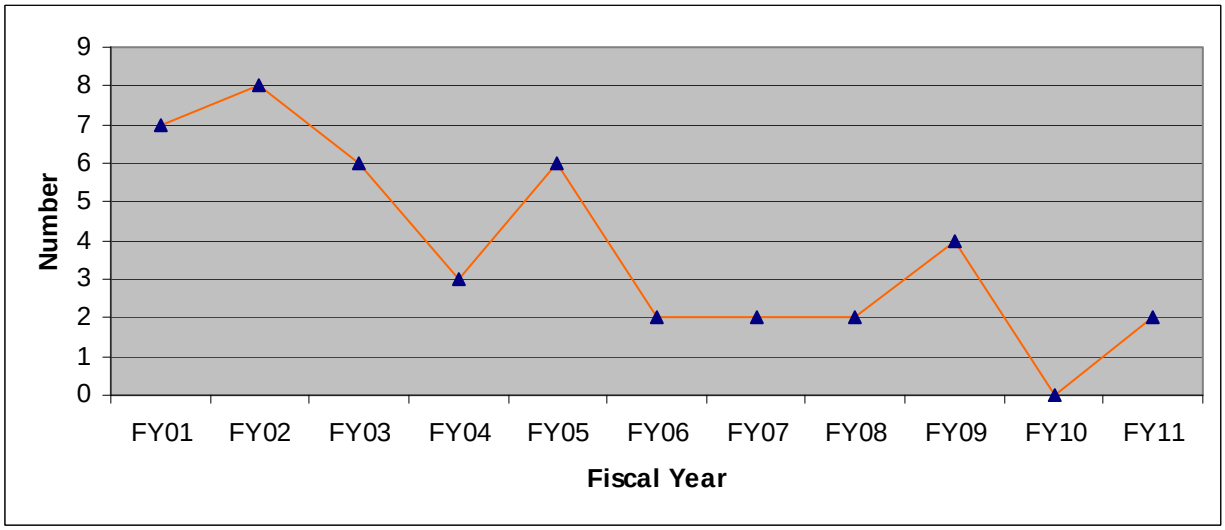
Figure 4: Microbial Infection by Implicated Blood Product, FY2007 through FY2011



	RBC	Pooled Platelets	Platelets Pheresis
FY07	3	1	2
FY08	5	0	2
FY09	0	1	4
FY10	1	1	0
FY11	1	1	2

Red Blood Cells microorganisms: *B. microti (9), B. MO1(1)*
Pooled Platelets microorganisms: *S. aureus (1), E. coli (1), S. dysgalactiae (1), S. pneumoniae (1)*
Platelets Pheresis microorganisms: *S. aureus (4), S. marcescens (1), S. epidermidis (1), M. morganii (1), K. oxytoca (1), S. viridans (1), S. warneri (1), K. pneumoniae (1)*

Figure 5: Bacterial Infection by Apheresis Platelets, FY2001 through FY2011



E. Transfusion Not Ruled Out

As noted above, 28 (41%) of the 69 reported fatalities in FY2011 were cases in which the transfusion could not be ruled out as the cause of the fatality. In these reported fatalities, the reporting facilities were unable to identify a specific complication of transfusion as the cause of death. Often, these patients had multiple co-morbidities, and after review of the investigation documentation, our medical reviewers could neither confirm nor rule out the transfusion as the cause of the fatality (Table 4). Therefore, we did not include these 28 reported fatalities in the analysis in Sections II.A through II.D (transfusion-related fatalities), above.

F. Not Transfusion Related

After reviewing the initial fatality reports and the investigation documentation, we categorized 11 (16%) of the 69 reported fatalities as "Not Transfusion Related." Our medical reviewers concluded that, while there was a temporal relationship between transfusion and subsequent death of the recipient, there was no evidence to support a causal relationship (Table 4). Thus, we did not include these reported fatalities in the analysis in Sections II.A through II.D (transfusion-related fatalities), above.

Table 4: Fatalities Not Related to Transfusion or Transfusion Not Ruled Out, FY2007 through FY2011

	FY07	FY08	FY09	FY10	FY11
Transfusion Not Ruled Out	11	8	22	24	28
Not Transfusion Related	13	18	8	7	11
Totals	24	26	30	31	39

G. Post-Donation Fatalities

In FY2011, we received seven reports of fatalities following Source Plasma donation, and one reported fatality following a Double Red Blood Cell (apheresis) donation. For all eight cases, although the donations could not be definitively ruled out as being implicated in the donor's death, our medical reviewers found no evidence to support a causal relationship between the donation and subsequent death of the donor.

We received two FY2011 reports of fatalities following Whole Blood donation. In one case, the donation was ruled out as being implicated in the donor's death. In the remaining case, although the donation could not be definitively ruled out as being implicated in the donor's death, our medical reviewers found no evidence to support a causal relationship between the donation and subsequent death of the donor.

Over the five-year reporting period, there was one FY2010 Source Plasma donation, in addition to the FY2011 Whole Blood donation mentioned above, in which the donation was definitively ruled out as the cause of the fatality. For the remaining cases, our medical reviewers concluded that, while there was a temporal link between the donations and the fatalities, there was no

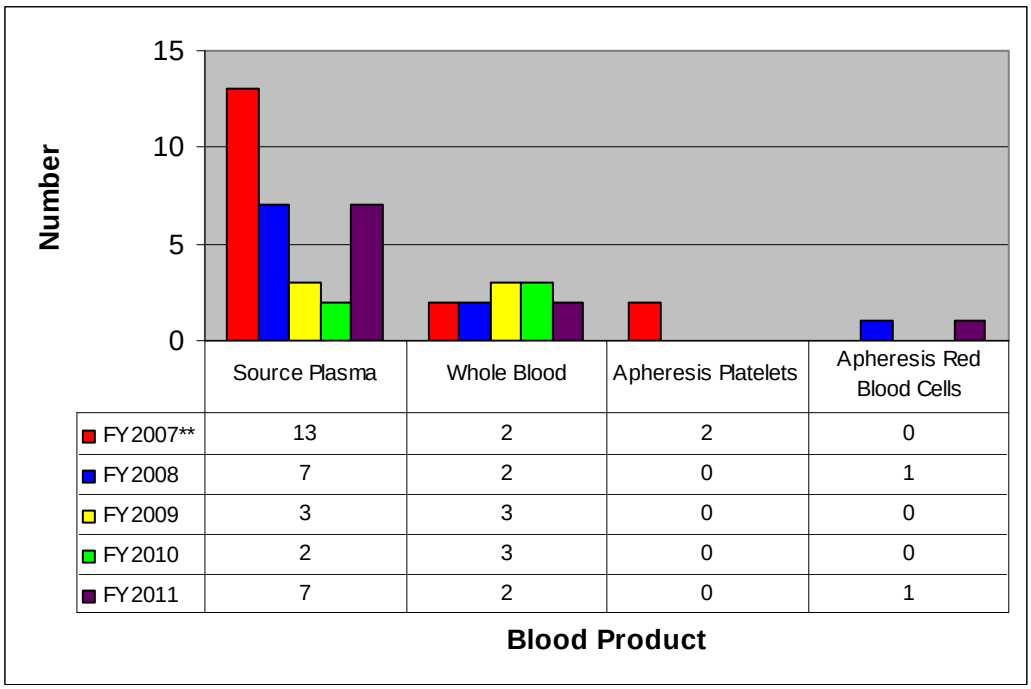
evidence to support a causal relationship between the donations and subsequent death of the donors (Table 5 and Figure 6).

Table 5: Post-Donation Fatality Reports by Donated Product, FY2007 through FY2011

Donated Product	FY07	FY08	FY09	FY10	FY11
Source Plasma	13	7	3	2	7
Whole Blood	2**	2	3	3	2
Apheresis Platelets	2	0	0	0	0
Apheresis Red Blood Cells	0	1	0	0	1
Total	17	10	6	5	10

**Both were autologous donations

Figure 6: Post-Donation Fatality Reports, FY2007 through FY2011



**Both Whole Blood donations in FY2007 were autologous