Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2010

I. Background

As previously mentioned in the annual summary of fatalities reported to the FDA in Fiscal Years (FY) 2005 through FY2009, 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 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, and 64 in FY2010.

CBER is distributing this summary of transfusion fatality reports received by the FDA to make public the data received in FY2010, to provide the combined data received over the last six fiscal years, and to compare the FY2010 reports to the fatality reports received in the previous five fiscal years. 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.[3]

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.

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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] 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,
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 FY2010 (October 1, 2009, through September 30, 2010), we received a total of 76 fatality reports. Of these reports, 71 were transfusion recipient fatalities and 5 were post-donation fatalities.

Of the 71 transfusion recipient fatality reports, we concluded:

a) 40 of the fatalities were transfusion-related,
b) 24 of the fatalities were cases that transfusion could not be ruled out as the cause of the fatality,
c) 7 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 FY2005 through FY2010

In combined Fiscal Years 2005 through 2010, Transfusion Related Acute Lung Injury (TRALI) caused the highest number of reported fatalities (47%), followed by hemolytic transfusion reactions (24%) due to non-ABO (15%) and ABO (9%) incompatibilities. Complications of

microbial infection, Transfusion Associated Circulatory Overload (TACO), and anaphylactic reactions each accounted for a smaller number of reported fatalities (Table 1 and Figure 1). Over the last six fiscal years, we have seen an overall increase in reports of TACO fatalities – from one report in FY2005 to 12 reports in FY2009, and 8 reports in FY2010.[4] The number of transfusion related deaths due to anaphylaxis has remained very small over the last 6 fiscal years, and reports indicate that patient IgA deficiency was ruled out in all 11 cases.[5] In one of these cases, a possible haptoglobin deficiency may have been implicated in the patient's anaphylactic reaction.[6]

Table 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2010

Complication	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	FY09	FY09	FY10	FY10	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
TRALI	29	47%	35	56%	34*	65%	16*	35%	13*	30%	18*	45%	145	47%
HTR (non-ABO)	16	26%	9	14%	2	4%	7	15%	8	18%	5	13%	47	15%
HTR (ABO)	6	10%	3	5%	3	6%	10	22%	4	9%	2	5%	28	9%
Microbial Infection	8	13%	7	11%	6	12%	7	15%	5	11%	2	5%	35	11%
TACO	1	2%	8	13%	5	10%	3	7%	12	27%	8	20%	37	12%
Anaphylaxis	0	0%	1	2%	2	4%	3	7%	1	2%	4	10%	11	4%
Other	2**	3%	0	0%	0	0%	0	0%	1**	2%	1**	3%	4	1%
Totals	62	100%	63	100%	52	100%	46	100%	44	100%	40	100%	307	100%

*In FY2007, our review committee began using the Canadian Consensus Conference criteria[7,8] for evaluating TRALI cases – these numbers includes both "TRALI" and "possible TRALI" cases

**Other:

FY2005: Includes 1 case of Graft vs. Host Disease (GVHD) and 1 therapeutic plasma exchange (TPE) error (use of a treatment column contraindicated due to patient's medical history)

FY2009: Hypotensive Reaction[9]

FY2010: Includes 1 case of GVHD

[4] Popovsky MA. Transfusion associated circulatory overload: the plot thickens. Transfusion 2009;49:2-4.

[5] Nara A, Aki T, et al. Death due to blood transfusion-induced anaphylactic shock: A case report. Legal Medicine 2010:12:148-150.

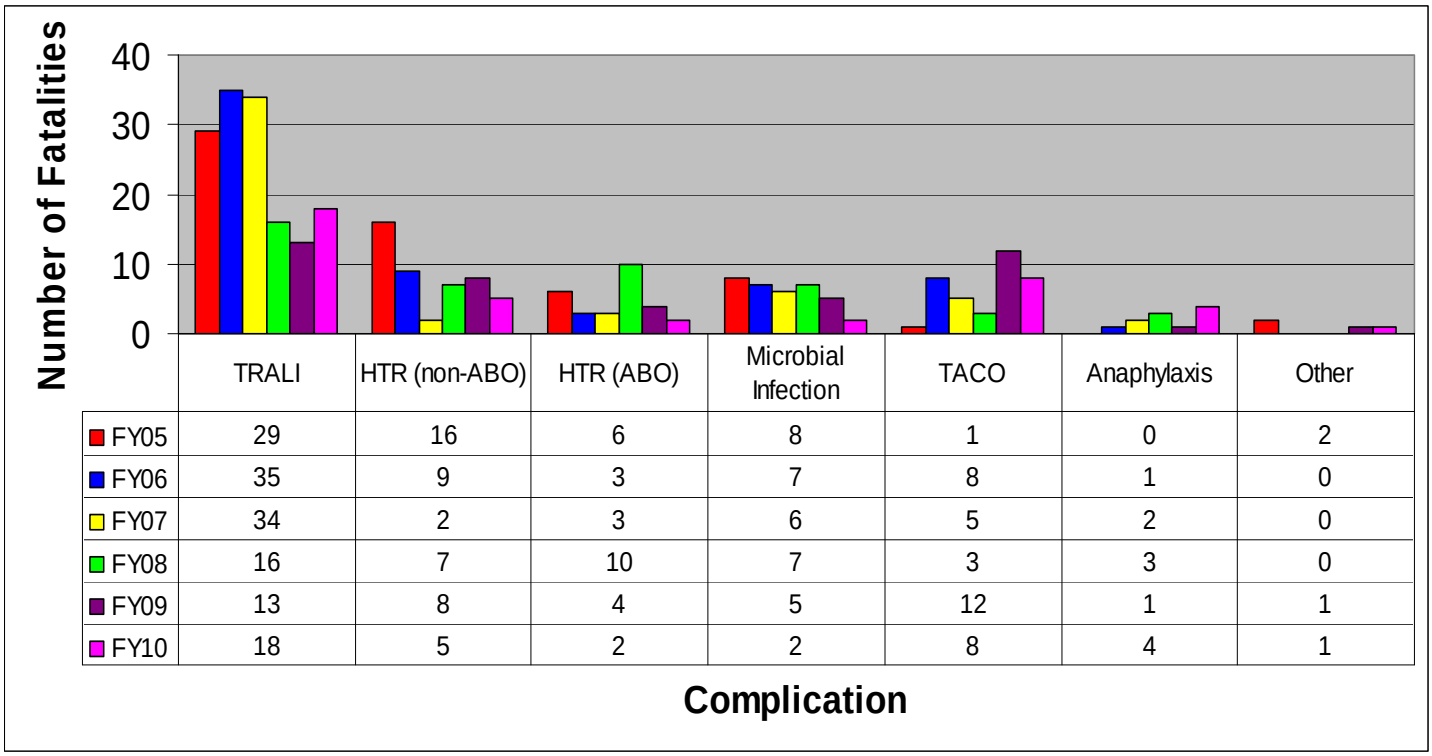
[6] Shimada E, Odagiri M, Chaiwong K, et al. Detection of Hp^{del} among Thais, a deleted allele of the haptoglobin gene that causes congenital haptoglobin deficiency. Transfusion 2007;47:2315-2321.

[7] 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.

[8] 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.

[9] Centers for Disease Control and Prevention. The National Healthcare Safety Network (NHSN) Biovigilance Component protocol. 2009:17.

Figure 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2010



	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY05	29	16	6	8	1	0	2
FY06	35	9	3	7	8	1	0
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

B. Transfusion Related Acute Lung Injury (TRALI)

TRALI represented 47% of confirmed transfusion related fatalities reported to CBER over the last six fiscal years. While there was an increase in TRALI fatalities, from 13 (30% of confirmed transfusion related fatalities) in FY2009 to 18 (45% of confirmed transfusion related fatalities) in FY2010, there has been an overall decrease in TRALI fatalities, from 34 (65% of confirmed transfusion related fatalities) in FY2007, to 18 (45% of confirmed transfusion related fatalities in FY2010) (Table 1). The number of TRALI fatalities associated with receipt of Plasma products has decreased from 23 (66% of TRALI cases) in FY2006, to 4 (22%) in FY2010. In FY2010, there was one TRALI fatality (6% of TRALI cases) associated with receipt of Apheresis Platelets, compared to 2 (15% of TRALI cases) in FY2009, and 5 (31% of TRALI cases) in FY2008 (Figure 2).

In Calendar Year 2008, transfused plasma products accounted for approximately 19% of all transfused components, platelet units (using apheresis equivalent units) – approximately 9%, and red blood cell-containing products – approximately 63%.[10] In comparison, for the combined fiscal years 2005-2010, Fresh Frozen Plasma (FFP) and other plasma accounted for 43% (62/145) of reported TRALI fatalities, apheresis platelets accounted for 10% (15/145), and Red Blood Cells accounted for 28% (41/145).

[10] Report of the US Department of Health and Human Services, op.cit. pp. 25-28.

In FY2010, the 18 TRALI cases were temporally associated with products from 86 donors. HLA/HNA antibody test results were available for only 41 of these donors. Similarly, donor genders were identified for only 53 of these donors. Our limited data do not elucidate the role of particular donor antibodies or donor gender.

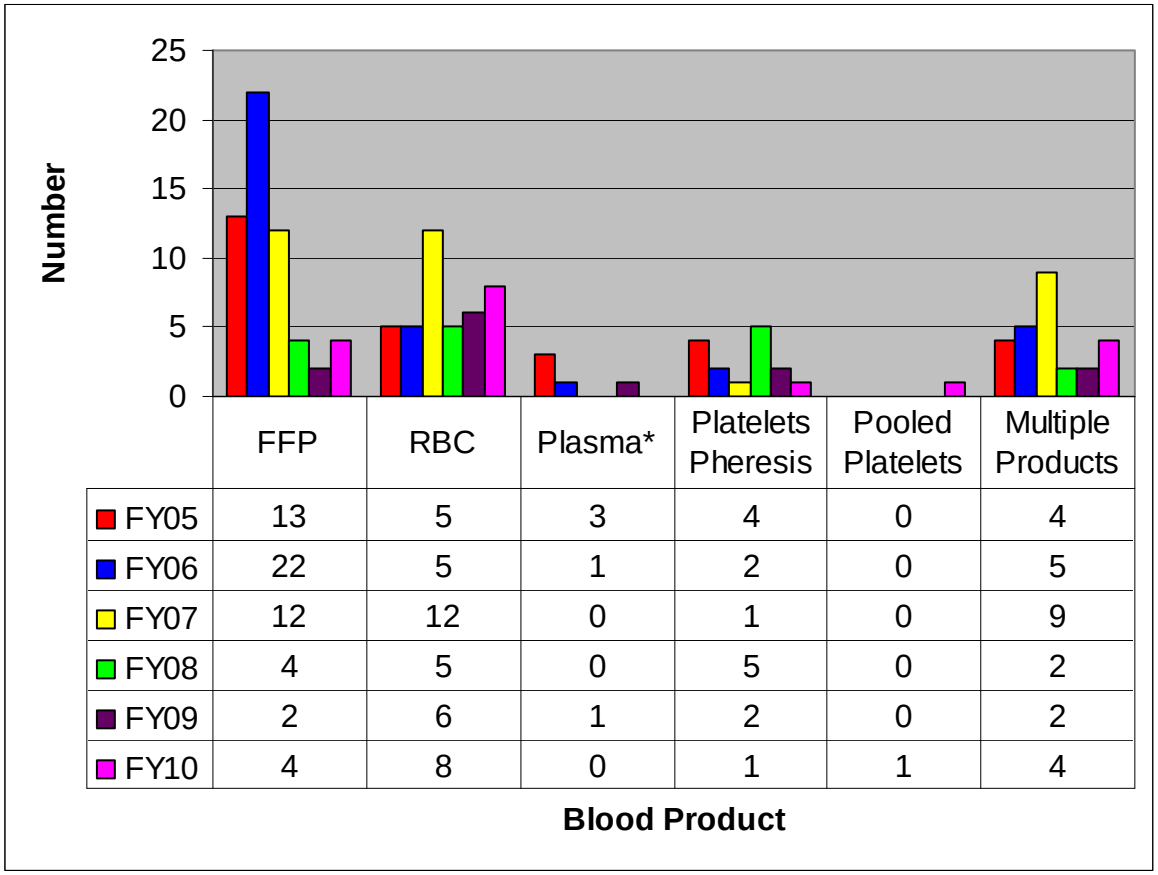
In 7 cases, reporters who included patient testing data were able to match donor antibodies with recipient cognate antigens; however, there were no antigen/antibody combinations that appeared more frequently than others.

In one TRALI case the recipient had antibodies that matched donor antigens.

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.[11,12,13,14]

[11] 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.
[12] 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 2010 Dec 6.doi:10.1111/j.1537-2995.2010.02969.x. [Epub ahead of print].
[13] Shaz BH, Stowell SR, Hillyer CC. Transfusion-related acute lung injury: from bedside to bench and back. Blood 2011;117:1463-1471.
[14] 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.

Figure 2: Reports of TRALI Cases by Implicated Blood Product, FY2005 through FY2010



	FFP	RBC	Plasma*	Platelets Pheresis	Pooled Platelets	Multiple Products
FY05	13	5	3	4	0	4
FY06	22	5	1	2	0	5
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

*FY2005: Includes 2 FP24 (Plasma frozen within 24 hours after collection) and 1 Liquid Plasma
*FY2006: Includes 1 FP24
*FY2009: Includes 1 FP24

C. Hemolytic Transfusion Reactions

In FY2010, the number of reported fatal hemolytic transfusion reactions decreased from 12 (27%) in FY2009 to 7 (18%) of confirmed transfusion related fatalities. There were decreases in both ABO hemolytic reactions - from 4 (9%) in FY2009, to 2 (5%) in FY2010, and non-ABO hemolytic reactions – from 8 (18%) in FY2009 to 5 (13%) in FY2010 (Figure 1 and Table 2). We continue to see an overall decrease in the number of reported fatalities due to hemolytic transfusion reactions since FY2001 (Figure 3).

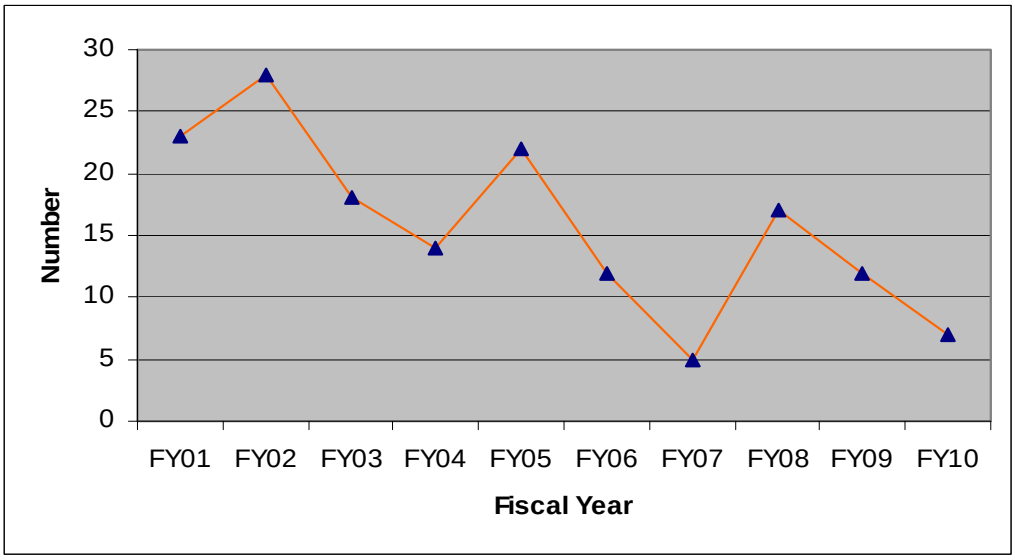
Table 2: Hemolytic Transfusion Reactions by Implicated Antibody, FY2005 through FY2010

	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	FY09	FY09	FY10	FY10	Total	Total
Antibody	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
ABO	6	27%	3	25%	3	60%	10	59%	4	33%	2	29%	28	37%
Multiple Antibodies*	6	27%	4	33%	1	20%	1	6%	2	17%	3	43%	17	23%
Jk[b]	3	14%	0	0%	0	0%	2	12%	0	0%	1	14%	6	8%

Other**	3	14%	0	0%	0	0%	0	0%	2	17%	0	0%	5	7%
Kell	1	5%	1	8%	0	0%	2	12%	0	0%	0	0%	4	5%
Jk^a	1	5%	1	8%	1	20%	0	0%	2	17%	0	0%	5	7%
Fy^a	0	0%	1	8%	0	0%	2	12%	1	8%	0	0%	4	5%
Fy^b	0	0%	1	8%	0	0%	0	0%	0	0%	0	0%	1	1%
E	1	5%	0	0%	0	0%	0	0%	0	0%	0	0%	1	1%
I	1	5%	0	0%	0	0%	0	0%	0	0%	0	0%	1	1%
Js^a	0	0%	1	8%	0	0%	0	0%	0	0%	0	0%	1	1%
Js^b	0	0%	0	0%	0	0%	0	0%	1	8%	0	0%	1	1%
Co^a	0	0	0	0%	0	0%	0	0%	0	0%	1	14%	1	1%
Totals	22	100%	12	100%	5	100%	17	100%	12	100%	7	100%	75	100%

*FY2005 antibody combinations included E+c, Fy^a+K, Fy^a+Jk^b, E+I+A_1, possible C+E+K, Wr^a+warm autoantibody.
*FY2006 antibody combinations included E+c, S+K, Jk^b+cold agglutinin, unidentified auto- and alloantibodies.
*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
**FY2005: Includes one report of non-immune hemolysis, one report of an unidentified antibody to a low incidence antigen, and one report of Cold Agglutinin Syndrome due to *Mycoplasma pneumonia* or Lymphoma.
**FY2009: Includes one report of an unidentified warm autoantibody and one report of Hyperhemolysis Syndrome[15]

Figure 3: Hemolytic Transfusion Reactions, FY2001 through FY2010



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

In FY2010, there were two reports of fatal hemolytic transfusion reactions due to ABO-incompatible blood transfusions:

- 1 case: recipient identification error at the time of transfusion (nursing error)
- 1 case: following an ABO mismatched cord blood transplant, red blood cells of the donor's ABO group were transfused (no apparent error)

D. Microbial Infection

In FY2010, there were 2 reported fatalities attributed to microbial infection, compared to 5 in FY2009. *Babesia microti,* associated with RBC transfusion, was implicated in one of these fatalities and *Escherichia coli*, associated with transfusion of Pooled Platelets, was implicated in the other. *Babesia* now accounts for 31% (11/35) of reported deaths due to microbial infection over the previous six fiscal years, followed by *Staphylococcus aureus*, which accounts for 20% (7/35) (Table 3).

After seven years with no reported deaths due to transfusion-transmitted Babesiosis, CBER received reports of 11 transfusion-transmitted Babesiosis deaths during fiscal years 2006 through 2010. Recent articles provide additional information about this topic.[16,17]

There was one strict anaerobe, *Eubacterium limosum,* implicated in a fatal bacterial infection during the 5-year reporting period; this fatality occurred in FY2005. The remaining bacteria are facultative anaerobes.

For the first time since posting the Fatality Annual Summary Report, there were no reports in FY2010 of fatal microbial infections associated with apheresis platelets (Figure 4). Figure 5 shows the overall decrease in the number of bacterial infections associated with apheresis platelets since FY2001.

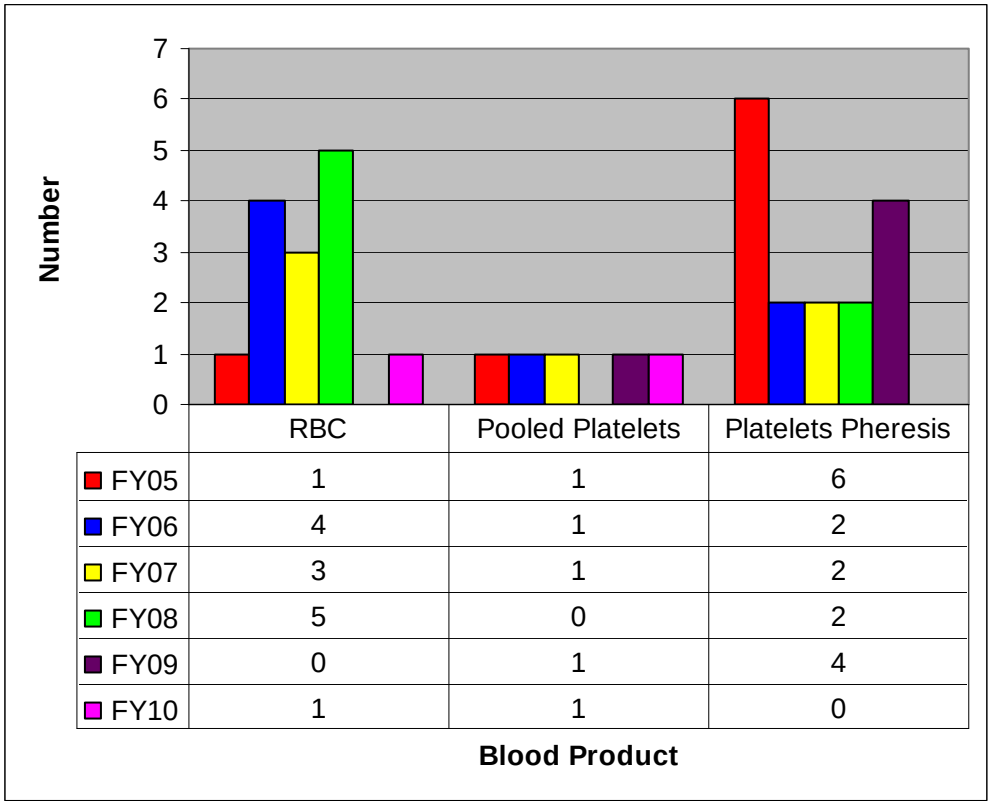
[16] Gubernot DM, Nakhasi HL, Mied PA, et al.Transfusion-transmitted babesiosis in the United States: summary of a workshop. Transfusion 2009;49:2759-2771.
[17] Tonetti L, Eder AE, Dy B, et al. Transfusion-transmitted *Babesia Microti* identified through hemovigilance. Transfusion 2009;49:2557-2563.

Table 3: Microbial Infection by Implicated Organism, FY2005 through FY2010

Organism	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	FY09	FY09	FY10	FY10	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
*Babesia**	0	0%	2	29%	3	50%	5	71%	0	0%	1	50%	11	31%
Staphylococcus aureus	3	37%	0	0%	1	17%	1	14%	2	40%	0	0%	7	20%
Escherichia coli	0	0%	3	43%	0	0%	0	0%	0	0%	1	50%	4	11%
Serratia marcescens	2	24%	0	0%	0	0%	0	0%	0	0%	0	0%	2	6%
Staphylococcus epidermidis	1	13%	0	0%	0	0%	1	14%	0	0%	0	0%	2	6%
Staphylococcus lugdunensis	1	13%	0	0%	0	0%	0	0%	0	0%	0	0%	1	3%
Eubacterium limosum	1	13%	0	0%	0	0%	0	0%	0	0%	0	0%	1	3%
Morganella morganii	0	0%	1	14%	0	0%	0	0%	0	0%	0	0%	1	3%
Yersinia enterocolitica	0	0%	1	14%	0	0%	0	0%	0	0%	0	0%	1	3%
Streptococcus dysgalactiae (Group C)	0	0%	0	0%	1	17%	0	0%	0	0%	0	0%	1	3%
Klebsiella oxytoca	0	0%	0	0%	1	17%	0	0%	0	0%	0	0%	1	3%
Streptococcus viridans	0	0%	0	0%	0	0%	0	0%	1	20%	0	0%	1	3%
Streptococcus pneumoniae	0	0%	0	0%	0	0%	0	0%	1	20%	0	0%	1	3%
Staphylococcus warneri	0	0%	0	0%	0	0%	0	0%	1	20%	0	0%	1	3%
Total	8	100%	7	100%	6	100%	7	100%	5	100%	2	100%	35	100%

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

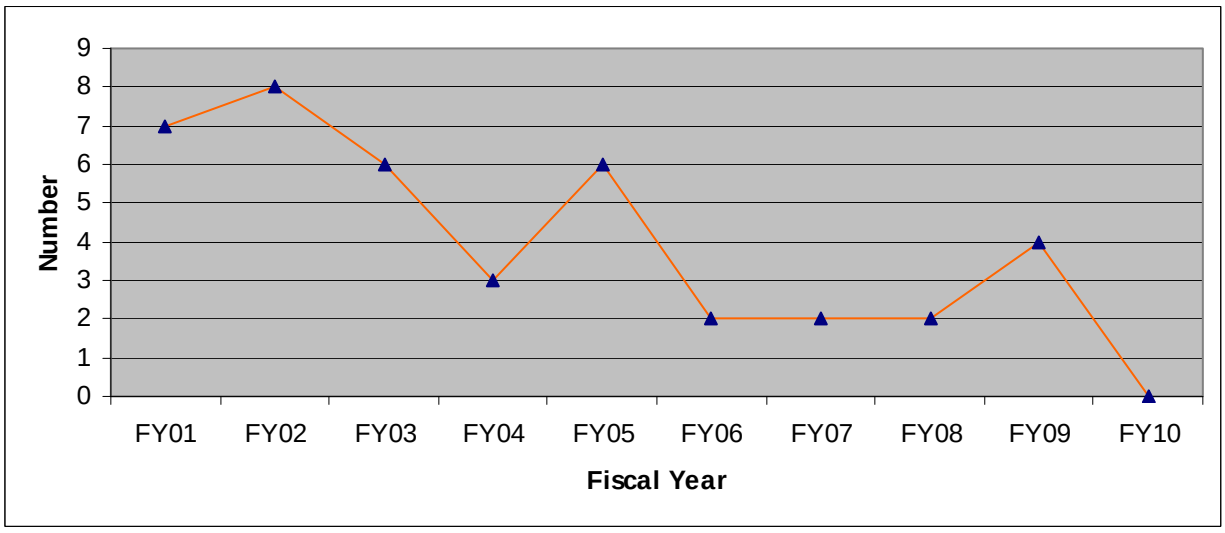
Figure 4: Microbial Infection by Implicated Blood Product, FY2005 through FY2010



	RBC	Pooled Platelets	Platelets Pheresis
FY05	1	1	6
FY06	4	1	2
FY07	3	1	2
FY08	5	0	2
FY09	0	1	4
FY10	1	1	0

Red Blood Cells microorganisms: *S. marcescens (1), E. coli (1), Y. enterocolitica (1), B. microti (10), B. MO1(1)*
Pooled Platelets microorganisms: *S. aureus (1), E. coli (2), S. dysgalactiae (1), S. pneumoniae (1)*
Platelets Pheresis microorganisms: *S. aureus (6), S. marcescens (1), S. lugdunensis (1), S. epidermidis (2), E. limosum (1), E. coli (1), M. morganii (1), K. oxytoca (1), S.viridans (1), S. warneri (1)*

Figure 5: Bacterial Infection by Apheresis Platelets, FY2001 through FY2010



E. Transfusion Not Ruled Out as Cause of 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). We did not include these reported fatalities in the analysis in Sections II.A through II.D (transfusion-related fatalities), above. Combining the transfusion related fatalities with those that our medical officers could not rule out, there were a total of 64 reported fatalities in FY2010, as compared to 66 in FY2009, and 54 in FY2008.

F. Not Transfusion Related

After reviewing the initial fatality reports and the investigation documentation, we categorized a number of 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, FY2005 through FY2010

	FY05	FY06	FY07	FY08	FY09	FY10
Not Transfusion Related	21	8	13	18	8	7
Not Ruled Out	14	10	11	8	22	24
Totals	35	18	24	26	30	31

G. Post-Donation Fatalities

FY2010 showed a continued decrease since FY2007, in the number of reported fatalities following Source Plasma donation (Table 5). We received two FY2010 reports of fatalities following Source Plasma donation. In one FY2010 case, the donation was definitively ruled out as the cause of the fatality. In the remaining cases (FY2005 through FY2010), 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.

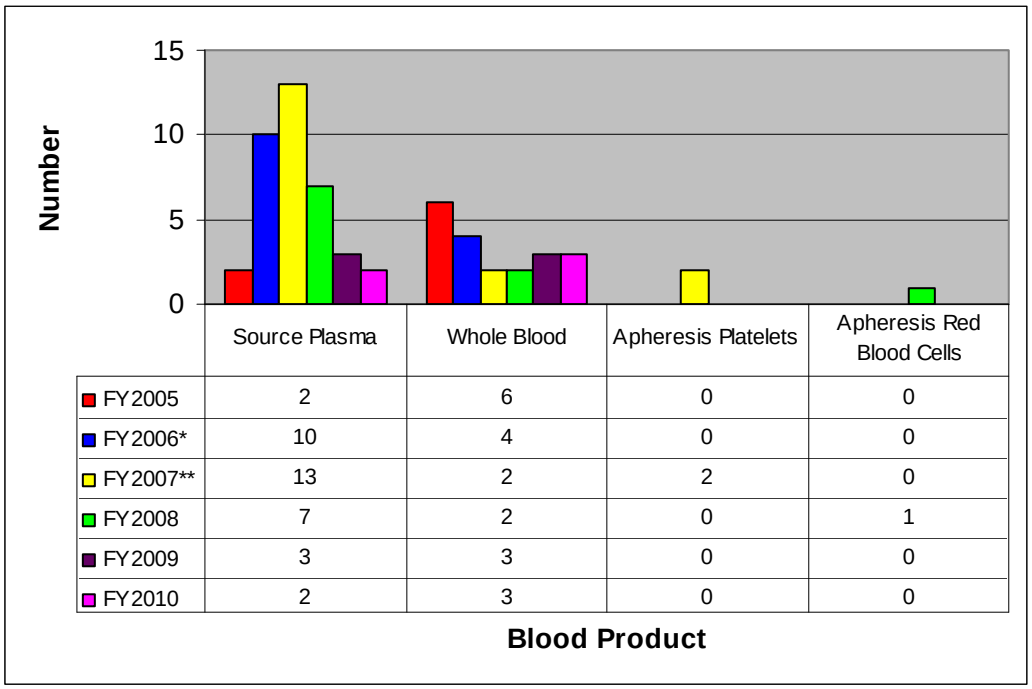
We received three FY2010 reports of fatalities following Whole Blood donation collected by manual methods. In all three of these cases, although the donation could not be definitively ruled out as being implicated in the donor's death, our medical reviewers found no evidence to support a causal relationship between the donation and subsequent death of the donor.

Table 5: Post-Donation Fatality Reports by Donated Product, FY2005 through FY2010

Donated Product	FY05	FY06	FY07	FY08	FY09	FY10
Source Plasma	2	10	13	7	3	2
Whole Blood	6	4*	2**	2	3	3
Apheresis Platelets	0	0	2	0	0	0
Apheresis Red Blood Cells	0	0	0	1	0	0
Total	8	14	17	10	6	5

*Includes 2 autologous donations
**Autologous donations

Figure 6: Post-Donation Fatality Reports, FY2005 through FY2010



*Includes 2 autologous Whole Blood donations
**Both Whole Blood donations in FY07 were autologous