Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2019

I. Background

FDA's Center for Biologics Evaluation and Research (CBER) is issuing this summary of fatality reports received by the FDA to make public the data received in Fiscal Year (FY) 2019 (October 1, 2018, through September 30, 2019), to provide the combined data received over the last five fiscal years, and to compare the FY2019 summary to the fatality reports received in the previous four fiscal years.[1] 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, but relatively constant, in comparison to the total number of transfusions. In calendar year 2019, 10.8 million whole blood and red cells, 1.9 million apheresis platelets, and 2.1 million plasma components were transfused, with a with a slight increase in demand for RBCs compared to 2017 (10.6 million) and reversing a decline that started in 2008.[2] During FY2015 there were 37 fatalities determined to be transfusion related. The corresponding fatalities were 43 in 2016, 37 in 2017, 31 in 2018, and 44 in 2019. Throughout this report we note changes over time in the number of reported fatalities, 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 greater than what the numbers would otherwise suggest.

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 2019, 11.5 million whole blood and red cell units, 2.5 million platelet components, and 2.6 million of plasma components were collected, and there were 53.5 million source plasma donations made in the U.S compared to 48.7 million in 2018.[3] Over the combined five-year reporting period (FY2015 – FY2019) there were 87 reported donation-associated fatalities (associated with a variety of donated products), with 15 cases since 2015 having an imputability of *definite*, *probable*, or *possible*.

Fatality reporting requirements can be found under Title 21, Code of Federal Regulations 606.170(b). For information regarding the notification process, see our web page, Notification Process for Transfusion Related Fatalities and Donation Related Deaths, https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/transfusiondonation-fatalities. 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] The FY2005 - FY2013 data are available at: http://wayback.archive-it.org/7993/20171114012113/https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/default.htm

[2] Jefferson Jones, CDC, Updates from the 2019 National Blood Collection and Utilization Survey (NBCUS) and Beyond. AABB 2020 Annual Meeting

[3] https://www.pptaglobal.org/images/Data/Plasma_Collection/Total_Yearly_Collections_2008-2019.pdf

[4] Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion, September, 2003. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/notifying-fda-fatalities-related-blood-collection-or-transfusion

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

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2. Call us at 240-402-9160, or
3. Write us at: Food and Drug Administration
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II. Changes in Our Evaluation Approach:

Starting with the annual report of FY2015, and in support of the FDA's international harmonization efforts, and to provide consistency between US government agencies, we modified our approach to the review and classification of fatality reports to align with the case definitions and imputability criteria used by the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network,[5] (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[6] (https://www.aabb.org/research/hemovigilance/Documents/Donor-Standard-Definitions.pdf), the British Serious Hazards of Transfusion (SHOT)[7], and the Haemovigilance activity report of the French National Agency for Medicines and Health Products Safety (ANSM)[8].

In fiscal years prior to FY2015, we classified fatalities in one of three imputability groups that define the strength of the evidence (causality) between the transfusion/donation and the fatality: *transfusion/donation-related, not ruled out, or not related*. Beginning in FY2015, fatalities that were previously classified either as *transfusion/donation-related*, or *not ruled out* are assigned a level of imputability, specifically *definite, probable, possible, doubtful,* and *not assessable* (Table 1). Fatalities previously defined as *not transfusion/donation related* continue to be classified as *ruled out*.

To achieve a more comprehensive review, we added three new categories of transfusion reactions beginning with FY2016: No Transfusion Reaction, Possible TRALI (previously tallied with TRALI), and Transfusion Reaction, Type Not Determined (Table 2). In FY18, we added Unlikely Transfusion Reaction.

[5] Center for Disease Control and Prevention National Healthcare Safety Network, Biovigilance Component, Hemovigilance.

[6] 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.

[7] Annual Serious Hazards of Transfusion Report, 2014.

[8] French National Agency for Medicine and Health Product Safety (ANSM), 2013 Haemovigilance Activity Report.

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 classification approach allows the review team to conduct effective evaluations and improve consistency in case classifications, in an effort to add clarity and allow comparability with other domestic and international haemovigilance systems.

Table 1: Imputability Definitions[7,8], FY2015 - FY2019

Imputability	Definition
Definite	Conclusive evidence beyond reasonable doubt for attributing the fatality to the transfusion/donation
Probable	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	Evidence in favor of attributing the fatality to an alternative cause, but transfusion/donation cannot be excluded.
Ruled Out	Conclusive evidence beyond reasonable doubt for attributing the fatality to cause other than transfusion/donation
Not Assessable	Insufficient information/relationship unknown

III. FY2019 Results

During FY2019, we received a total of 81 fatality reports. Of these reports, 61 were potentially associated with transfusion, and 20 were potentially associated with donation.

Of the 61 potentially transfusion-associated fatality reports, we determined the imputability of the transfusions to the fatalities as follows:

a) Forty-four (72%) of the fatalities were classified as either *definite, probable,* or *possible* imputability.
b) Nine (15%) of the fatalities were classified as either *doubtful*, or *not assessable* imputability.
c) Eight (13%) of the fatalities were classified as *ruled out* imputability.

Of the 20 potentially donation-associated fatality reports, we determined the imputability of the donations to the fatalities as follows:

a) Five (25%) of the fatalities were classified as *probable, or possible* imputability.
b) Nine (45%) of the fatalities were classified as either *doubtful*, or *not assessable* imputability.
c) Six (30%) of the fatalities were classified as *ruled out* imputability.

We summarize the results of our review in Table 2.

Table 2: Fatality Complication Breakdown by Imputability, FY2019

CATEGORY	Definite	Probable	Possible	Doubtful	Ruled Out	Not Assessable	TOTAL REPORTS
Transfusion							
Allergy/Anaphylaxis	2	-	-	-	-	-	2
Contamination (Bacterial)	-	1	-	1	-	-	2
HTR (ABO)	4	-	-	-	-	-	4
HTR (non-ABO)	5	2	4	2	-	-	13
No Transfusion Reaction	-	-	-	-	7	-	7
Not Assessable*	-	-	-	-	-	2	2
Other**	-	-	-	-	1		1
Possible TRALI	1	2	4	1	-	-	8
TACO	-	6	6	2	-	-	14
Transfusion Reaction, Type Not Determined	-	2	-	-	-	1	3
TRALI	2	2	1	-	-	-	5
Donation							
Donor Fatality	-	1	4	5	6	4	20

TRALI = Transfusion Related Acute Lung Injury; TACO = Transfusion Associated Circulatory Overload; HTR = Hemolytic Transfusion Reactions
The Row Header refers to Imputablility to Death
*Category and Imputability Not Assessable
**Other: Febrile Non-Hemolytic Reaction

For the purpose of comparison with previous fiscal years, the FY2015 through FY2019 imputabilities of *definite*, *probable*, and *possible* transfusion fatalities in the tables and figures of sections A through E of this document would most accurately compare with fatalities classified in previous years as *transfusion related*. Sections F and G present the transfusion fatalities classified respectively as *doubtful*, and *not assessable*, which would most accurately compare with fatalities classified in previous years as *transfusion not ruled out*. Section H presents the transfusion fatality reports classified as *ruled out*, which would compare with fatalities classified in previous years as *not transfusion related*. Section I presents the reported fatalities with donation.

A. Overall Comparison of Transfusion-Associated Fatalities Reported from FY2015 through FY2019

In combined FYs 2015 through 2019, TACO[9,10] cases caused the highest number of reported fatalities (34%), followed by the combined TRALI and Possible TRALI (24%), microbial contamination (14%), HTR due to non-ABO incompatibilities (13%), HTRs due to ABO incompatibilities (7%), anaphylaxis reactions (7%), and hypotensive reactions (1%).(Table 3).

[9] 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.

[10] http://anesthesiology.pubs.asahq.org/article.aspx?articleid=2598362

TACO was the leading cause of reported transfusion-associated deaths for FY16 through FY18, and in FY 2019, TACO and TRALI represented the leading causes of transfusion-associated death (12 cases each). TACO is currently the leading cause of transfusion-associated fatalities over the 5-year reporting period (FY2015 - FY2019). Prior to FY2016, TRALI was the consistent leading cause of transfusion-associated fatalities.

The number of reported transfusion-associated deaths attributable to anaphylaxis[11,12,13,14,15,16,] has remained small over the last five fiscal years. For FY2015 through FY2019, 14 anaphylactic reactions were identified. Five cases were found to have normal IgA levels, one case had a slightly low IgA level, and IgA levels were not tested in the remaining eight cases. Anaphylactic reactions have been reported in haptoglobin-deficient patients with serum haptoglobin antibodies.[17] Of the two anaphylaxis cases identified in FY2019, no haptoglobin levels were reported, and no serum-haptoglobin antibodies have been reported for FY2015 through FY2019. (Tables 2 and 3).

The number of reported transfusion-associated deaths attributable to hypotensive reactions has also remained small over the last five fiscal years, with one case in both FY2015 and FY2016, and none in FY2017, FY2018, and FY2019. 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 each of the reported cases, all other adverse reactions presenting with hypotension were excluded.

Table 3: Transfusion-Associated Fatalities by Complication, FY2015 – FY2019

Complication	FY15 No.	FY15 %	FY16 No.	FY16 %	FY17 No.	FY17 %	FY18 No.	FY18 %	FY19 No.	FY19 %	Total No.	Total %
Anaphylaxis	2	5%	5	12%	3	8%	2	6%	2	5%	**14**	**7%**
Contamination	5	14%	5	12%	7	19%	7	23%	1	2%	**25**	**13%**
HTR (ABO)	2	5%	4	9%	1	3%	2	6%	4	9%	**13**	**7%**
HTR (Non-ABO)	4	11%	1	2%	6	16%	4	13%	11	25%	**26**	**14%**
Hypotensive Reaction	1	3%	1	2%	0	0%	0	0%	0	0%	**2**	**1%**
TACO	11	30%	19	44%	11	30%	12	39%	12	27%	**65**	**34%**
TRALI**	12	32%	8	19%	9	24%	4	13%	12	27%	**45**	**23%**
Transfusion Reaction, Type Not Determined	0	0%	0	0%	0	0%	0	0%	2	5%	**2**	**1%**

Note: FY2015-FY2019 only includes cases with an imputability of *definite*, *probable*, or *possible*
**FY2015-FY2019 numbers combine both *TRALI* and *Possible TRALI* cases [18,19]

[11] 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.

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

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

[14] 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.

[15] 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.

[16] 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.

[17] 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.

[18] 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.

[19] 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.

B. Transfusion Related Acute Lung Injury (TRALI)

In FY2019, TRALI was one of two leading causes of transfusion-associated fatalities. There was one case of Possible TRALI classified with an imputability to death of *definite*, two cases classified with an imputability to death of *probable*, and four cases classified with an imputability of *possible*. There were also two cases of TRALI classified with an imputability to death of *definite*, two cases classified with an imputability to death of *probable*, and one case classified with an imputability to death of *possible*. Altogether, there were a total of 12 TRALI cases. Of the cases reported in FY2019, there were two where testing matched donor antibodies with recipient cognate antigens (one case HLA DR4 & DQ7, and one case HNA-3a). The remaining cases were either negative or contained incomplete donor/recipient testing. The limited data provided to FDA do not elucidate the role of particular donor antibodies or donor gender in the etiology of the TRALI reactions.

TRALI represented 24% of transfusion-associated fatalities reported to CBER over the last five fiscal years, and 29% in FY2019 (Table 3). Figure 1 shows a rise in TRALI cases between FY2004 and FY2007, followed by an abrupt decline in FY2008 and an overall downward trend between FY2010 and FY2018 and an uptick in 2019. Red blood cells continue to be the most frequently implicated product since 2015 (Figure 2).

Although TRALI 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 paralleled with a reduction in the number of TRALI deaths. Current literature describes the results of continued international efforts to reduce the incidence of TRALI.[20,21,22,23,24,25,26,27,28,29,30]

[20] Muller MCA, Juffermans NP. Transfusion-related acute lung injury: a preventable syndrome? Expert Rev. Hematol. 2012;5(1):97-106.

[21] Schmidt AE, Adamski J. Pathology Consultation on Transfusion-Related Acute Lung Injury. Am J Clin Pathol 2012;138:498-503

[22] Arinsburg SA, Skerrett DL, Karp JK, et al. Conversion to low transfusion-related acute lung injury (TRALI)-risk plasma significantly reduces TRALI. Transfusion 2012;52:946-952.

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

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

[25] 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.

[26] 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.

[27] 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.

[28] 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.

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

[30] 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 1: TRALI Cases, FY2004 - FY2019

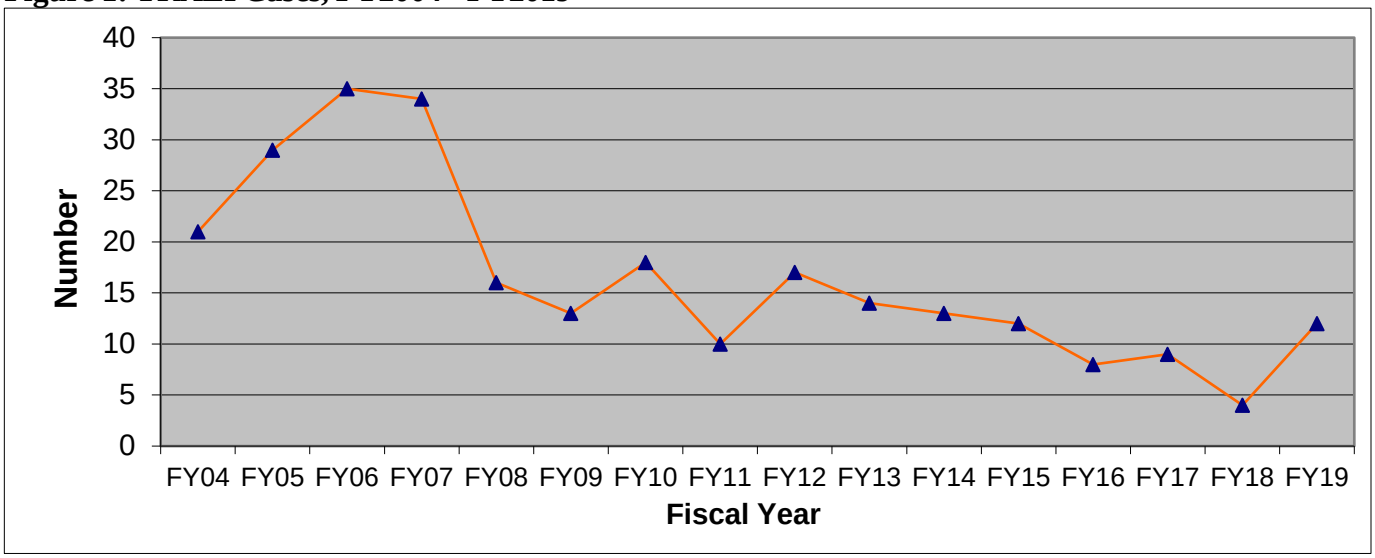
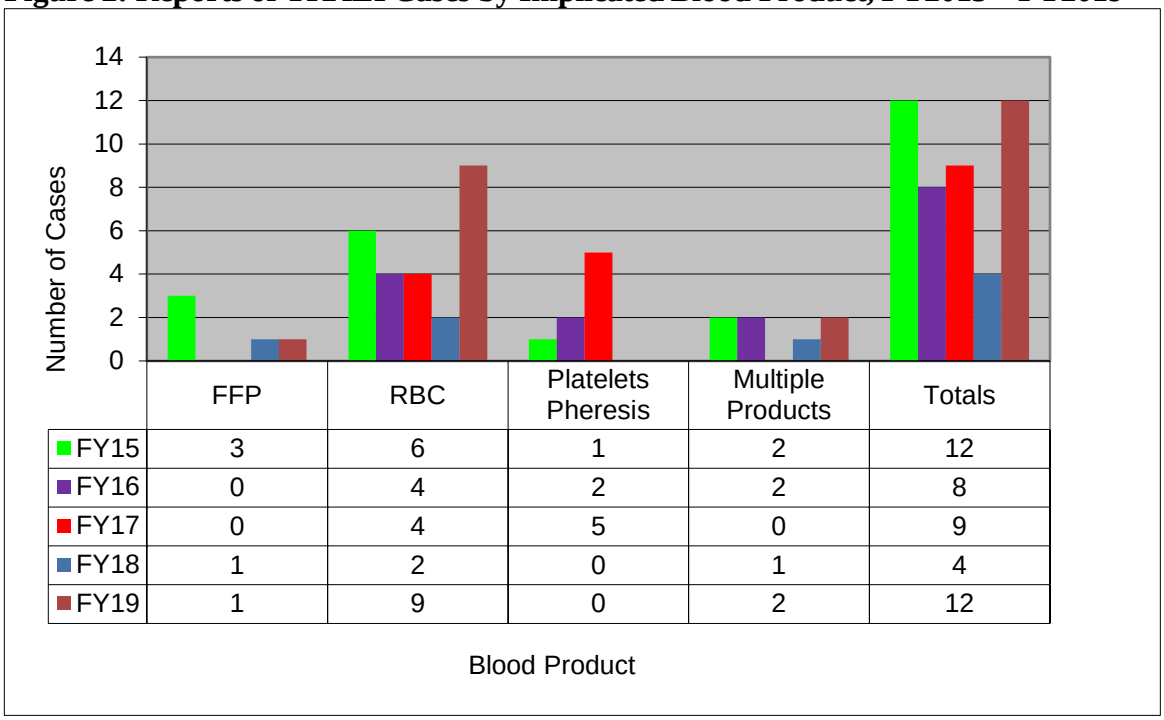


Figure 2: Reports of TRALI Cases by Implicated Blood Product, FY2015 – FY2019



	FFP	RBC	Platelets Pheresis	Multiple Products	Totals
FY15	3	6	1	2	12
FY16	0	4	2	2	8
FY17	0	4	5	0	9
FY18	1	2	0	1	4
FY19	1	9	0	2	12

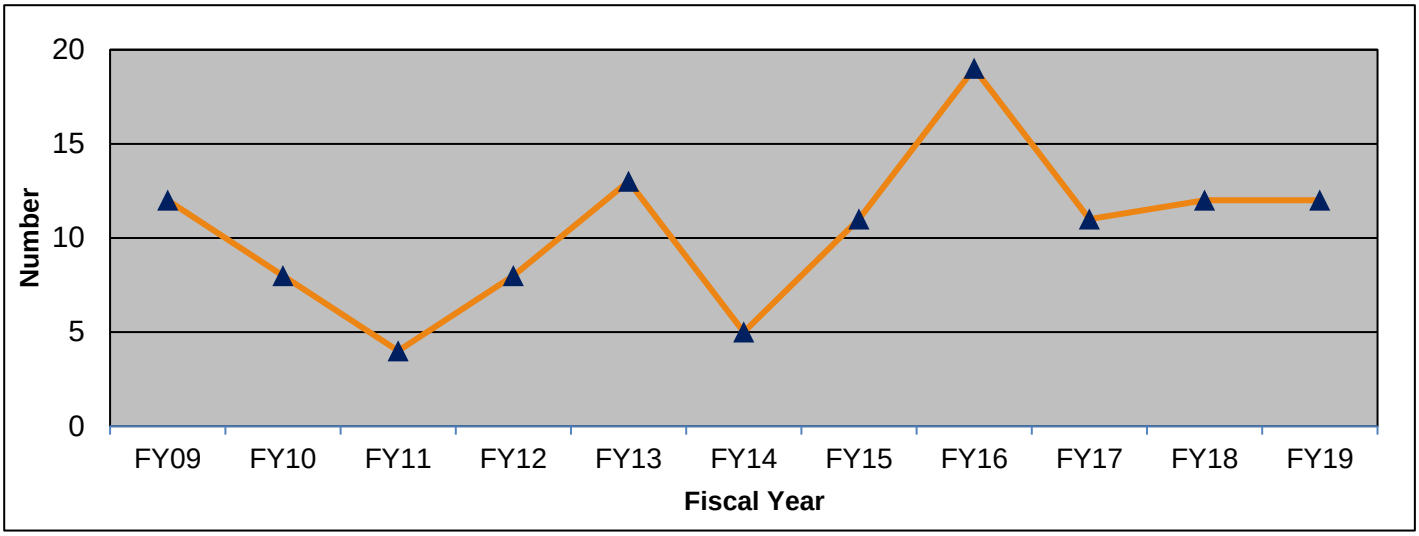
FFP – Fresh Frozen Plasma
RBC – Red Blood Cells

C. Transfusion Associated Circulatory Overload (TACO)

In FY2019, there were 12 cases of TACO with an imputability of d*efinite*, *probable*, or *possible.* TACO was the second of the two leading causes of transfusion-associated fatalities reported to FDA. Among these 12 reports, one was associated with platelet transfusion, seven were associated with RBC transfusion, and four were associated with multiple products.

TACO has been the leading cause of transfusion-associated fatality reported to FDA in the last four annual reports (FY2016-FY2019). The number TACO fatalities (Figure 3) has not shown significant change in since FY2015. Active surveillance systems found the incidence of TACO to be approximately one case per 100 patients transfused,[31] and risk factors include cardiac, pulmonary or renal disease, older age, and pre-transfusion positive fluid balance. A revised international surveillance case definition was recently described,[32] and it is anticipated that a standardized definition may facilitate clinicians to better identify, understand, and prevent TACO. The National Healthcare Safety Network expects to incorporate a new definition for TACO in the Hemovigilance Module in January 2021 to reflect the international effort to standardize reporting.[33]

Figure 3: TACO Cases, FY2009 – FY2019



D. Hemolytic Transfusion Reactions (HTR)

In FY2019, there were four reported ABO hemolytic transfusion fatalities classified as d*efinite* (10% of confirmed transfusion-associated fatalities), and 11 non-ABO hemolytic transfusion fatalities; five with an imputability of *definite*, two with an imputability of *probable*, and four with an imputability of *possible* (26% of confirmed transfusion-associated fatalities) (Tables 3 and 4).

[31]Roubinian NH, Hendrickson JE, Triulzi DJ, et al. Incidence and clinical characteristics of transfusion-associated circulatory overload using an active surveillance algorithm. Vox Sang. 2017;112(1):56–63. doi:10.1111/vox.12466.
[32]Revised international surveillance case definition of transfusion-associated circulatory overload: a classification agreement validation study Wiersum-Osselton, Johanna C et al. The Lancet Haematology, Volume 6, Issue 7, e350 - e358.
[33]National Healthcare Safety Network E-Newsletter. Volume 14, Issue 4, December 2019.

HTR (ABO)

1. **HTR (ABO) – *Definite***
   A group B recipient was transfused a group O unit of apheresis platelets. The patient experienced a hemolytic transfusion reaction. It was subsequently determined that isohemagglutinin titers for the platelet product were 1:128 at immediate spin and 1:512 at anti-human globulin (AHG) phase.

2. **HTR (ABO) – *Definite***
   A group O recipient was given group A RBCs due to a labeling error that occurred in the blood bank. The patient experienced a hemolytic transfusion reaction. The recipient's label was erroneously placed on another patient's sample tube which resulted in the patient testing as group A and subsequently receiving two units of group A RBCs.

3. **HTR (ABO) – *Definite***
   A group B recipient was given a unit of group A RBCs and a unit of group A FFP. The patient experienced a hemolytic transfusion reaction. There was a failure to properly identify the patient prior to collection which resulted in a Wrong Blood in Tube error.

4. **HTR (ABO) – *Definite***
   A group O recipient received a group A RBC and suffered a hemolytic transfusion reaction. It was subsequently determined that this was a result of a blood administration error, where the O recipient received blood intended for another patient in error, while blood sent to the floor for the O recipient was transfused to another patient in error.

HTR (non-ABO) *Definite*, *Probably* and *Possible* Imputability to Death

There was a total of 11 hemolytic transfusion reaction cases due to non-ABO antibodies. Five cases had an imputability to death of *definite*. In four of these cases, the recipients had a past medical history for Sickle Cell Disease and developed new antibodies (including a case of anti-Fy(a), a case of anti-Jk(b), a case of anti-V, and a case of anti-D due to a variant partial D) prior to detection. In the remaining case, units were required under an emergency release protocol and the recipient suffered a hemolytic transfusion reaction due to anti-K.

There were two cases determined to have an imputability to death of *probable*. In one case, the recipient's clinical status required emergent transfusion support prior to availability of compatible blood, and the patient experienced a hemolytic reaction due to anti-f. In the second case, the recipient had an anti-Jk3 that was misinterpreted as a warm autoantibody. In these cases, the evidence clearly favored the hemolytic transfusion reaction as the cause of the patient's demise.

There were four cases determined to have an imputability to death of *possible*. These cases consisted of a possible clinically significant anti-M, an anti-Jk(a), a likely warm autoimmune hemolytic antibody (WAIHA), and a recipient that experienced a hemolytic transfusion reaction with no definitive serological findings. In these cases, the recipients had underlying co-morbidities that potentially contributed to their demise.

The number of hemolytic transfusion reactions has remained low in recent years, particularly ABO HTRs, where the error is most frequently preventable misidentification of the patient or the patient's sample. From FY2008, there has been an overall downward trend in the total number of reported fatalities due to HTRs (both ABO and non-ABO) until FY2019, where there was a relative increase, particularly with non-ABO HTRs. (Figure 4).

Table 4: Antibodies identified in the Hemolytic Transfusion Reactions FY2015 – FY2019

Antibody	FY15 No.	FY16 No.	FY17 No.	FY18 No.	FY19 No.	Total No.
ABO	2	4	1	2	4	**13**
Multiple Antibodies	2	-	1	-	1	**4**
Other**	1	-	2	2	2	**7**
D	-	-	-	-	1	**1**
c	1	1	-	-	-	**2**
e	-	-	1	-	-	**1**
f	-	-	-	-	1	**1**
V	-	-	-	-	1	**1**
K	-	-	-	-	1	**1**
Fy^a	-	-	1	1	1	**2**
Jk^a	-	-	-	-	1	**1**
Jk^b	-	-	-	1	-	**1**
Jk3	-	-	-	-	1	**1**
M	-	-	-	-	1	**1**
U	-	-	1	-	-	**1**
Wr^a	-	-	-	1	-	**1**
Total	**6**	**5**	**7**	**7**	11	**33**

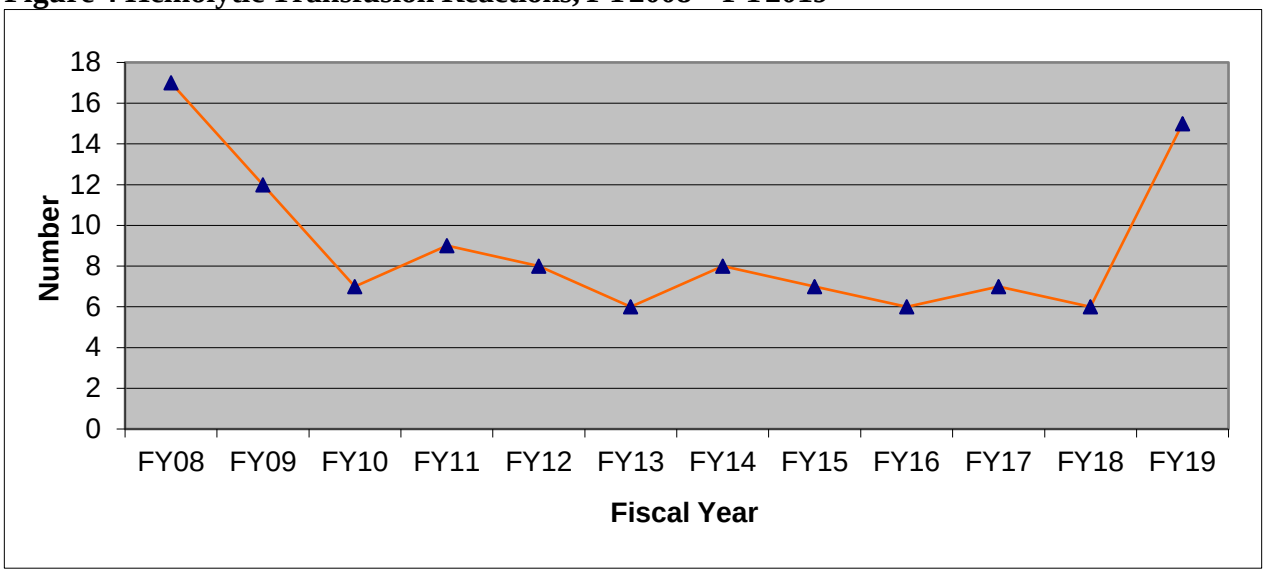
*Multiple Antibodies: FY2015: antibody combinations include: $E+K+Jk^a+M+Co^b+Cw$**;** $C+E+S+Jk^b+Fy^a+Fy^b$
FY2017: antibody combinations include: Jk^a+M
FY2019: antibody combinations include Fy^a + Jk^b

**Other: FY2015: Includes one report of Hyperhemolysis Syndrome in which no new or additional antibody was identified[34,35]
FY2017: Includes one report of Hyperhemolysis Syndrome in which no new or additional antibody was indentified, and one case of a hemolytic transfusion reaction where no new or additional antibody was identified
FY2018: 1) The case with anti-Jk^b, also demonstrated anti-S and a Hyperhemolysis Syndrome 2) A case of transfused Cold Autoimmune Hemolytic Anemia
FY2019: 1) Likely WAIHA 2) HTR with no definitive serological findings

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

[35] 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 4 Hemolytic Transfusion Reactions, FY2008 – FY2019



E. Microbial Contamination

In FY2019, there was one case of a contamination-related fatality attributed to bacterial contamination with an imputability to death of *probable* (Table 6). This case was associated with a pooled platelet transfusion consisting of four whole blood derived platelet units. Following development of symptoms consistent with a septic transfusion reaction, a cultured aliquot of the platelet product grew *Serratia marcescens*. The recipient's blood cultures showed no growth after six days; however, the patient was receiving antibiotic therapy.

There were no cases of bacterial contamination of pooled platelets in the previous four years.

In FY2019, there were no reports of fatality related to apheresis platelets. *Staphylococcus aureus* remains the most frequently identified infectious agent in apheresis platelets over the past five years (Table 6).

Figure 5 shows the microorganisms implicated by product type. *Babesia microti* infections were associated with three of the seven RBC transfusions implicated in reported fatalities. Recent articles provide additional information on transfusion transmitted *Babesia* and the current effort to screen the blood supply using investigation tests in endemic states.[36,37] The WNV infections were associated with both apheresis platelets and thawed plasma.

[36]Erin D. Moritz, et al. Screening for *Babesia microti* in the U.S. Blood Supply. New England Journal of Medicine. 2016;375:2236-45.

[37]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.

The five *Staphylococcus aureus* infections were associated with transfusion of apheresis platelets. (Figure 5). Recent articles provide additional information about bacterial contamination of platelet products[38,39,40,41]

Figure 6 shows the trend of contamination (bacterial) associated with apheresis platelets from FY2004 to FY2019. While there were no fatality reports of bacterial contamination in apheresis platelets reported in FY 2019, bacterial contamination of platelet components remains a public health concern which FDA has addressed in a Final Guidance (https://www.fda.gov/media/123448/download) on controlling the risk of bacterial contamination to enhance the safety and availability of platelets for transfusion. Refer to Title 21, Code of Federal Regulations 606.145 for requirements regarding control of bacterial contamination of platelets.

Table 6: Contamination of Apheresis Platelets by Implicated Organism, FY2015 - FY2019

Organism	FY15	FY16	FY17	FY18	FY19	TOTAL
Acinetobacter pittii	-	-	-	1	-	**1**
Anaplasma phagocytophilum	-	-	1	-	-	**1**
Babesia microti	-	2	-	1	-	**3**
Clostridium perfringens	-	-	2	1	-	**3**
Coagulase-negative staphylococci	1	1	-	-	-	**2**
Enterobacter aerogenes	-	1	-	-	-	**1**
Enterococcus faecium	1	-	-	-	-	**1**
Klebsiella pneumoniae	-	-	1	-	-	**1**
Pseudomonas fluorescens	-	1	-	-	-	**1**
Pseudomonas veronii	-	-	-	1	-	**1**
Pseudomonas aeruginosa	-	-	-	1	-	**1**
Serratia marcescens	-	-	-	-	1	**1**
Staphylococcus aureus	3	-	-	2	-	**5**
Staphylococcus epidermidis	-	-	1	-	-	**1**
West Nile virus	-	-	2	-	-	**2**
TOTAL	**5**	**5**	**7**	**7**	**1**	**25**

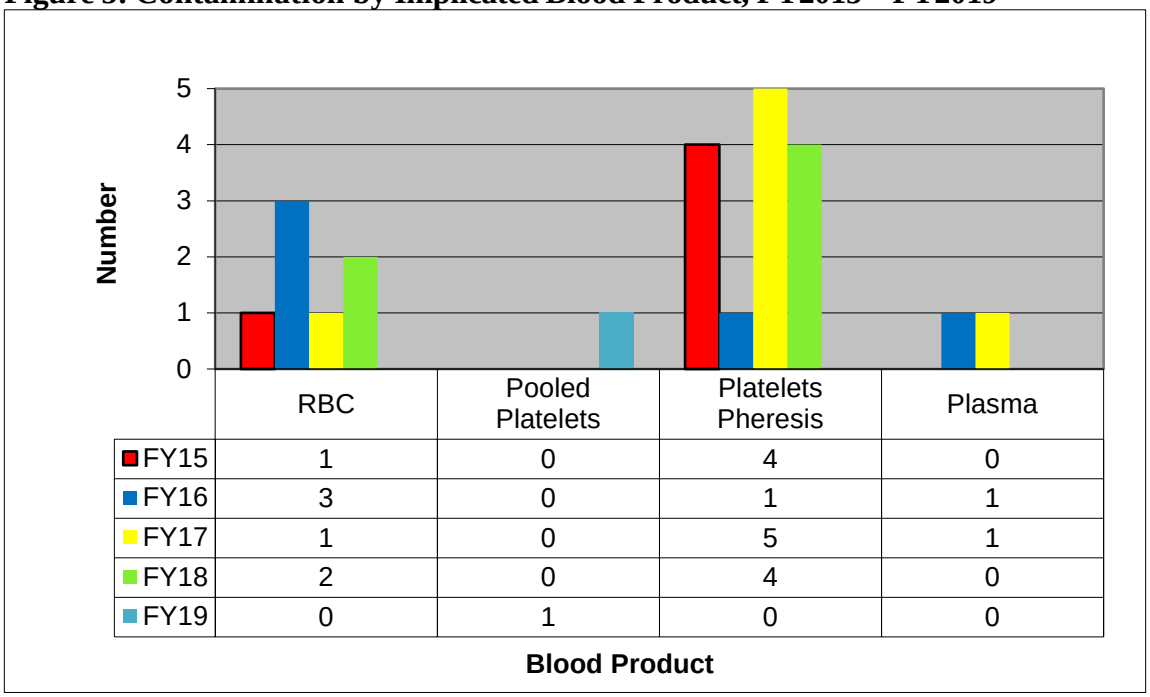
[38]Rollins MD, Molofsky AB, Nambiar A, et al. Two Septic transfusion reactions presenting as transfusion-related acute lung injury from a split

[39]Plateletpheresis unit. Crit Care Med 2012;40:2488-2491.

[40]Palavecino EL, Ymotovian RA, Jacobs MR Bacterial contamination of platelets. Transfus Apher Sci 2010;42:71-82.

[41]Eder AF, et al. Apheresis technology correlates with bacterial contamination of platelets and reported septic transfusion reactions. Transfusion 2017;00;00-00. 2009;49:1554-1563.

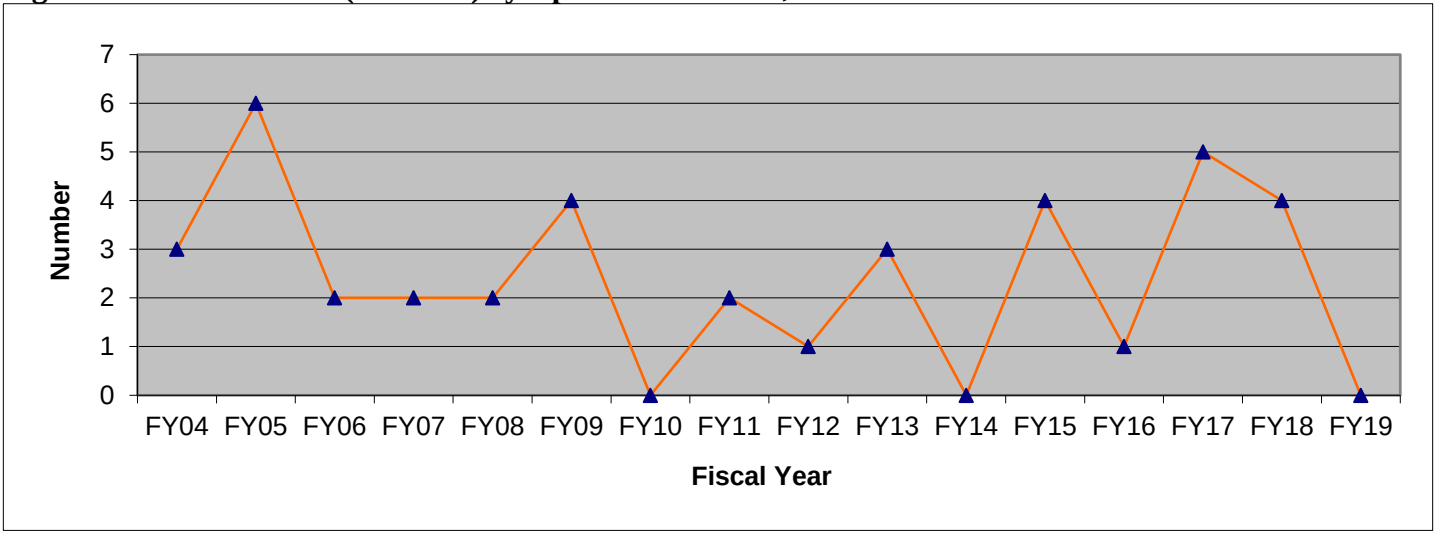
Figure 5: Contamination by Implicated Blood Product, FY2015 – FY2019



	RBC	Pooled Platelets	Platelets Pheresis	Plasma
FY15	1	0	4	0
FY16	3	0	1	1
FY17	1	0	5	1
FY18	2	0	4	0
FY19	0	1	0	0

Red Blood Cells microorganisms: *B. microti (3), P. fluorescens (1), E. faecium (1), Anaplasma phagocytophilum (1), P. veronii (1)*
Pooled Platelets microorganisms: *S. Marcescens (1)*
Platelets Pheresis microorganisms: *S. aureus (5), S. epidermidis (1),* coagulase-negative staphylococci *(1)*
West Nile virus *(1), A. pitti (1), E. aerogenes (1), K. pneumoniae (1), C. perfringens (3)*
Plasma: (TPE) coagulase-negative staphylococci (1), (thawed plasma) West Nile Virus (1)
Multiple products (specific product source unknown): *P. aeruginosa (1)* (not included in figure)

Figure 6: Contamination (bacterial) by Apheresis Platelets, FY2004 – FY2019



F. Transfusion Doubtful as Cause of Death

We classified 6 (10%) of the 61 cases described earlier as potentially associated with transfusion recipient fatalities in FY2019 as *doubtful*, including one contamination (bacterial) case, two HTR (non-ABO), one Possible TRALI, and two TACO cases. Although transfusion could not be excluded as a contributing factor, the evidence in each of these cases more strongly favored the patient's underlying medical condition(s). Thus, we did not include these reported fatalities in the analysis in Sections III.A through III.E.

G. Transfusion Not Assessable as Cause of Death

We classified three (5%) of the 61 cases described as potentially associated with transfusion recipient fatalities in FY2019 as *not assessable*. In these cases, there was insufficient information submitted/available to determine the type of reaction and the extent of the relation between the transfusions and the death. Thus, these reported fatalities were also not included in the analysis in Sections III.A through III.E.

H. Transfusion Ruled Out as Cause of Death

We classified 8 (13%) of the 61 cases described as potentially associated with transfusion recipient fatalities in FY2019 as *ruled out*. Our medical reviewers concluded that either no transfusion reaction occurred, or, 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 (e.g., underlying condition) other than transfusion. Thus, we did not include these reported fatalities in the analysis in Sections III.A through III.E.

I. Donation Fatalities

The processes of blood and plasma donation are generally safe and determining that a causal link exists between a donation and the fatality remains uncommon among reported donation fatalities. For FY2019, there were no donation fatalities classified as *definite*, one classified as pr*obable*, and there were four donations classified as *possible.* There were five donation fatalities classified as *doubtful*, six donation fatalities classified as *ruled out*, and four donation fatalities classified as *not assessable* (Table 7).

- **Donation – *Probable***
  There was one fatality following Whole Blood donation where the complication was probably related to the donation. The evidence was clearly in favor for attributing the fatality to the donation.

- **Donation – *Possible***
  There were four fatalities following Source Plasma donation where the complication was possibly related to the donation; however, the evidence was indeterminate for attributing the fatality to the donation or an alternative cause.

- **Donation – *Doubtful***
  There were five fatalities following Source Plasma donations and one fatality following Whole Blood donation, in which the relationship between the donation and subsequent death was classified as *doubtful.* In these five cases, the evidence was in favor of attributing the death to a cause other than the donation (e.g., underlying medical conditions), but the donation could not be excluded.

- **Donation – *Ruled Out***
  There were six fatalities following Source Plasma donation in which the donations were classified as *ruled out*. 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 Assessable***
  There were four fatalities following Source Plasma donation in which the donation was classified as *not assessable*. In these cases, there was insufficient information submitted/available to determine the extent of the relation between the donations and the cause of death.

Table 7: Donation Fatalities with Imputability by Product, FY2019

DONATION TYPE	Definite	Probable	Possible	Doubtful	Ruled Out	Not Assessable	TOTAL REPORTS
Source Plasma	-	-	4	4	6	4	**18**
Whole Blood	-	1	-	1	-	-	**2**
Apheresis Platelets	-	-	-	-	-	-	-
Apheresis Red Cells	-	-	-	-	-	-	-
Total	**-**	**1**	**4**	**5**	**6**	**4**	**20**

The row header refers to Imputablility to Death

In years prior to FY2015, and in most donation cases the donation could not be definitively ruled out as the cause of the donor's death following a thorough medical review which determined that the available evidence did not definitively rule out the donation, nor did the available evidence support a causal relationship between the donation and the donor's death.

For FY2019, the cases classified as *doubtful*, and *not assessable* would most accurately compare to the *donation not ruled out* cases from years prior to FY2015 (Table 8).

Table 8: Donation with *Doubtful* or *Not Assessable* Imputability to Death by Product, FY2015- FY2019

Donated Product	FY15	FY16	FY17	FY18	FY19	TOTAL REPORTS
Source Plasma	12	5	6	4	8	**35**
Whole Blood	1	2	1	2	1	**7**
Apheresis Platelets	1	0	0	0	0	**1**
Apheresis Red Blood Cells	0	1	0	0	0	**1**
Total	**14**	**8**	**7**	**6**	**9**	**44**

Finally, the number of donation fatalities definitively ruled out as being implicated in the donor's death is markedly smaller than the combination of cases classified as *donation not ruled out*, *doubtful*, and *not assessable* in FY2015 to FY2019. These reported donation fatality cases have been classified in years prior to FY2015 as *donation ruled out* (Table 9).

Table 9: Donation *Ruled Out* by Product, FY2015-FY2019

Donated Product	FY15	FY16	FY17	FY18	FY19	TOTAL REPORTS
Source Plasma	4	3	5	9	6	**27**
Whole Blood	1	-	-	-	-	**1**
Apheresis Platelets	-	-	-	-	-	-
Apheresis Red Blood Cells	-	-	-	-	-	-
Total	**5**	**3**	**5**	9	6	**28**