Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2021

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) 2021 (October 1, 2020, through September 30, 2021), to provide the combined data received over the last five fiscal years, and to compare the FY21 summary to the fatality reports received in the previous four fiscal years.[1] In FY2021, there were a total of 42 fatalities evaluated as at least possibly related to transfusion. 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 2021, 10.8 million whole blood and apheresis red blood cells (RBCs), 2.3 million platelets, and 3.0 million plasma components were transfused, with stable demand for RBCs compared to 2019 (10.8 million).[2] 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.

We also include information on the infrequent reports of donation-associated fatalities reported to FDA. The number of donation-associated fatalities reported to the FDA also remains small in comparison to the total number of units collected. In 2021, U.S blood establishments collected 11.8 million whole blood and apheresis red blood cell units, 2.5 million platelet units, and 3.1 million plasma components.[2] In 2021, there were approximately 44 million source plasma donations made in North America compared to almost 54 million in 2019.[3] Over the combined five-year reporting period (FY2017 – FY2021) there were 109 reported donation-associated fatalities (associated with a variety of donated products), with 23 cases since 2017 having an imputability of *definite (n=0), probable (n=4),* or *possible (n=19)*.

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, updated August 2021.[4]

[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] https://pubmed.ncbi.nlm.nih.gov/37070720/

[3] https://www.pptaglobal.org/resources/plasma-collection-and-manufacturing

[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
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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 among U.S. 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 Hemovigilance 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).

[5] Centers 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 Hemovigilance 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 includes a team of CBER medical officers who conduct a detailed review of the documentation submitted by the reporting facilities 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 hemovigilance systems.

Table 1: Imputability Definitions, FY2017-FY2021

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. FY2021 Results

During FY2021, we received a total of 91 fatality reports. Of these reports, 60 were potentially associated with transfusion and 31 were potentially associated with donation.

Of the 60 potentially transfusion-associated fatality reports, we determined the imputability of the transfusions to the fatalities as follows:

a) Forty-two (70%) of the fatalities were classified as either *definite, probable,* or *possible.*
b) Ten (17%) of the fatalities were classified as either *doubtful*, or *not assessable.*
c) Eight (13%) of the fatalities were classified as *ruled out.*

Of the 31 potentially donation-associated fatality reports, we determined the imputability of the donations to the fatalities as follows:

a) Seven (23%) of the fatalities were classified as *probable, or possible.*
b) Seventeen (54%) of the fatalities were classified as either *doubtful*, or *not assessable.*
c) Seven (23%) of the fatalities were classified as *ruled out.*

We summarized the results of our review in Table 2

Table 2: Fatality Complication Breakdown by Imputability, FY2021

CATEGORY	Definite	Probable	Possible	Doubtful	Ruled Out	Not Assessable	TOTAL REPORTS
Transfusion							
Allergy/Anaphylaxis	2	1	1	-	-	-	4
Contamination (Bacterial)	3	1	1	-	-	-	5
HTR (ABO)	3	1	1	-	-	-	5
HTR (non-ABO)	-	1	1	-	-	-	2
No Transfusion Reaction	-	-	-	2	8	-	10
Other*	-	-	1	-	-	-	1
Possible TRALI	-	1	4	1	-	-	6
TACO	5	7	3	4	-	-	19
Transfusion Reaction, Type Not Determined	-	1	2	2	-	1	6
TRALI	1	1	-	-	-	-	2
Total	14	14	14	9	8	1	60
Donation							
Donor Fatality	-	1	6	8	7	9	31

TRALI = Transfusion Related Acute Lung Injury; TACO = Transfusion Associated Circulatory Overload; HTR = Hemolytic Transfusion Reaction
The Row Header refers to Imputability to Death
*Other: Includes a case with features of a febrile, non-hemolytic transfusion reaction complicated by severe tachycardia in a patient with underlying cardiac and pulmonary disease

For the purpose of comparison with previous fiscal years, the FY2017 through FY2021 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 FY2017 through FY2021

In combined FYs 2017 through 2021, TACO cases caused the highest number of reported fatalities (32%), followed by the combined TRALI and Possible TRALI (21%), HTR due to non-ABO incompatibilities (14%), microbial contamination (13%), anaphylaxis reactions (9%), HTRs due to ABO incompatibilities (7%), transfusion reaction type not determined (3%), and Other (1%), (Table 3, and Figure 1).

TACO was the leading cause of reported transfusion-associated deaths for FY2017 through FY2018, and in FY2019, TACO and TRALI equally represented the leading causes of transfusion-associated deaths. In FY2020 and FY2021, TACO continued to be the leading cause of transfusion-associated deaths. Prior to FY2017, TRALI was the consistent leading cause of transfusion-associated fatalities.

The number of reported transfusion-associated deaths attributable to anaphylaxis has appeared relatively steady over the last five fiscal years. Four anaphylaxis fatalities were reported in FY2021, compared to six cases in FY2020 and three or fewer cases in the preceding three years (Table 3). For FY2017 through FY2021, 17 anaphylactic reactions were identified. While IgA and haptoglobin deficiencies have been historically implicated as a contributory factor in anaphylactic reactions[9,10], only a subset of cases was tested for IgA or haptoglobin levels, and no deficiencies were observed in any of the reported cases where testing was performed.

Table 3: Transfusion-Associated Fatalities by Complication, FY2017 – FY2021

Complication	FY17 No.	FY17 %	FY18 No.	FY18 %	FY19 No.	FY19 %	FY20 No.	FY20 %	FY21 No.	FY21 %	Total No.	Total %
Anaphylaxis	3	8%	2	6%	2	5%	6	21%	4	10%	**17**	**9%**
Contamination	7	19%	7	23%	1	2%	4	14%	5	12%	**24**	**13%**
HTR (ABO)	1	3%	2	6%	4	9%	2	7%	5	12%	**14**	**7%**
HTR (Non-ABO)	6	16%	4	13%	11	25%	2	7%	2	5%	**25**	**14%**
TACO	11	30%	12	39%	12	27%	8	27%	15	36%	**58**	**32%**
TRALI*	9	24%	4	13%	12	27%	6	21%	7	16%	**38**	**21%**
Transfusion Reaction, Type Not Determined	0	0%	0	0%	2	5%	1	3%	3	7%	**6**	**3%**
Other	0	0%	0	0%	0	0%	0	0%	1	2%	**1**	**1%**
Total	37		31		44		29		42		**183**	

Note: FY2017-FY2021 only includes cases with an imputability of *definite, probable*, or *possible*
*FY2017-FY2021 numbers combine both *TRALI* and *Possible TRALI* cases

[9] 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.

[10] 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.

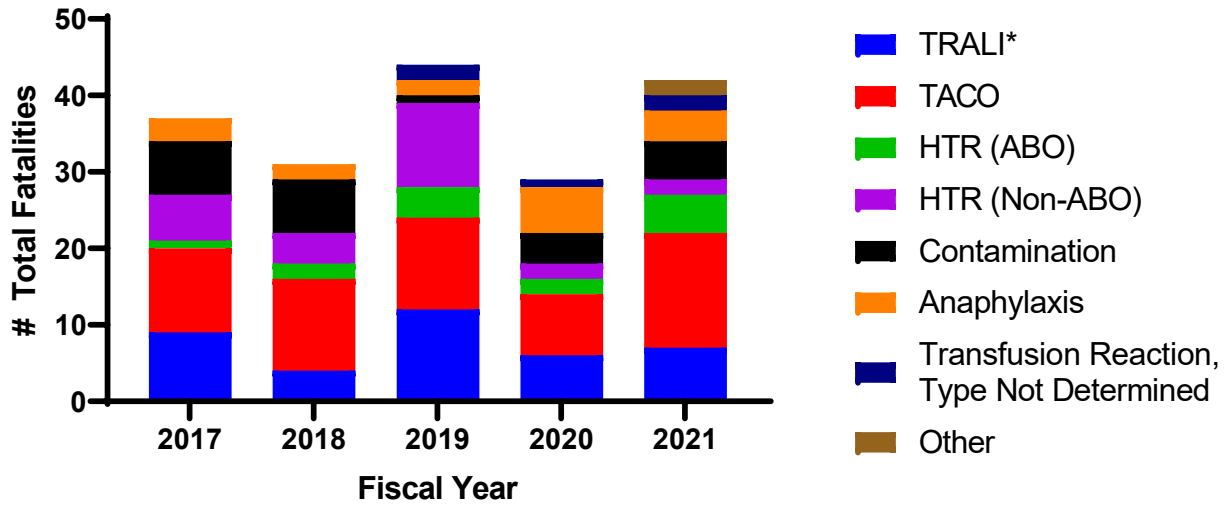

Figure 1: Transfusion-Associated Fatalities by Complication, FY2017 – FY2021

Note: FY2017-FY2021 only includes cases with an imputability of *definite, probable*, or *possible*
*FY2017-FY2021 numbers combine both *TRALI* and *Possible TRALI* cases

B. Transfusion Related Acute Lung Injury (TRALI)

In FY2021, TRALI was the second leading cause of transfusion-associated fatalities. There was one case of Possible TRALI classified with an imputability to death of *probable*, and four cases classified with an imputability of *possible*. There was also one case of TRALI classified with an imputability to death of *definite* and one case classified with an imputability to death of *probable*. Including both TRALI and possible TRALI, there were a total of seven TRALI cases. For FY2021, there was one case in which the donor of a unit of plasma was positive for HLA antibodies to B44,45, and the recipient was positive for the B44 antigen. There were no additional cases where testing matched donor antibodies with recipient cognate antigens due to either negative or 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 21% of transfusion-associated fatalities reported to CBER over the last five fiscal years, including FY2021 (Table 3). As documented in prior annual summaries, a rise in TRALI cases between FY2005 and FY2007 was followed by an abrupt decline in FY2008. There has been an overall downward trend since FY2012 (Figures 1 and 2), although with an uptick in FY2019, followed by a decline in FY2020 and FY2021. RBCs are the most frequently implicated product since 2018 (Figure 3).

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 the reduction in the number of TRALI deaths described above. Efforts to reduce the incidence of TRALI have been examined and reviewed.[11,12]

[11] Otrock, ZK, et al. Transfusion-related acute lung injury risk mitigation: an update. Vox Sang 2017;112:694-703
[12] Vossoughi S et al. Ten years of TRALI mitigation: measuring our progress. Transfusion 2019;58:2567-2574

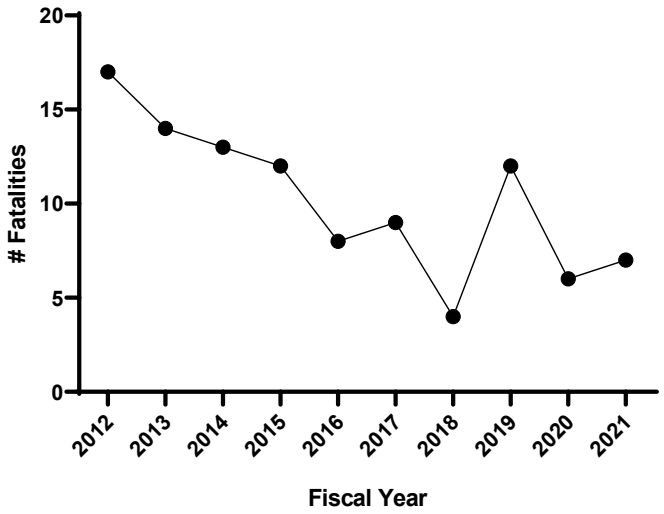

Figure 2: TRALI Fatalities, FY2012-FY2021

FY	FFP	RBC	Apheresis Platelets	Multiple Products
2012	0	6	5	4
2013	1	7	0	5
2014	1	4	1	7
2015	3	6	1	2
2016	0	4	2	2
2017	0	4	5	0
2018	1	2	0	1
2019	1	9	0	2
2020	0	5	0	1
2021	1	3	2	1

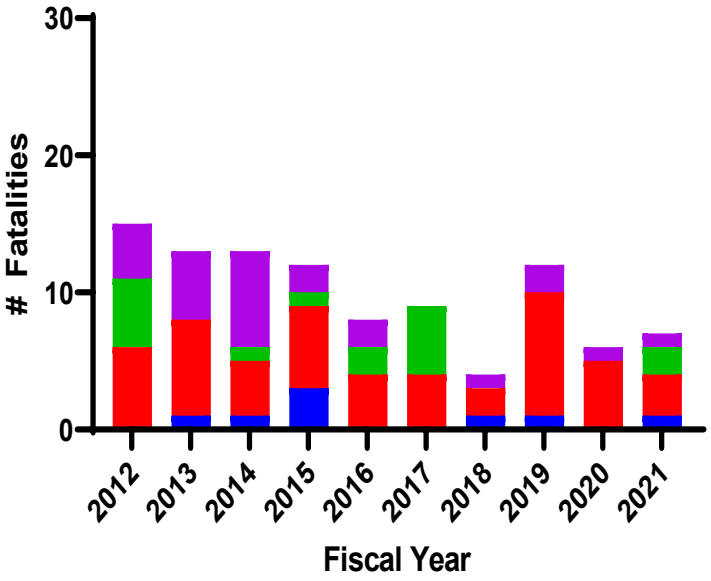

Figure 3: TRALI Fatalities by Implicated Blood Product, FY2012 – FY2021

C. Transfusion Associated Circulatory Overload (TACO)

In FY2021, TACO was the leading cause of transfusion-associated fatalities reported to FDA. There were 15 cases of TACO with an imputability of d*efinite*, *probable*, or *possible.* Among these 15 cases, one was associated with apheresis platelets, 10 were associated with RBC transfusion, and four were associated with multiple blood products.

TACO has been the leading cause of transfusion-associated fatalities reported to FDA in the last five years (FY2017-FY2021). Active surveillance systems found the incidence of TACO to be approximately one case per 100 patients transfused,[13] 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,[14] and it is anticipated that a standardized definition may facilitate clinicians to better identify, understand, and prevent TACO. The CDC's National Healthcare Safety Network recently incorporated revised criteria to define TACO in the Hemovigilance Module in April 2021 to reflect the international effort to standardize reporting.[15]

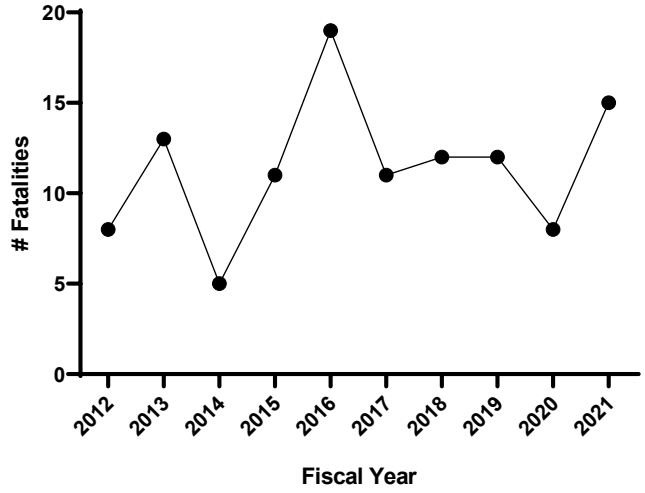

Figure 4: TACO Fatalities, FY2012-FY2021

D. Hemolytic Transfusion Reactions (HTR)

In FY2021, there were five reported ABO hemolytic transfusion fatalities classified as *definite, probable,* and *possible* (12% of confirmed transfusion-associated fatalities), and two non-ABO hemolytic transfusion fatalities; with an imputability of *probable* and *possible* (5% of confirmed transfusion-associated fatalities) (Tables 3 and 4).

[13] 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;112:56–63. doi:10.1111/vox.12466.

[14] Wiersum-Osselton, Johanna C et al. Revised international surveillance case definition of transfusion-associated circulatory overload: a classification agreement validation study. The Lancet Haematology, Volume 6, Issue 7, July 2019; e350 - e358.

[15] https://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf

HTR (ABO)

1. **HTR (ABO) – *Definite***
   A mix-up of patient samples led to a group O patient receiving group B RBCs. The patient experienced an acute hemolytic transfusion reaction. Failure to follow blood bank procedures and failure to perform two-person verification at the patient's bedside prior to transfusion may have contributed to the transfusion of the wrong unit of blood.

2. **HTR (ABO) – *Definite***
   A group O patient was transfused with group A RBCs due to a blood administration error. The patient experienced a hemolytic transfusion reaction, including severe hypotension. It was determined that this error was related to switching blood coolers at the nursing station.

3. **HTR (ABO) – *Definite***
   A group AB patient received a unit of group O platelets. The patient experienced back pain, hematuria, and abdominal cramping during the transfusion. Signs, symptoms, laboratory findings, and transfusion reaction investigation were consistent with an acute hemolytic reaction caused by anti-A antibodies present in the plasma of the transfused O platelets. Anti-A titer in the transfused unit was 1:512. The transfusing facility's procedure outlines a consult for risk of ABO hemolysis when a patient needs more than three out-of-group apheresis platelets in a single calendar day.

4. **HTR (ABO) – *Probable***
   Three B positive RBC units were transfused to an O positive patient in critical condition with multiple comorbidities. The blood bank mistakenly issued group B red blood cell units due to errors including incomplete history check and comparison to records of a patient with a similar name. The patient suffered a cardiac arrest within 30 minutes of receiving the blood. There were no post-transfusion test results to confirm evidence of a hemolytic reaction. Given the clinical course after the transfusion of the incompatible blood, a hemolytic transfusion reaction could not be ruled out as a contributing factor.

5. **HTR (ABO)** – ***Possible***
   A group A patient was erroneously transfused a group B red blood cell unit during a massive transfusion protocol that included multiple group A red blood cells, and one group B red blood cell unit that had been crossmatched and tagged for a different patient. The patient developed worsening hypotension in the context of hemorrhagic shock. Considering the patient's underlying severe hemorrhage, the imputability of the transfusion reaction to the patient's death was considered possible. It was determined that this error was related to retrieval of a unit from a tube station that was crossmatched and tagged for a different patient, which was then handed off to a different care team.

HTR (non-ABO)

1. **HTR (non-ABO) – *Probable***
   A patient with a history of multiple alloantibodies received ten uncrossmatched RBCs under emergency release prior to completion of a type and screen and antibody workup. The patient developed signs of a delayed hemolytic transfusion reaction. It was subsequently determined that the patient had anti-C, anti-E, anti-K, anti-Jk^b, anti-Fy^a, and anti-Fy^b antibodies. Transfusion reaction investigation revealed the transfused units were found incompatible and positive for two or more of the corresponding antigens. The patient had multiple trauma injuries due to a motor vehicle accident.

2. **HTR (non-ABO) – *Possible***
   A patient with multiple comorbidities presented with bleeding and anemia. A positive screen revealed anti-K and anti-Fy^a antibodies. The patient was antigen tested and typed negative for K and weakly positive for Fy^a. The patient developed marked hypotension several hours after receiving two units of K-negative red blood cells. It was later determined that one of the transfused units was positive for the Fy^a antigen, and the patient showed signs consistent with the clinical evidence of a delayed hemolytic transfusion reaction. The patient's underlying medical condition may have also been a contributing factor.

While the number of fatalities attributable to hemolytic transfusion reactions were low overall in FY2021, there were five fatalities due to ABO HTRs, four of which are attributable to errors. Based on recent trends in ABO-incompatible transfusion-related fatalities, we would expect about two cases per year. [16] Therefore, the observation of four ABO HTR fatalities attributable to errors highlights continued gaps in best practices to prevent transfusion errors. From FY2008, there was 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 spike in non-ABO HTRs. (Figure 5).

Table 4: Antibodies identified in fatalities due to hemolytic transfusion reactions, FY2017-FY2021

Antibody	FY17 No.	FY18 No.	FY19 No.	FY20 No.	FY21 No.	Total No.
ABO	1	2	4	2	5	**14**
Multiple* Antibodies	1	-	1	1	1	**4**
Other**	2	2	2	-	-	**6**
D	-	-	1	-	-	**1**
e	1	-	-	-	-	**1**
f	-	-	1	-	-	**1**
V	-	-	1	-	-	**1**
K	-	-	1	-	-	**1**
Fy^a	1	1	1	-	1	**4**
Jk^a	-	-	1	-	-	**1**
Jk^b	-	1	-	-	-	**1**
Jk3	-	-	1	-	-	**1**
M	-	-	1	-		**1**
U	1	-	-	-	-	**1**
Wr^a	-	1	-	-	-	**1**
Total	**7**	**7**	**15**	**3**	**7**	**39**

*Multiple Antibodies: FY2017: antibody combinations include: Jk^a+M
FY2019: antibody combinations include Fy^a + Jk^b
FY2020: antibody combinations include E + Jk^a + S
FY2021: antibody combinations include C+E+K+Jk^b+Fy^a+Fy^b

**Other: FY2017: Includes one report of Hyperhemolysis Syndrome in which no new or additional antibody was identified, 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 Warm Autoimmune Hemolytic Anemia 2) HTR with no definitive serological findings

[16] Storch, Emily K., et al. "Trends in ABO-Incompatible RBC Transfusion-Related Fatalities Reported to the FDA, 2000-2019." *Transfusion*, vol. 60, no. 12, 16 Oct. 2020, pp. 2867-2875, https://doi.org/10.1111/trf.16121.

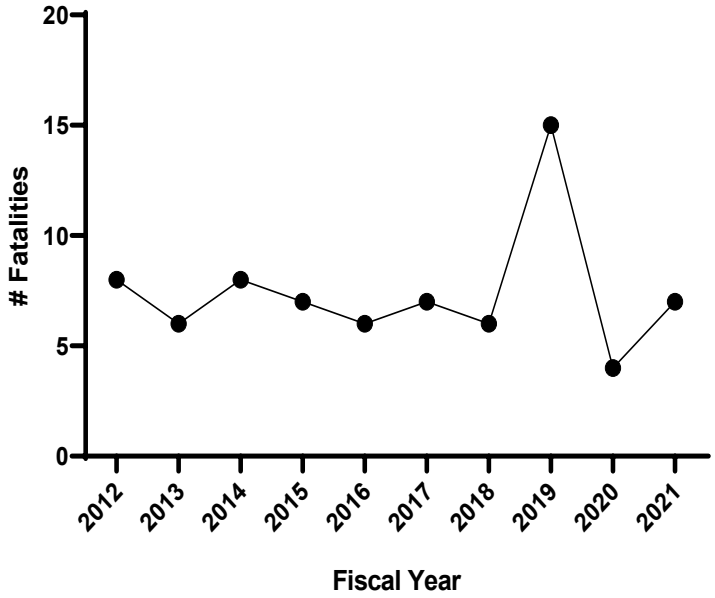

Figure 5: Hemolytic Transfusion Reaction Fatalities, FY2012 – FY2021

E. Microbial Contamination

In FY2021, there were five cases of contamination-related fatalities, all attributed to apheresis platelets contaminated with bacteria (Tables 5 & 6). Two of the cases were co-components from the same collection. Cultures from the implicated units grew *Escherichia coli, Staphylococcus aureus, Staphylococcus saprophyticus, Corynebacterium, Bacillus (not anthracis), Acinetobacter baumannii* complex, and *Leclercia adecarboxylata.*

Table 5: Contamination Breakdown, FY2021

Product	Organism	Imputability
Psoralen treated Apheresis Platelets	*Bacillus species (not anthracis), Acinetobacter baumannii complex, Leclercia adecarboxylata,* and *Staphylococcus saprophyticus.*	Definite
Apheresis Platelets	*Staphylococcus aureus*	Definite
Apheresis Platelets (Split unit)	*Escherichia coli*	Definite
Apheresis Platelets (Split unit)	*Escherichia coli*	Probable
Apheresis Platelets	*Corynebacterium striatum*	Possible

1. Contamination (*Bacillus species (not anthracis), Acinetobacter baumannii* complex, *Leclercia adecarboxylata, and Staphylococcus saprophyticus.) – *Definite*
A patient with comorbidities developed symptoms of a septic transfusion reaction upon receiving multiple blood products, including a psoralen-treated apheresis platelet unit on day five of storage. Gram stain of the returned partially transfused platelet unit grew many gram-positive bacilli and moderate gram-negative bacilli. Bacterial species identified following culture included *Bacillus species (not anthracis), Acinetobacter baumannii* complex*, Leclercia adecarboxylata, and Staphylococcus saprophyticus.* This case is part of a cluster of cases under investigation by FDA and CDC.[17]

2. Contamination (*Staphylococcus aureus*) – *Definite*
A patient receiving a unit of apheresis platelets on day five of storage as an outpatient developed signs and symptoms of a septic reaction during the transfusion including nausea, faintness, and hypotension, leading to discontinuation of the transfusion. Gram stain of the platelet unit was positive for gram-positive cocci in clusters and *Staphylococcus aureus* was identified in the residual platelet and the patient blood cultures. Culture of the main collection performed on day one of storage had been negative. The implicated unit was part of a triple platelet collection. A co-component failed visual inspection and was discarded but was not cultured. A second co-component was transfused to another patient without apparent complication.

3. Contamination (*E. coli*) – *Definite*
The patient received a single unit of apheresis platelets on day three of storage and developed signs and symptoms of a septic reaction including rigors, chills, hypoxia, and hypotension, progressing to shock and disseminated intravascular coagulation. *E. coli* was identified in the residual unit and the patient's blood culture. A platelet co-component from the same collection was also implicated in a septic transfusion reaction included in this annual report (see case 4 below) and grew the same organism. Culture of the main collection had been performed at 24 hours after collection and was negative.

4. Contamination (*E. coli*) – *Probable*
A critically ill patient with a complex medical history including respiratory failure requiring extracorporeal membrane oxygenation (ECMO) developed signs and symptoms of a septic reaction after receiving three units of packed red blood cells and a unit of apheresis platelets on day three of storage. The unit, a co-component of a contaminated collection (see case 3 above), was cultured and grew *E. coli*. The patient was already critically ill at the time of transfusion but deteriorated rapidly after transfusion; therefore, the imputability of the reaction to death was classified as *probable*.

5. Contamination *(Corynebacterium striatum) – Possible*
Six hours after transfusion of a unit of apheresis platelets on day three of storage, a patient with neutropenia and concern for disseminated intravascular coagulopathy developed signs of septic shock and the patient's blood culture grew *Corynebacterium striatum*. The implicated unit was not available for assessment or sampling. The unit was part of a triple platelet collection and each unit had been tested by bacterial culture and found to be negative. A co-component had been returned for a possible leak, but no leak was identified by the blood establishment. Considering the implicated unit was not tested, it was determined that the reaction was possibly related to a septic transfusion reaction, which possibly led to the patient's death.

[17] Important Information for Blood Establishments and Transfusion Services Regarding Bacterial Contamination of Platelets for Transfusion: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-information-blood-establishments-and-transfusion-services-regarding-bacterial

Table 6: Bacterial Contamination by Implicated Organism, FY2017 - FY2021

Organism	FY17	FY18	FY19	FY20	FY21	TOTAL
Acinetobacter spp.	-	1	-	-	-	**1**
Anaplasma phagocytophilum	1	-	-	-	-	**1**
Clostridium perfringens	2	1	-	-	-	**3**
Corynebacterium striatum	-	-	-	-	1	**1**
Escherichia coli	-	-	-	-	2	**2**
Klebsiella pneumoniae	1	-	-	-	-	**1**
Pseudomonas aeruginosa	-	1	-	-	-	**1**
Pseudomonas fluorescens	-	-	-	1	-	**1**
Pseudomonas veronii	-	1	-	-	-	**1**
Rahnella species	-	-	-	1	-	**1**
Serratia marcescens	-	-	1	-	-	**1**
Staphylococcus aureus	-	2	-	-	1	**3**
Staphylococcus epidermidis	1	-	-	-	-	**1**
Polymicrobial*	-	-	-	1	1	**2**
TOTAL	**5**	**6**	**1**	**3**	**5**	**20**

*FY2020 case of polymicrobial contamination involved *Acinetobacter sp.*, *Leclercia adecarboxylata*, and *Staph. Saprophyticus.* FY2021 case involved *Bacillus species (not Bacillus anthracis), Acinetobacter baumannii complex, Leclercia adecarboxylata, and Staphylococcus saprophyticus.*

FY	RBC	Pooled Platelets	Apheresis Platelets	Plasma
2017	1	0	5	1
2018	2	0	4	0
2019	0	1	0	0
2020	3	0	1	0
2021	0	0	5	0

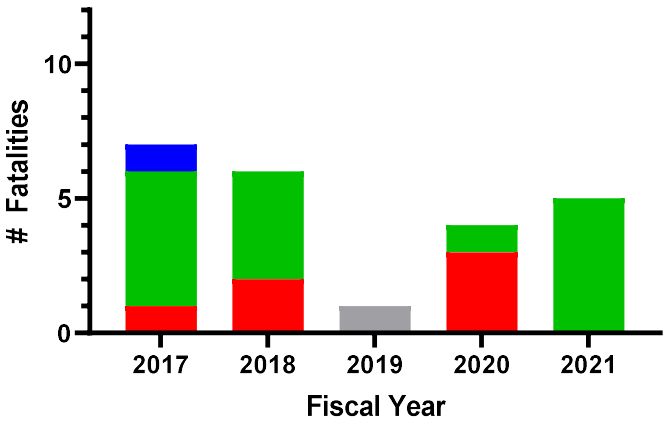

Figure 6: Contamination by Implicated Blood Product, FY2017-FY2021

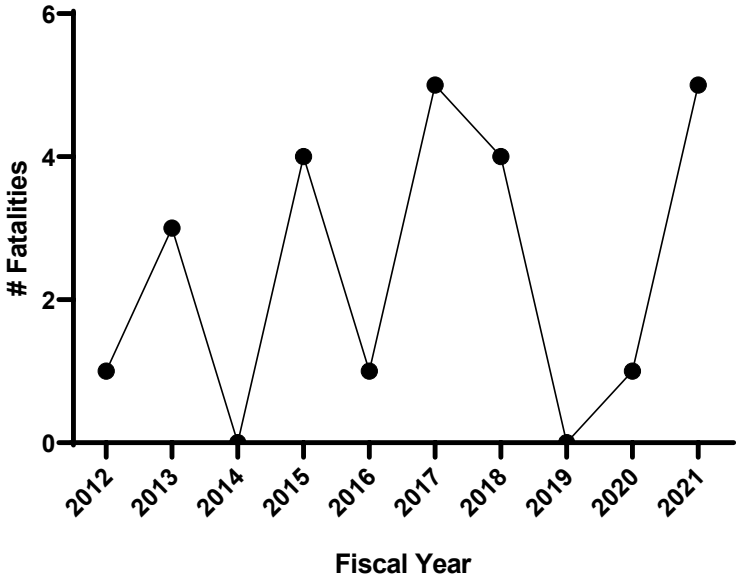

Figure 7: Contamination (bacterial) by Apheresis Platelets, FY2012 – FY2021

Figure 7 shows the trend of contamination (bacterial) associated with apheresis platelets from FY2012 to FY2021. There were five fatality reports of bacterial contamination in apheresis platelets reported in FY2021, a relative increase compared to 2020. Bacterial contamination of platelet components remains a public health concern which FDA has addressed in regulation (21 CFR 606.145), with additional considerations on controlling bacterial risk provided in the guidance document "*Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion*".[18] As the recommended implementation date of that guidance was October 1, 2021, this report covers a period in which bacterial risk mitigation strategies described in the guidance may not have been fully implemented.

[18] https://www.fda.gov/media/123448/download

F. Transfusion Doubtful as Cause of Death

We classified nine (15%) of the 60 cases described earlier as potentially associated with transfusion recipient fatalities in FY2021 as *doubtful,* including two No Transfusion Reaction, four TACO, one Possible TRALI, and two Transfusion Reaction, Type Not Determined. Although transfusion reactions could not be excluded as a contributing factor, the evidence in each of these cases more strongly favored the patients' underlying medical conditions. 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 one (2%) of the 60 cases described as potentially associated with transfusion recipient fatalities in FY2021 as *not assessable*. In this case, there was insufficient information submitted/available to determine the type of reaction and the extent of the relation between the transfusion and the death. Thus, the reported fatality was also not included in the analysis in Sections III.A through III.E.

H. Transfusion Ruled Out as Cause of Death

We classified eight (13%) of the 60 cases described as potentially associated with transfusion recipient fatalities in FY2021 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 FY2021, there were no donation fatalities classified as *definite*, one classified as pr*obable,* and there were six donations classified as *possible.* These numbers are similar to those reported in recent annual summaries (Figure 8). There were eight donation fatalities classified as *doubtful,* seven donation fatalities classified as *ruled out,* and nine donation fatalities classified as *not assessable* (Table 7).

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

- **Donation – *Possible***
  There were six 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 eight fatalities following Source Plasma donations in which the relationship between the donation and subsequent death was classified as *doubtful.* In these eight 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 seven fatalities following Source Plasma donation in which the donations were classified as *ruled out*. In these cases, there was 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 nine 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, FY2021

DONATION TYPE	Definite	Probable	Possible	Doubtful	Ruled Out	Not Assessable	TOTAL REPORTS
Source Plasma	-	1	6	8	7	9	**31**
Whole Blood	-	-	-	-	-	-	-
Apheresis Platelets	-	-	-	-	-	-	-
Apheresis Red Cells	-	-	-	-	-	-	-
Total	**-**	**1**	**6**	**8**	**7**	**9**	**31**

The row header refers to Imputabilility to Death

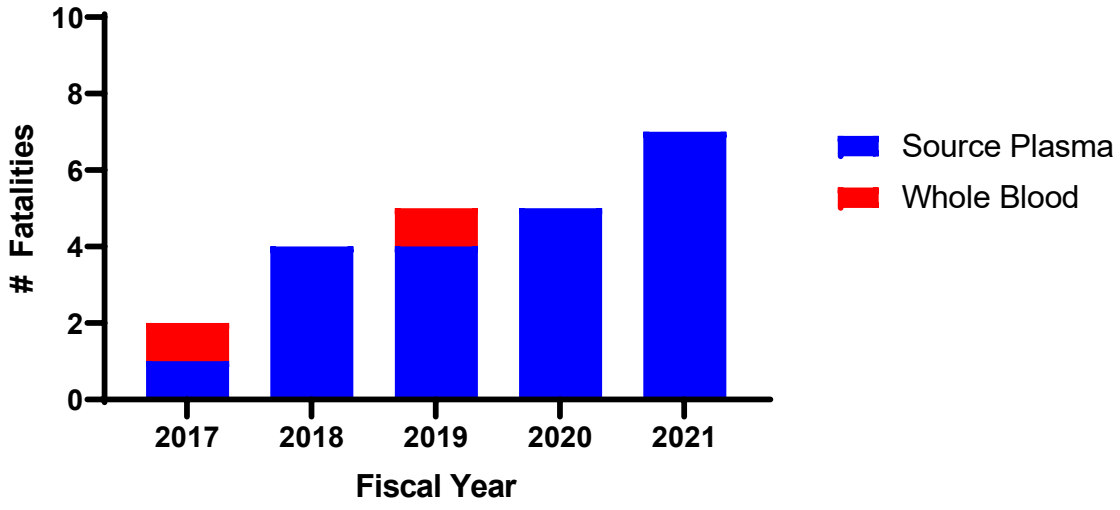

Figure 8: Donation Fatalities with *Possible, Probable*, or *Definite* Imputability by Product Type, FY2017-FY2021

Table 8: Donation with *Doubtful* or *Not Assessable* Imputability to Death by Product, FY2017-FY2021

Donated Product	FY17	FY18	FY19	FY20	FY21	TOTAL REPORTS
Source Plasma	6	4	8	11	17	**46**
Whole Blood	1	2	1	0	0	**4**
Apheresis Platelets	0	0	0	0	0	**0**
Apheresis Red Blood Cells	0	0	0	1	0	**1**
Total	**7**	**6**	**9**	**12**	**17**	**51**

Cases classified as *doubtful*, and *not assessable* would most accurately compare to the *donation not ruled out* cases from years prior to FY2015.

Table 9: Donation *Ruled Out* by Product, FY2017-FY2021

Donated Product	FY17	FY18	FY19	FY20	FY21	TOTAL REPORTS
Source Plasma	5	9	6	8	7	**35**
Whole Blood	-	-	-	-	-	**-**
Apheresis Platelets	-	-	-	-	-	**-**
Apheresis Red Blood Cells	-	-	-	-	-	**-**
Total	**5**	**9**	**6**	**8**	**7**	**35**