The ARC Hemovigilance Program: advancing the safety of blood donation and transfusion

A.F. Eder, B.A. Dy, J. Barton, J.M. Kennedy, and R.J. Benjamin

Since 2005, the American Red Cross (ARC) Hemovigilance Program has systematically evaluated adverse reactions and complications after blood donation and transfusion, which has led to improvements in safety for both donors and patients. After establishing baseline estimates of the risk of transfusion reactions such as transfusion-related acute lung injury (TRALI) and sepsis from bacterially contaminated platelet components, the program has demonstrated that the preventive measures that were implemented to reduce their occurrence were effective.[1–4] Reports of transfusion-transmitted infections, most commonly babesiosis linked to RBC components, have identified the need for targeted interventions.[5] The program has also described the spectrum of adverse reactions experienced by healthy volunteers after whole blood or apheresis donation, including systemic (e.g., vasovagal), phlebotomy-related, and other complications.[6,7] The information about donor reactions has led to several initiatives to reduce the already low rates of complications among the most susceptible groups and improve the donors' experience.[8,9] In this report, we present annual data on donation and transfusion complications in the ARC in 2007 and discuss the strengths and limitations of our national hemovigilance program.

Overview: Complications of Blood Transfusion

To meet safety goals (Table 1), the ARC Hemovigilance Program compiles and analyzes data from the 35 ARC regional blood centers across the United States and Puerto Rico. The regional blood centers investigate complications of transfusion reported by the hospitals and transfusion services that may be related to the blood donor or to the manufacture of the blood components.[10] Common transfusion reactions, such as allergic and febrile nonhemolytic reactions, as well as acute or delayed hemolytic reactions, are not usually reported, unless the blood centers also provide transfusion services to hospitals or a donor- or product-related issue is suspected to have caused the reaction. When a complication of transfusion is confirmed to be fatal, the facility that performed the compatibility testing must report the death to the U.S. Food and Drug Administration (FDA).[10] In these cases, the ARC Hemovigilance Program also provides a voluntary, supplemental report to the FDA with a medical assessment of the transfusion reaction along with the results of our donor and manufacturing investigation. When any transfusion reaction is reported, the blood centers take immediate action, if needed, to gain control and prevent transfusion of other components from the involved or prior donations, to temporarily defer the individual from donation, and to address any suspected problems with the manufacturing process or procedures.

After completing the investigation, the ARC physician evaluates all the information in the case and assigns a probability score on a 6-point scale, to classify the likelihood that the transfusion caused the reaction (Table 2). All cases are counted on a tally in the month that the investigation is closed and reported to the ARC Hemovigilance Program. The ARC Hemovigilance Program maintains a national database of investigated transfusion reactions to monitor, track, and analyze trends in donor and recipient complications at each region and across the system. The number of transfusion reactions investigated by the 35 ARC regions in calendar year 2007 is shown in Figure 1.

Table 1. ARC Hemovigilance Program goals

▪ To improve safety for recipients of blood components
▪ To minimize procedure risk for blood donors
▪ To identify significant trends that emerge from analysis of reports of uncommon events
▪ To identify strategies to reduce the risk of complications in susceptible patient and donor groups
▪ To monitor the effectiveness of the interventions introduced to improve safety

Table 2. Probability scores for transfusion reactions

P6 – The clinical information is consistent with a transfusion reaction, and a transfusion source is confirmed or highly probable (e.g., a donor or component was implicated).
P5 – The clinical information is supportive of a transfusion reaction, but a transfusion source is not identified.
P4 – The clinical information suggests that a transfusion reaction is posible or a transfusion reaction cannot be ruled out, but the case is not typical and a transfusion source is not identified.
P3 – The clinical information suggests that a transfusion reaction is possible but other etiologies are present and equally or more likely the cause of the reaction.
P2 – The clinical information does not support the diagnosis of a specified transfusion reaction.
P1 – There is insufficient information to investigate the case or case is rescinded by the reporting institution.

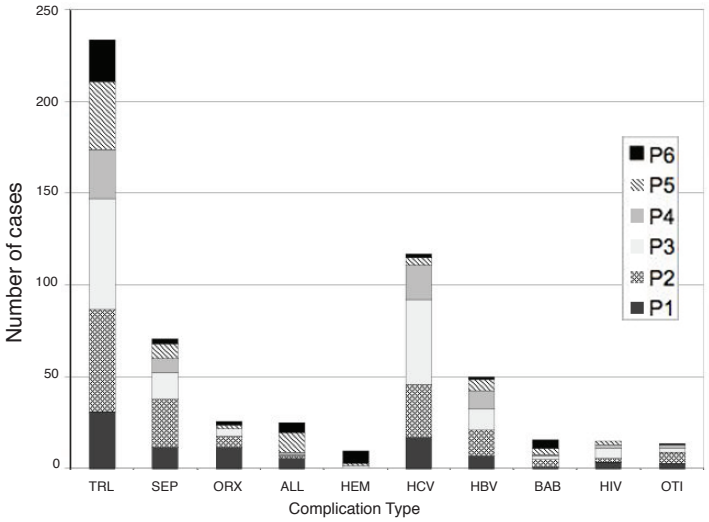

Fig. 1. The number of cases with complications after transfusions reported to the ARC Hemovigilance Program in 2007 is shown for all complication types. ALL = allergic; BAB = babesiosis; HBV = hepatitis B; HCV = hepatitis C; HEM = hemolytic; ORX = other transfusion reaction; OTI = other infection; SEP = septic; TRL = transfusion-related acute lung injury. P1-P6, see probability scores, Table 2.

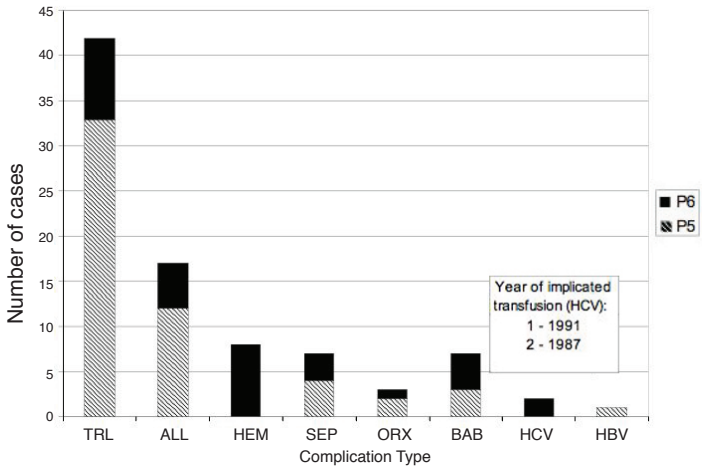

Fig. 2. The number of cases with complications after transfusions in 2007 reviewed by the ARC Hemovigilance Program is shown for all complication types, except hepatitis C (HCV). The number of cases open in 2007 is shown for HCV, with the year of transfusion in each case indicated on the graph. ALL = allergic; BAB = babesiosis; HBV = hepatitis B; HEM = hemolytic; ORX = other transfusion reaction; SEP = septic; TRL = transfusion-related acute lung injury. P5-P6, see probability scores, Table 2.

In addition to the monthly tallies of transfusion reactions, the ARC regions convey complete information to the ARC Hemovigilance Program on all suspected transfusion-related fatalities and adverse reactions determined to have a probable or confirmed transfusion source (i.e., cases assigned probability codes P5 or P6). These "high-probability" cases are reviewed by the national medical director of the ARC Hemovigilance Program and further characterized. This evaluation affords the advantage of having one physician review all high-probability cases to confirm that appropriate actions were taken and to achieve consistency in coding cases across the system. Moreover, the ARC Hemovigilance Program has developed more-specific case definitions for certain transfusion complications (e.g., *Babesia* infection) in an effort to more accurately describe the current transfusion risk, as described in greater detail in the following sections. The number of high-probability transfusion reactions reviewed by the ARC Hemovigilance Program in 2007 are shown in Figure 2. Focusing on the transfusion reactions most consistently reported to our blood centers, the ARC Hemovigilance Program has conducted in-depth analysis that has advanced transfusion safety for patients and identified the need for further interventions to improve clinical outcomes of transfusion.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) emerged as a leading cause of morbidity and mortality associated with blood component therapy, accounting for most of the deaths reported to the FDA since 2004.[11] The United Kingdom was the first to introduce precautionary measures, in 2003, to reduce TRALI by the preferential use of plasma from male donors. In the ensuing 5 years, their Serious Hazards of Transfusion program (SHOT) registered fewer TRALI cases and no fatalities associated with plasma transfusion.[12] Although 2008 saw three cases of TRALI that implicated a female donor of fresh-frozen plasma, SHOT reported no TRALI cases in 2005, 2006, or 2007.[12]

Similar to the United Kingdom's experience, the ARC Hemovigilance Program found that plasma components were responsible for the majority (63%) of probable TRALI fatalities and that a female antibody-positive donor was identified in 75 percent of these cases.[3] The number of reported TRALI cases increased each year between 2003 and 2006. In late 2006, the ARC began shifting plasma components collected from female donors to further pharmaceutical manufacturing so that the plasma distributed for transfusion to patients was collected predominantly from male donors. The proportion of plasma components collected from male donors progressively increased from 55 percent in 2006, to 78 percent in 2007, and to more than 95 percent in 2008. Concurrently, the number of probable TRALI cases among reported fatalities that involved only plasma transfusion was significantly decreased in 2008 (0 cases) compared with 2006 (6 cases) or 2007 (5 cases; $p < 0.05$).[4] Moreover, probable TRALI was more likely to be associated with plasma than RBC transfusion in 2006 and 2007, but not in 2008.[4]

Both the ARC Hemovigilance Program and the United Kingdom's SHOT organization acknowledge the limitations inherent to passive surveillance and retrospective review, including incomplete hospital and regional blood center

participation, and potential investigational, reporting, and analytical bias. Regardless, the encouraging reports from SHOT and the corroborative data from the ARC Hemovigilance Program suggest that limiting transfusion of leukocyte antibody–containing plasma components reduces the morbidity and mortality associated with TRALI.

In formulating a rational, and incremental, approach to TRALI prevention in the United States, blood centers are currently planning measures to reduce the risk of TRALI associated with apheresis platelet transfusion, while balancing the effect of any measures on availability of components for transfusions. Data on the effectiveness of these precautionary measures are not yet available but are being collected by the ARC Hemovigilance Program and other centers as the measures are introduced.

Septic Transfusion Reactions

In response to a new AABB Standard in 2004, most blood centers introduced methods to limit and detect bacteria in platelet components, which decreased but did not eliminate the risk of sepsis after apheresis platelet transfusion (Fig. 3).[1,2,13] The ARC Hemovigilance Program subsequently demonstrated incremental improvements in limiting contamination and increasing the sensitivity of bacterial testing to further reduce the risk of septic reactions to platelet transfusion. First, an association was observed between a method to collect apheresis platelets and subsequent transfusion-related sepsis. The increased risk with apheresis platelet donations from two-arm (double-needle) procedures compared with one-arm (single-needle) procedures was both clinically apparent as reported septic transfusion reactions and detected by routine quality-control bacterial culture of apheresis platelet donations.[1] The data implicated skin bacteria in the vast majority of clinical reactions and all reported fatalities. The most notable difference between the two procedure types was that two-arm collection sets did not discard or divert the initial 10 to 20 mL of blood collected from the draw line into a separate container or tubes during two-arm procedures, unlike the one-arm procedures. The lack of this feature on the collection set, commonly referred to as sample diversion, may have contributed to the higher amount of skin flora contamination of platelet components collected with the two-arm procedures.

To address this possibility, the ARC converted all apheresis collection procedures to use inlet-line sample diversion in 2006. Concomitantly, the sample volume taken for quality-control bacterial culture was increased from 4 mL to 8 mL from each apheresis platelet donation.[2] This change to double the sample volume was predicted to increase culture sensitivity by about 25 percent.[13] The ARC Hemovigilance Program reported the outcome after introducing the two operational changes and demonstrated that each measure contributed to a substantial improvement in safety for apheresis platelet transfusion.[2] First, inlet-line diversion decreased bacterial contamination during two-arm collections by more than 46 percent. Second, doubling the sample volume was associated with a 54 percent relative increase in culture sensitivity, which corresponded to the predicted absolute increase of 25 percent.[2,14] Similar benefit of initial sample diversion was observed for whole-blood–derived platelet pools when bacterial culture was introduced.[15] Ongoing surveillance by the ARC Hemovigilance Program and operational trials will continue to focus on the residual risk of septic reactions to platelet transfusion, to identify additional opportunities for improvement.

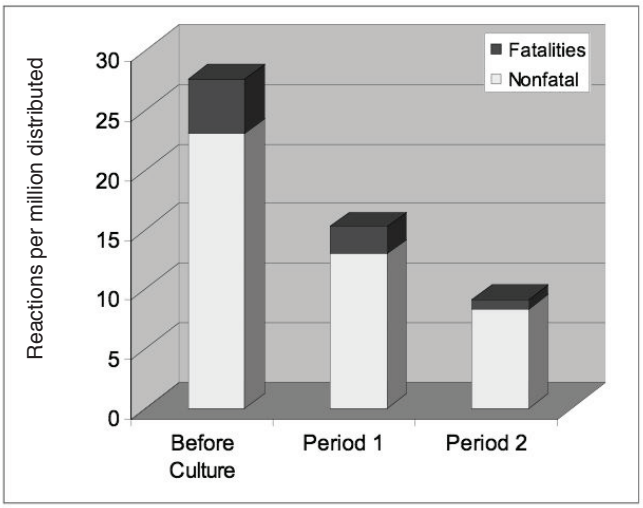

Fig. 3. The rate of septic transfusion reactions (per million apheresis platelet components created) before and after introducing routine quality control bacterial culture in Period 1 (39 percent of collection procedures with sample diversion; 4-mL sample volume cultured) and Period 2 (100 percent collection procedures with sample diversion, 8-mL sample volume cultured).[1,2,13] Reported fatalities are shown in red. The rate of septic reactions significantly decreased with time (Before Culture vs. Period 2, odds ratio, 0.33; 95 percent confidence interval, 014 to 0.76).

Infectious Complications of Transfusion

The ARC Hemovigilance Program also monitors all suspected transfusion-related infections reported to the 35 ARC blood centers that are investigated by regional physicians. Not surprisingly, transfusion-transmitted infectious diseases for which the blood supply is screened are rarely identified through passive surveillance even though hundreds of cases of suspected transfusion-transmitted infections are considered each year. Since the introduction of infectious disease testing more than 20 years ago and nucleic acid amplification testing (NAT) in 1999, the risk of infection with human immunodeficiency virus (HIV) or hepatitis C virus (HCV) through a blood transfusion has been reduced to an estimated 1 in 2 million.[16] FDA-mandated "lookback" procedures, which are initiated after a returning donor has a confirmed-positive HIV test result,

have identified only four reported breakthrough HIV cases from three implicated donations (nonreactive by minipool NAT) since 1999 in the United States.[16,17] HCV lookback is also required by the FDA; similarly, recipient-tracing is often performed for HBV and other infections, even though not required by FDA, when a donor is subsequently found to have confirmed positive test results. In addition, patients suspected of contracting infection through transfusion are reported and investigated by blood centers in an effort to determine whether any of the involved donations, which tested negative for all markers at the time of donation, were from donors who subsequently had positive test results. The ARC Hemovigilance Program has identified cases of transfusion-transmitted HCV and HIV; however, all transfusions occurred before 1999, and the implicated donors had previously triggered lookback, although the notification at the time had not identified the infected recipient. As expected, the rarity of definite cases of transfusion-transmitted infections identified through passive surveillance supports the known low risk of infection with viruses for which the blood supply is screened.

More importantly, the ARC Hemovigilance Program has delineated the risk of infections for which blood donors are not tested.[5] *Babesia microti* accounts for most of the infections investigated by the ARC, with five to ten definite or probable cases of transfusion transmission each year. Because of the difficulty in assessing whether infection was acquired through a blood transfusion or other means (e.g., tick exposure) in endemic areas, more specific definitions than the standard six-point imputability scale were developed by the ARC Hemovigilance Program to further define the likelihood of a transfusion source of infection (Table 3). The value in having detailed information on suspected cases is that it allows further characterization, which is not possible in other hemovigilance systems that do not capture primary data about the event. Although passive surveillance will not identify all cases, the scope of the problem defined by the ARC Hemovigilance Program supports the need for targeted interventions to reduce the risk of transfusion-transmitted *Babesia* infection.[18]

Table 3. Transfusion-transmitted *Babesia* classification

Cases in which the patient had a proven *B. microti* infection after transfusion that was not related to known prior infection were classified as

- "definite" if the patient was not a resident in a *Babesia*-endemic state (CT, NJ, NY, MN, WI), had no known risk factors for *Babesia* infection, was diagnosed with clinical disease within 3 months of transfusion, and a donor was identified and tested positive for *Babesia* antibodies or had evidence of recent infection;
- "probable" if the patient was a resident in a *Babesia*-endemic state (CT, NJ, NY, MN, WI) or had another risk factor for *Babesia* infection and a donor tested positive for *Babesia* antibodies or had evidence of recent infection; or
- "possible" if the donor was not tested but was a resident of an endemic area or had a recent travel history to an endemic area.

Donation-Related Complications

Although public attention, government regulation, and the industry effort are traditionally focused on patient safety, blood centers also have an obligation to make blood donation as safe as possible for healthy volunteers. Each year, the ARC evaluates about 7.8 million individuals who present to donate whole blood or apheresis components and provides about 40 percent of the blood for transfusion in the United States. The blood supply depends entirely on the daily commitment of volunteers, who gain only intangible personal benefit from blood donation but are exposed to potential risk of discomfort or, in rare cases, injury resulting from the collection procedure. About 2 to 12 percent of all presenting donors experience an adverse reaction that is documented at the collection site, most being classified as mild symptoms (e.g., lightheadedness, dizziness) that resolve promptly but are still unpleasant for the donor.[6,7] Serious injury is rare, but typically follows from a loss of consciousness, either at the donation site or after leaving the premises, or from nerve injury after the phlebotomy.[6]

All adverse reactions occurring at ARC collection sites are managed by collection staff and documented on the blood donation record according to the standard procedures. All donors are also instructed to contact the donor center if they experience problems or have concerns about their health after donation. Donor complications are classified according to the reaction type (systemic, phlebotomy-related, other) and severity of the symptoms (minor, major; Table 4). The reactions coded on the blood donation record by collections staff are captured in a centralized database; reactions that are called back to donor centers and cases that received outside medical care are captured in a separate database. The ARC Hemovigilance Program compiles and analyzes data on complications after whole blood donation that occurred at the collection site or that were reported to the blood center after the donor left the site and on all cases involving donors who were referred for outside medical care by staff or later reported that they sought or received care from another health-care provider (Table 5). Most syncopal-type reactions occurred at the collection site, but many cases involving loss of consciousness (LOC), prolonged recovery, or syncope-related injury were recognized or classified after the donation. About 15 percent of syncopal reactions result in injury (e.g., head trauma, lacerations, contusions), with about a third of these incidents requiring outside medical care (0.57 per 10,000 donations). Phlebotomy-related adverse events (e.g., large hematoma, suspected nerve irritation) more often become apparent after the donor leaves the collection site. Taking these reactions into account, the rate of suspected nerve irritation was 3.2 cases per 10,000 donations; only 13 percent of donors with possible nerve irritation reported receiving outside medical care (0.43 per 10,000 donations). The ARC Hemovigilance Program has evaluated the risks to certain groups of donors who are more susceptible to reactions after donation (e.g., young, first-time, female donors).[8] Future study will analyze the risk factors associated with delayed reactions and cases of out-

Table 4. Definitions of donor complications in the ARC

Systemic (syncopal-type):	
Minor category	***Major category***
Presyncopal (prefaint) Pallor, weakness, light-headedness, dizziness, diaphoresis, nausea/vomiting, no loss of consciousness	
Loss of consciousness (LOC), short: lasting less than 1 minute	LOC, long: lasting 1 minute or more or complicated by seizures or convulsions or loss of bladder or bowel control Prolonged recovery: Presyncopal symptoms, loss of consciousness or other reaction that does not resolve within approximately 30 minutes Injury associated with symptoms of prefaint or LOC (e.g., head injury, fractures, abrasions, lacerations)
Phlebotomy-related:	
Minor category	***Major category***
Hematoma, small: Involved area measures 2 × 2 inches or less	Hematoma, large: Involved area measures more than 2 × 2 inches Suspected nerve irritation: Suggested by pain, tingling, numbness, or sharp shooting pains after phlebotomy Suspected arterial puncture: Suggested by rapid (< 3 min) bleed time, pulsatile flow, or bright red blood
Other Reaction Types	
Minor category	***Major category***
Citrate reactions*: Perioral or peripheral tingling or numbness that does not resolve with reduced flow rate or oral calcium supplementation (e.g., Tums) or when accompanied by additional symptoms such as nausea, muscle tightness, or cramping; other symptoms	Citrate reactions*: Symptoms of minor citrate plus prolonged or exaggerated muscle spasm (tetany), vomiting, chest tightness
Allergic reaction, localized: Itching, rash, or redness of skin; hives	Allergic reaction, systemic: Symptoms of minor allergic reactions, plus swelling of the face, neck, or throat, wheezing, or respiratory difficulty
Other reaction: Symptom profile different from established categories (e.g., anxiousness, hyperventilation, headache)	Other reaction: Symptom profile different from established categories (e.g., chest pain, thrombophlebitis)

*Automated procedures only.

Table 5. Complications after whole blood donation, ARC Hemovigilance Program

Complication type	Complications after 12,033,323 whole blood donations					
	At collection site		All major reactions (subset, minor)*		Outside medical care	
	Number	Rate†	Number	Rate†	Number	Rate†
Systemic (syncopal-type)						
Minor categories						
Presyncopal (prefaint)	324,129	269	(766)	(0.64)	69	0.06
LOC (< 1 min)	11,081	9.21	(733)	(0.61)	107	0.09
Major categories						
LOC (≥ 1 min)	1,839	1.53	2,050	1.70	251	0.21
Prolonged recovery	2,623	2.18	4,228	3.51	829	0.69
LOC with injury	1,239	1.03	2,181	1.81	680	0.57
Subtotal‡	**340,911**	**283**	**9,958**	**8.28**	**1,936**	**1.61**
Phlebotomy-related						
Minor categories						
Small hematoma	125,082	104	(2,625)	(2.18)	87	0.07
Major categories						
Large hematoma	792	0.66	4,932	4.09	556	0.46
Suspected nerve irritation	1,021	0.85	3,858	3.20	513	0.43
Suspected arterial puncture	1,302	1.08	1,644	1.37	112	0.09
Subtotal‡	**128,197**	**107**	**13,059**	**10.9**	**1,268**	**1.05**
Other Reaction Types						
Minor categories						
Allergic (minor, local)	123	0.10	(166)	(0.14)	19	0.02
Other	458	0.38	(1,153)	(0.96)	141	0.12
Major categories						
Allergic (systemic)	10	0.01	17	0.01	11	0.01
Other	252	0.21	1,208	1.00	352	0.29
Subtotal‡	**843**	**0.70**	**2,544**	**2.11**	**523**	**0.43**
Total (all categories)	**469,951**	**391**	**25,561**	**21.2**	**3,727**	**3.10**

* This column includes all major events documented at the collection site and reactions reported after donation, which are reviewed by an ARC physician. The subset of minor reactions reviewed by an ARC physician, typically identified through callbacks, are included in parentheses.
† Rate per 10,000 donations (successful and unsuccessful [QNS] collections).
‡ Subtotals are of minor and major categories.
LOC = loss of consciousness.

side medical care to identify or refine preventive strategies for these more medically severe reactions or other symptoms after donation that lead to additional medical attention.

Conclusions

The ARC Hemovigilance Program is one aspect of a continuous improvement effort at the ARC to advance the safety of blood donation and transfusion. Data from the program have informed policy and have prompted changes in procedures to reduce the risk to both transfused patients and blood donors. The program's strength lies in its ability to analyze uncommon or rare events and to recognize trends that may be associated with certain donor selection or blood component manufacturing practices. Another advantage offered by a blood center–driven hemovigilance program is the ability to capture detailed information about each reported transfusion event and every donation-related complication, rather than summary information derived from the final assignment of reaction codes or aggregate data to estimate denominators. Challenges that the program faces are the inherent limitation of passive surveillance and the likelihood that hospitals do not report all transfusion reactions to the blood center. Regardless, the sample size is adequate to estimate the scope of TRALI, septic transfusion reactions, and transfusion-transmitted babesiosis. Finally, blood centers are typically focused on issues related to blood component manufacturing and donor selection; consequently, their hemovigilance programs are not designed to capture common, idiosyncratic transfusion reactions (e.g., allergic) or problems associated with medical errors or near misses, such as ABO incompatible transfusion, overtransfusion, or inappropriate transfusion practice. In this regard, the US Biovigilance Network, a unique public-private collaboration between the federal government (e.g., CDC, FDA) and organizations involved in blood collection, transfusion, and tissue and organ transplantation (e.g., AABB) promises to address this need in a national hemovigilance program for the United States.[19] In conclusion, blood centers have a dual responsibility to provide an adequate supply of blood components to the community and to protect the safety of volunteer donors. We have made our data available to highlight our continued focus on improving donor and patient safety.

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Anne F. Eder, MD, PhD; Beth A. Dy; Jessica Barton; Jean M. Kennedy, RN, and Richard J. Benjamin, MD, PhD, American Red Cross, National Headquarters, Biomedical Services, Medical Office, 15601 Crabbs Branch Way, Rockville, MD 20855

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