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## Blood Component Recalls and Market Withdrawals: Frequency, Reasons, and Management in the United States

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### ARTICLE INFO

#### Article history:

Available online 1 February 2013

### ABSTRACT

In a previous article, we reviewed the management of blood component recalls and withdrawals (G. Ramsey. *Transfusion Med Rev* 2004;18:36–45). Since then, US rates of recall and biological product deviation for blood components have improved significantly, particularly with regard to reduced recalls for donor infectious disease risks or testing. However, analysis of the current data from the US Food and Drug Administration suggests that 1 (0.4%) in 250 blood components is involved in market withdrawals and quarantines, with 1 in 5800 components formally recalled. Most of these units, unfortunately, had already have been transfused. The US Food and Drug Administration has issued several recent guidances that address transfusion service actions for dealing with specific infectious disease problems. This present article updates our 2004 recommendations as to when to notify physicians about transfused nonconforming blood components.

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IN 2004 IN this journal, we reviewed the topic of managing blood component recalls and market withdrawals, mainly from the viewpoint of the transfusion service [1]. We examined the most common postdistribution problems with blood components, according to recall notices and biological product deviation (BPD) reports from the US Food and Drug Administration (FDA). We summarized regulatory and accreditation requirements, advocated establishment of standard operating procedures for the immediate response to blood supplier notices, and provided suggestions as to when to notify physicians about problems found in retrospect after transfusions to patients.

Since then, several new issues and problems have evolved, and the FDA has published or revised a number of guidelines on postdonation problems. The purpose of this article is to update our previous review with data trends, developments, and relevant publications since 2004. Interested readers may consult our earlier article for an overview with background information and general perspectives.

### Blood Component Recalls: 20 Years of Progress

The term *recall* is commonly used generically to refer to notices from blood suppliers to consignees about blood components. Table 1 summarizes the FDA's legal definitions for recalls and market

withdrawals. All recalls are published in the weekly US FDA Enforcement Reports [3]. Market withdrawals are not published.

Table 2 displays the annual numbers of recalled blood components extracted from FDA Enforcement Reports in 1990 to 1998 [4,5], in 2006 [6], and in 2011. Units for manufacturing (eg, source plasma) were not included. The recall reasons for 1998, 2006, and 2011 were categorized according to the 1990's analyses for comparison. Please note that the 1990 to 1997 data exclude 2 large recalls for incorrect syphilis testing, involving 135 300 units.

Recalls published in 2011 totaled 4743 blood components, involved in 1072 recalls (4.4 units per recall). There were no class I recalls representing the highest concern. Eighty-three percent of the recalls including 64% of the recalled units were class II recalls, and the rest were included as class III recalls. The 2011 figures were significantly less than were reported in previous years, with the bulk of this decline coming from a reduction in the number of infectious disease problems. The combined numbers of units with infectious disease issues—incorrect testing, past or present positive donor test results, or possible bacterial contamination—declined from more than 7000 units annually in the 1990s to less than 500 in 2011. In contrast, donor screening and donor risk issues have remained fairly high and relatively constant over the years. Blood collection, storage, and shipping issues accounted for the most recalled units over the period of observation.

In 1990 to 1998 and 2006, the overall estimated rate of recalls of available blood components was 1 in 1500 to 1 in 2000 units. For a 2011 rate estimate, we calculated the US annual total available blood components to be 27 705 000 units, using the latest 2009 National Blood Collection and Utilization Survey Report (2008 data) [7]. This figure included all available whole blood/red blood cell (RCB) units

Funding: None.

Conflict of interest: None.

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plus all non-RBC components produced and subtracted the RBC and non-RBC components, which outdated at blood centers. We counted whole blood-derived (WBD) platelets as individual units, not pools; the proportion of WBD platelets issued as pre-pooled doses from blood centers (and therefore subject to recall as 1 unit, not 5) was not given in the survey. Using this denominator, the recall rate for the annualized 2011 data was 1 in 5800 units, one-third of the rates seen in earlier years. To the extent that pre-pooled WBD platelets would reduce this denominator, the rate would be somewhat higher.

### Improving Trends in BPDs

Blood banks and transfusion services in the United States must report BPDs to the FDA [8]. Biological product deviations occur when blood products are issued and later found to be unsuitable due to safety, potency, or labeling problems. Recalls and market withdrawal notices sent to transfusion services originate from problems reportable as BPDs. The FDA issues annual reports summarizing the numbers and categories of BPDs. Figure 1 shows annual BPD numbers for fiscal years (FY) 2007 to 2011 for facilities licensed for interstate commerce, mainly blood centers. (The US federal FY starts on September 1 of the previous calendar year.) The 3 most common reasons among these BPDs are postdonation donor information and geographical deferrals for risk of malaria and variant Creutzfeldt-Jacob disease (vCJD). Also shown are the numbers of BPDs that the FDA deemed serious enough to be “potential recalls.” The numbers of blood components in BPDs are not reported.

Biological product deviations, both overall and within the 3 major categories shown, declined 14% to 22% from FY 2007 to FY 2011. The annual numbers of potential recalls in the BPDs declined even further, 66%, paralleling the decline in recalled units in the Enforcement Reports from 13 758 units in 2006 to 4743 units in 2011 (Table 2). The annual numbers of recall BPDs in Figure 1 do not correlate precisely with the annual recalls in the FDA Enforcement Reports because the latter reports lag months or years behind the recall actions. We excluded Enforcement Report recalls of units for further manufacture (eg, source plasma) from our analysis. However, the 2011 rate of 1072 blood component recalls per year in the Enforcement Reports is of similar magnitude to the BPD statistics of 1189 and 838 potential recalls in the preceding FY 2009 and 2010.

### Frequency of Notifications About Blood Components

Although the downward trend in BPDs is gratifying, the total number of BPDs is far greater than the recall BPDs—37 times greater in FY 2011. Therefore, the total number of blood components subject to market withdrawal is probably far greater than the number of recalled units contained in the Enforcement Reports. If transfusion services were notified about all 24 754 of these BPDs and if the average

number of blood components per BPD is 4.4, as in the 2011 Enforcement Reports for recalls, then 108 900 blood components annually may be associated with post-issue notices, or about 1 (0.39%) in 254 available components.

Although this rate is an extrapolation, our current experience is of similar magnitude at Northwestern Memorial Hospital in Chicago. In 2 years from 2008 to 2010, we received 146 200 blood components and, over the same period, received 326 notices about 671 blood components, or 1 (0.46%) in 218 units. Some of these notices were for quarantines, which were subsequently lifted after donor center investigations; such notices therefore may not become BPDs in the FDA statistics but add to the totals managed by the transfusion services.

### Food and Drug Administration and AABB Publications Since 2003

Table 3 lists by topic the most current versions of various federal publications addressing the notification of transfusion recipients when blood components are found in retrospect to have been out of compliance. The following section summarizes updates since our January 2004 publication. Also noted below are recommendations from the AABB regarding platelets found to contain bacteria.

#### *Human Immunodeficiency Virus and Hepatitis C Virus*

Lookback regulations for tracing past recipients of blood components from human immunodeficiency virus (HIV)- and hepatitis C virus (HCV)-reactive blood donors were modified in 2007 by the FDA for blood banks and by the US Centers for Medicare and Medicaid Services (CMS) for hospitals [12–15,18]. These modified rules incorporated donor nucleic acid testing (NAT). The FDA issued a May 2010 guidance on donor HIV and HCV NAT, which included test result algorithms on which donors needed to have a lookback performed and a December 2010 guidance on performing HCV lookback [16,17]. In some cases, donors with ambiguous HIV NAT results must still have lookbacks performed as a precaution. All historical lookbacks on donors identified before February 2008, which permitted the hospital transfusion service 1 year to trace and notify recipients, were to have been completed by 2009. For current lookbacks, the consignees have 12 weeks to make reasonable attempts to complete their notifications. However, the CMS rule says if the hospital cannot locate the recipient, it can document in the patient medical record extenuating circumstances beyond the hospital's control as to why more than 12 weeks was needed [14]. Either the patient or the physician of record can be notified by the transfusion service or the hospital, but in either case, the recipient must be notified, according to commentary accompanying the rules changes [13]. For deceased recipients of HIV lookback units (in case of potential exposure to others) and for legally incompetent or minor recipients, the next of kin or legal representative must be notified. These rule changes also increased the FDA requirement for record retention of all blood component dispositions from 5 to 10 years [12,18].

#### *West Nile Virus*

The June 2005 guidance expanded the previously recommended timeframes of donations from West Nile virus (WNV)-suspected donors for which recipient notifications are recommended [25]. For donors with a medical diagnosis of WNV, recipients of donations from –14 to +120 days from illness onset should be notified. For donors identified as the likely source of a transfusion-transmitted WNV infection, recipients of other units donated from –120 to +120 days from the infectious donation should be notified.

**Table 1**  
FDA definitions of recalls and market withdrawals, 21 CFR 7.3 [2]

Recall: removal or correction of a marketed product that the FDA considers to be in violation of the law it administers and against which the agency would initiate legal action, eg, seizure
Recall classification for use of, or exposure to, a violative product:
Class I: reasonable probability [of] serious adverse health consequences or death
Class II: may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote
Class III: not likely to cause adverse health consequences
Market withdrawal: removal or correction of a distributed product that involves a minor violation that would not be subject to legal action by the FDA
or that involves no violation, eg, normal stock rotation practices, routine equipment adjustments, and repairs

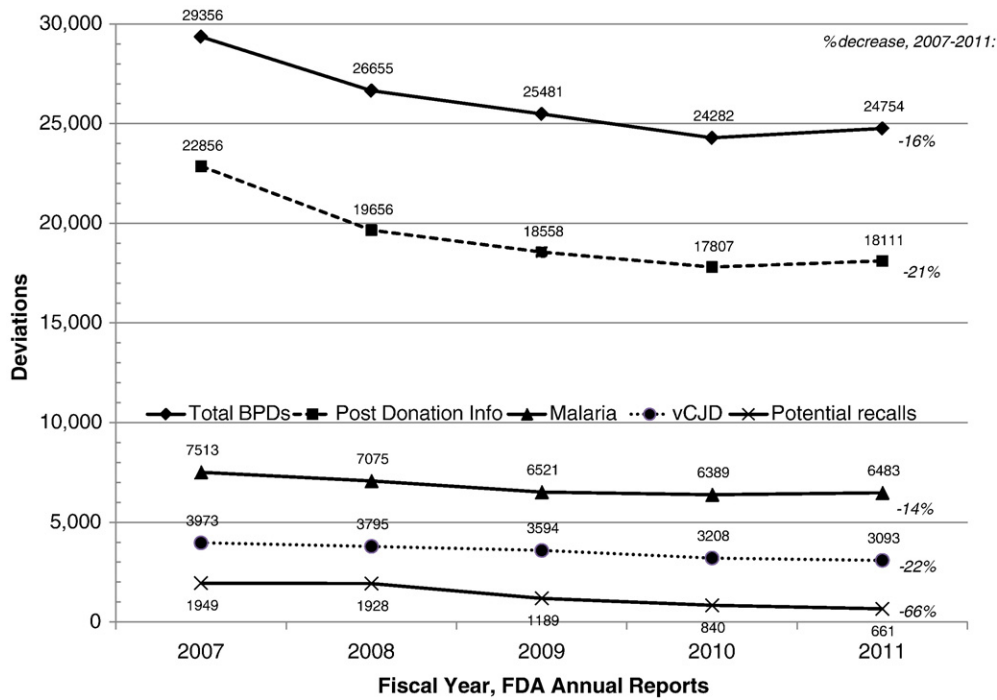


Fig 1. Biological product deviation reports from US licensed blood establishments, 2007 to 2011 [8].

*Trypanosoma cruzi* (Chagas Disease)

A December 2010 guidance addresses past recipients of donors with a positive history or screening test result for *T cruzi* [24]. For seropositive donors who lived in, or whose mother lived in, an endemic area (possible vertical transmission), or if a donor is otherwise diagnosed as having *T cruzi* infection, the transfusion service is encouraged to notify past recipients' physicians of a possible increased risk of *T cruzi* transmission. This notification should be done within 12 weeks.

No confirmed new *T cruzi* infections were found by the American Red Cross and United Blood Services in testing their first 4.2 million previously negative allogeneic repeat donors [27]. Twenty-one donors (1:200 000) became reactive for antibody by radioimmunoprecipitation assay, but none of these were confirmed as true infections in further investigation. Thus, unlike other infectious agents, repeat US

blood donors seldom develop new Chagas disease, which would generate notices to hospitals about past units. The 2010 FDA guidance recommends that testing each donor only once is sufficient [24].

Blood centers in the United States, Canada, and Spain recently analyzed their collective experience with tracing recipients from *T cruzi*-positive donors [28]. The only definite transmissions were in 6 of 45 platelet recipients; none of 197 RBCs and 80 frozen-thawed plasmas and cryoprecipitate units were infectious. Some of the infectious platelet units were leukoreduced.

*Creutzfeldt-Jacob Disease and vCJD*

In recent years, convincing evidence of transfusion-transmitted vCJD has emerged from Britain [29,30]. As part of the British response to this concern, transfusion recipients from donors who later

**Table 2**  
Categories and yearly numbers of recalled blood components, US FDA Enforcement Reports

Category	1990-1997 [4] (annualized)	1998 [5]	2006 [6]	2011
Inadequate donor history	1300	110	1166	625
Donor risk factors	280	720	863	938
Collection	540	200	3543	745
Component preparation	890	1000	4834	760
Labeling	580	290	195	253
Storage/Shipping	360	350	2060	1278
Multiple reasons	1420	0	0	0
Incomplete ID testing	340	20	59	7
Incorrect viral testing	5590	1400	108	450
Incorrect syphilis testing	220 <sup>a</sup>	560	597	30
History of positive ID test	1690	5350	120	116
Positive ID test	90	40	6	3
Suspected bacteria	19	12	207	56
Total ID reasons	7949	7382	1097	458
Total annual	13319	10052	13758	4739

ID, infectious disease.

<sup>a</sup> Excludes 2 large 1990's recalls, for incorrect syphilis testing, involving 135 300 units.

**Table 3**  
FDA and CMS publications addressing notices from blood collection facilities to consignees

Topic	Publication	Date	Reference
Anthrax	Guidance	October 17, 2001	[9]
Chagas disease: see <i>T cruzi</i>			
CJD, vCJD <sup>a</sup>	Guidance	May 2010	[10]
HBV	Memorandum	July 19, 1996	[11]
HCV lookback <sup>a</sup>	Rules	August 24, 2007	[12–15]
HCV lookback <sup>a</sup>	Guidance	December 2010	[16]
HCV NAT <sup>a</sup>	Guidance	May 2010	[17]
HIV lookback <sup>a</sup>	Rules	August 24, 2007	[14,15,18]
HIV NAT <sup>a</sup>	Guidance	May 2010	[17]
HTLV	Memorandum	July 19, 1996	[11]
HTLV	Guidance	August 15, 1997	[19]
Malaria <sup>a</sup>	Guidance, draft	June 2012	[20]
SARS	Guidance	September 2003	[21]
Smallpox vaccination	Guidance	December 30, 2002	[22]
Syphilis	Guidance, draft	June 25, 2003	[23]
<i>T cruzi</i> <sup>a</sup>	Guidance	December 2010	[24]
WNV <sup>a</sup>	Guidance	June 2005	[25]
Xenotransplantation	Guidance, draft	February 1, 2002	[26]

HTLV, human T-lymphotropic virus; SARS, severe acute respiratory syndrome.

<sup>a</sup> See text.

developed vCJD are notified [30,31]. In May 2010, the FDA issued guidance on CJD and vCJD donor issues, which included recommendations about recipient notification [10]. Notification was not recommended for recipients from donors deferred for vCJD geographical risk, use of bovine insulin, a single family member with CJD, or transfusions in Britain or France. (The FDA is considering whether to add Saudi Arabia to the vCJD risk regions [32].) For donors younger than 55 years subsequently found to have vCJD, suspected vCJD, or CJD, the FDA requests telephone notification and a BPD report from the collection facility as soon as possible, for review with the Centers for Disease Control and Prevention (CDC). For donors with CJD, suspected or diagnosed vCJD, or other risk factors, “consignee notification could enable the consignee to inform the physician...so that medically appropriate notification and counseling may be performed at the discretion of health care providers.” There is still no evidence to date of transfusion transmission of traditional CJD [33]. Transfusion services receiving a notice about donor CJD or vCJD may contact the FDA or the CDC for the most current advice on recipient counseling and evaluation.

### *Malaria*

A draft guidance in June 2012 proposed that collection facilities should notify consignees who received cellular and noncellular blood components from donors who should have been deferred for a clinical history of malaria without documented treatment [20]. If this draft guidance is adopted, physicians of patients who received these components would be advised to monitor the recipients for malaria for 3 months after transfusion. Frozen-thawed plasma and cryoprecipitate would be included, although in our setting, we would convey that the known risk from these units is very low.

### *Bacteria in Platelets*

Accrediting agencies now require bacterial testing of platelets, raising the possibility of posttransfusion discovery in samples from a platelet unit or its cocomponents. The AABB issued an Association Bulletin to its members in 2004, which included recommendations in this circumstance [34]. The transfused patient’s physician should be notified immediately and provided all available information about the positive test result and its follow-up evaluation. Any available units or cocomponents should have a Gram stain performed for immediate guidance. The recipient should have blood cultures even if no signs of sepsis are present. The 2004 Bulletin also recommended that the transfusing physician report back to the transfusion service on the clinical status and course of the recipient and that bacterial isolates from the recipient should be saved for comparison with the donor unit. Another Bulletin in 2012 emphasized prompt tracking and retrieval of cocomponents of units suspected of causing septic transfusion reactions [35].

A bacterial antigen detection test has been FDA cleared for platelet quality control. The positive predictive value of this test in trials of routine usage was 17% for WBD platelet pools (2 true of 12 total positives) and 2% for poststorage plateletpheresis units (3 true of 145 total positives) [36]. However, as a precaution in our practice, we would notify the transfusing physician about a reactive bacterial antigen test in a cocomponent, pending final resolution.

### *Emerging Infectious Disease Agents*

The AABB Transfusion-Transmitted Diseases Committee published a special supplement issue of *Transfusion* in 2009 on emerging infections and their possible implications for blood safety [37]. They compiled the characteristics and epidemiology of 68 agents including potential bioterrorism microbes. These summaries are a useful starting point for evaluating possible transfusion exposure to

an unusual infection. The committee’s highest-priority rated agent not currently addressed in donor screening or testing was dengue virus, which has since been confirmed to be transmitted by transfusion in Puerto Rico [38]. In case of donor or transfusion exposure to dengue, the closest analogy to current agents would be its fellow flavivirus, WNV.

### **Accreditation Requirements Updates**

Since our 2004 review, the following relevant changes have been made to the AABB Standards for Blood Banks and Transfusion Services and the College of American Pathologists accreditation checklist for transfusion medicine.

In the AABB Standards for Blood Banks and Transfusion Services, chapter 7 addresses product deviations and nonconformances, and standard 7.0 requires policies, processes, and procedures for managing deviations from product requirements [39]. One sentence was added to standard 7.0 in the 27th edition (2011): “The investigation shall, whenever applicable, include an assessment of the effect of the deviation on donor eligibility and donor and patient safety.” Since 2004, the College of American Pathologists added item TRM.42135: “Blood Supplier Notifications: The transfusion service has a procedure for managing quarantines, recalls, and market withdrawals issued by its blood suppliers” [40]. TRM.42120 requires a quarantine procedure for notices about donors testing reactive for infectious diseases, and TRM.42170 requires a lookback procedure consistent with local and national regulations and guidelines for notifying and counseling recipients transfused with potentially infectious blood components. The recommended “evidence of compliance” for these items is the pertinent records of notices and actions taken.

### **Recommendations for Managing Recalls and Withdrawals**

Our 2004 review discussed the following elements in a process for managing notifications from blood suppliers:

1. Have a standard operating procedure for directors and laboratory personnel.
2. Act immediately to quarantine, return, or discard blood components as instructed by the supplier.
3. Review and determine the medical implications of components already transfused.
4. Keep records as required of all notices and actions.
5. Consider involving the transfusion committee or its local equivalent.
6. As needed, consult other resources such as the infectious disease service, the ethics committee, public relations, risk management, or the legal office.

An analysis of the recall and withdrawal process in Canada was conducted by the Canadian Blood Services and McMaster University [41]. During extensive interviews with stakeholders, numerous problems were highlighted and recommendations were formulated for blood centers and hospitals. Good communication from collection facilities was a general theme, to provide the nature of the problem, the immediate course of action, and whether recipient notification should be performed. Recommendations to hospitals for handling notices were enumerated. The authors called for national or provincial guidelines for when to notify recipients and for mechanisms for expert input on unusual situations beyond such guidelines.

Subsequently, Canadian Blood Services and its National Advisory Committee on Blood and Blood Products developed a document entitled “Recommendations for the Notification of Recipients of a



**Table 4**  
Suggested approaches for the follow-up of blood components discovered after the transfusion to have been in nonconformance (BPDs)

Type of deviation	Notify patient's physician?
<b>Postdonation information</b>	
At donation of unit in question, donor should have been deferred for:	
Malaria-risk travel	No, if donor travel was in Mexico (see text) No, if apheresis platelets (see text), frozen-thawed plasma, cryoprecipitate Yes otherwise, if RBCs, granulocytes, or WBD platelets
vCJD risk travel, bovine insulin, 1 CJD relative, or UK/France transfusion	No (FDA guidance [10])
Other vCJD risks	See FDA guidance [10]
Tattoo or ear/body piercing	Yes, if sterility uncertain <sup>a</sup>
Cancer	No
Disease/surgery	Assess details for medical impact
Intravenous drug use	Yes <sup>a</sup>
Antibiotics or other medications	Yes, if teratogenic medication and pregnant recipient (see text) If possible bacterial contamination, did a transfusion reaction occur?
Smallpox vaccination	See FDA guidance [22]
Previously transmitting transfusion-related infection	Yes <sup>a</sup>
Seeking testing or asking for blood to be discarded	Yes <sup>a</sup>
Risk factors for HIV or hepatitis exposure	Yes <sup>a</sup>
Severe acute respiratory syndrome (SARS), or exposure	See FDA guidance [21]
After unit in question, donor later developed:	
HIV infection	Yes <sup>a</sup> (HIV lookback [14,15,17,18])
Clinical hepatitis, or confirmed anti-HCV, HCV RNA, or HBsAg	Yes <sup>a</sup> (lookback if HCV [12–17]) (Note: FDA does not require HBV lookback [11].)
Confirmed anti-HTLV-I or II	Yes <sup>a</sup> , if cellular product (although transmission unlikely after 10 d of refrigeration) (Note: FDA does not require HTLV lookback [11].)
Confirmed syphilis antibody	No (FDA draft guidance [23])
WNV illness or positive WNV NAT	Yes, if within dates of FDA guidance [25]
SARS	See FDA guidance [21]
CJD or vCJD	Contact FDA or CDC [10] (see text)
Indeterminate anti-HIV, anti-HCV, or anti-HTLV	No
Reactive screening test, but negative supplemental testing result	No
Reactive anti-HBc	No (anti-HBc, FDA memorandum [11])
Babesiosis	Yes, if cellular product (see text)
<b>Donor screening and deferral</b>	
Vital signs unacceptable or not documented	Did recipient have septic transfusion reaction?
Hematocrit unacceptable	No
Screening incomplete (history, arm check, donor signature)	No
Incorrect reentry after reactive screening test	Assess details of timing and results of testing
<b>Quality control and distribution</b>	
Clotted or hemolyzed unit or segment	Did recipient have transfusion reaction?
Outdated product	Did recipient have transfusion reaction?
Shipped or stored at incorrect temperature	Did recipient have transfusion reaction?
Unacceptable RBC, platelet, or clotting factor content	No
Not irradiated, leukoreduced, or CMV-reduced risk as ordered	Yes, if patient did not receive required product

**Table 4 (continued)**

Type of deviation	Notify patient's physician?
<b>Labeling</b>	
Recipient ID incorrect (including autologous)	Did wrong patient receive unit?
Expiration extended erroneously	If unit was given after true expiration, did recipient have transfusion reaction?
ABO, Rh, or RBC antigen label incorrect	Did recipient have transfusion reaction or receive Rh-incompatible RBC-containing product?
Irradiation, leukoreduction, or CMV status incorrect	Yes, if recipient did not receive required need
Donor number incorrect	No, but fix patient and laboratory record with correct unit number
Product type incorrect	Assess medical impact
Anticoagulant incorrect	No
Testing (of the unit in question)	
Incorrect infectious disease testing	Yes <sup>a</sup>
Reactive infectious disease testing	Yes, unless supplemental testing result is negative
Reactive bacterial antigen test in product or cocomponent	Yes, pending confirmation (see text)
Confirmed bacterial detection in product or cocomponent	Yes
Incorrect ABO, Rh, or RBC antigen testing	Did recipient have transfusion reaction or receive Rh-incompatible RBC-containing product?
Incorrect RBC antibody testing	No
Component preparation	
Incorrect irradiation or leukoreduction	Yes, if recipient did not receive required need
Sterility compromised	Did patient have transfusion reaction or infection?
Incorrect temperature	Did patient have transfusion reaction?
Additive solution not added, or added incorrectly	Was unit actually outdated when given?
Collection	
Sterility compromised	Did patient have transfusion reaction or infection?
Outdated collection bag	Did patient have transfusion reaction or infection?
Phlebotomy time or volume incorrect	No

HTLV, human T-lymphotropic virus; CMV, cytomegalovirus.

<sup>a</sup> Unless donor later tested negative for marker(s) in question, after the appropriate seroconversion period (Table 5 and text).

Blood Component Recall" [42]. Their general approach to these issues is similar to ours, as discussed later.

Wasserman and Dure [43] discussed their experience on a pediatric hospital ethics committee that considered the question of when to notify patients about blood component recalls and market withdrawals. The authors' viewpoint was that the patient's right to health information was most important, and therefore, transfusion recipients should be informed about all notices of any nature. However, the hospital decided to notify patients based on the level of risk for the problem. The authors criticized "amateur ethicists" who use "routine balancing of simplified principles to the exclusion of reflexive practices," as opposed to professionals with "ownership of ethical thought and the ability to work beyond principles as deterministic." However, Scofield [44] cited this work in his criticism of the concept of the "expert ethicist," in which he argued that ethicists should not impose their opinions in a democratic society.

#### Notification of the Recipient's Physician

By the time the transfusion service receives notice about problematic blood components, the transfusion usually already had occurred. The transfusion service should evaluate the potential impact on the recipient and whether the recipient's physician should be

notified. HIV and HCV lookbacks, as defined by the FDA, are legally mandated, and as discussed previously, the FDA or the AABB has provided recommendations for some specific issues.

Table 4 presents suggested considerations for the determination of whether to notify the physician of a transfusion recipient when a retrospectively noncompliant blood component has been given. This table was adapted from our previous review [1], and as noted previously, these are intended only to be recommendations for consideration based on our previous experience. Canadian recommendations are also available as noted earlier [42]. Others may choose different approaches.

### Malaria

In this version of Table 4 under donors with malaria risk travel, we have excluded physician notification for donor travel to Mexico and for apheresis platelets. More than 150 000 prospective donors are deferred annually in the United States for malaria risk travel [45]. The CDC has added information about deferring blood donations to the malaria section of its Yellow Book for travel medicine [46]. However, unrecognized malaria risk travel is still the most common single reason for BPDs in blood components (Fig 1). Donor travel to Mexico has been scrutinized in recent years. Malaria (*Plasmodium vivax*) has drastically declined in Mexico from historical levels, with reported cases down 98% from 1985 to 2005. Although Mexican travel is probably the most common locale for malaria deferrals in US donors, detailed analysis of local malaria infections by the Retrovirus Epidemiology Donor Study-II group showed that three-fourths of US donors deferred for Mexican travel went to areas where little or no local malaria is occurring, such as Quintana Roo (Cancun and Cozumel region, Yucatan peninsula) [45]. The FDA Blood Products Advisory Committee recommended in 2009 to lift the deferral for travelers to rural Quintana Roo, and the FDA's June 2012 draft guidance would do so, if adopted [20,45]. The Retrovirus Epidemiology Donor Study-II group estimated that with the exception of Oaxaca, which accounted for less than 3% of US donor deferrals for Mexican travel, the risk of malaria transmission from US blood donors returning from Mexico might be around 1 unit every 20 years nationwide [45]. Given this low probability, in our practice, we are not notifying the transfused patient's physician when Mexico is the donor's travel risk.

In the last 19 years of annual CDC surveillance reports on malaria (1992–2010 online), there were 15 transfusion-transmitted cases, but only 1 was from platelets [47]. Although contaminating RBCs in platelet transfusions can transmit malaria—6% of the US transfusion malaria cases from 1963 to 1999—the last reported case was from WBD platelets in 1992 [48]. (An apparently pre-1992 case from WBD platelets was published in 1996 [49].) Considering the low RBC content in today's apheresis platelets, and the dearth of reports from platelet transfusions over the past 2 decades, we are no longer notifying transfusing physicians about apheresis platelets from malaria-area travelers.

### Babesiosis

More than 150 transfusion-transmitted cases of babesiosis, some fatal, have been diagnosed in the United States [50,51]. In addition to RBCs, frozen-thawed RBCs and WBD platelets have been implicated. The AABB issued a membership Bulletin on babesiosis in 2009, which gave examples of approaches to handle blood donors found to have babesiosis [52]. Some blood centers were withdrawing previous cellular donations from such donors, but no recommendations were made by the AABB about patients who already had received these cellular transfusions. When lookback was conducted in New England on past cellular blood components from seropositive donors in a prevalence study, 7 of 38 RBC recipients and 1 of 15 WBD platelet recipients tested positive [53]. A donor testing study in progress in 2011 to 2013 in multiple US blood centers is performing lookback notifications and testing of prior recipients [54]. In our practice, we

would notify the transfusing physician about a cellular component from a *Babesia*-positive donor.

### Retinoid Medications

The longest US deferrals are for the long-lived retinoids etretinate [Tegison (Hoffman-LaRoche, Basel, Switzerland), permanent deferral] and acitretin [Soriatane (Stiefel Laboratories, Research Triangle Park, NC), 3-year deferral]. Workers in South Korea studied blood donors who were taking retinoids and their transfusion recipients. Thirty-two percent of donors on these drugs and 2 of 41 recipients of blood products from such donors had detectable plasma drug levels [55,56]. Nine women with pregnancies during or after such transfusions had no problems in their babies, although none of them were transfused during the first trimester, the greatest period of risk [57,58]. If a pregnant woman receives a blood component from a donor who should have been deferred for teratogenic medication use, we would notify the patient's physician, but the risk from acitretin-exposed donors appears to be very low.

### Viral Seroconversion After Donor or Recipient Exposure

In evaluating retrospective donor testing information, or for advising donors or transfusion recipients when to be retested after a possible exposure, seroconversion window periods (WPs) for viral markers are important considerations. Table 5 summarizes WP data for tests approved for blood donation in the United States or Canada; other clinical tests may have different WPs. In NAT, a larger donor pool size with more dilution lengthens the predicted WP. Individually tested donor or recipient NAT WPs are somewhat shorter, especially for hepatitis B virus (HBV) because of its slower ramp-up than HIV and HCV.

Another perspective of relevance for this issue is the recommended testing regimens for donor reentry or for occupational exposures such as needlesticks. The FDA's donor reentry guidance for possible false-positive tests for antibody to HBV core antigen (anti-HBc) recommends an 8-week period before retesting by HBV NAT, HBV surface antigen (HBsAg), and anti-HBc [63]. The CDC's testing guidelines after occupational exposure to HIV, HCV, and HBV are summarized in Table 6. In case of a very recent high-risk transfusion exposure in which rapid intervention may be warranted, an infectious disease consultant or the CDC can provide timely advice.

In contrast to these agents, WNV is usually a temporary infection. In newly infected blood donors, the initial WP is thought to be only 1 to 2 days of rapid ramp-up, followed typically by 6 to 9 days of viremia detectable as routinely tested in plasma with pooled NAT [67]. Then a "tail" of lower-level viremia has been detected for up to 3 months [68]. Donors could be infectious but NAT negative in the early or late stages of this sequence, depending in part on test sensitivity, for example,

**Table 5**

Viral seroconversion WPs for infectious disease tests approved for North American blood donors

Virus	Assay	Format	WP (d)	Range	Reference
HIV	Anti-HIV-1	EIA	22	6-38	[59]
	HIV NAT	16-pool	10	9-11 (95% CI)	[60]
		Individual	6		[61]
HCV	Anti-HCV	EIA	58	7-10 (95% CI)	[61]
	HCV NAT	16-pool	8		[60]
		Individual	5		[61]
HBV	HBsAg	EIA	44	37-50 (95% CI)	[62]
		ChLIA	39	33-44 (95% CI)	[60]
	HBV NAT	16-pool	30-35	20-25	[62]
		Individual	20-25		[62]
HTLV	Anti-HTLV-1	EIA	51	36-72	[59]

For practical purposes, days are rounded to up to the next whole day when the original report included fractional days. The range of HBV NAT WPs shown is based on calculations using assay sensitivities of either 10 or 40 copies/mL. EIA, enzyme-linked immunoassay; ChLIA, chemiluminescent immunoassay; CI, confidence interval; HTLV, human T-lymphotropic virus.

**Table 6**

CDC recommendations for follow-up testing after occupational exposure to blood-borne viruses

Virus	Test	Follow-up timing
HIV [64,65]	Anti-HIV	6 wk, 12 wk, 6 mo
	HIV NAT	Not recommended
HCV [65]	Anti-HCV and ALT	4–6 mo
	HCV NAT	4–6 wk
HBV [65,66]	Test recommendations not given in occupational guidelines	
	CDC HBV information: HBsAg detected 1–9 wk (average, 4 wk) after exposure	

Occupational exposure guidelines may be of relevance in evaluating possible exposures in blood donors or transfusion recipients. The CDC-endorsed National Clinicians' Post-Exposure Prophylaxis Hotline (+1-888-448-4911) provides immediate advice on HIV, HCV, and HBV and could be helpful in a very recent potential transfusion exposure. ALT, alanine aminotransferase.

switching to more sensitive individual-donor NAT when infections are identified locally. Whole blood specimens are under investigation for donor testing because they have higher WNV levels than plasma in the convalescent phase [68]. For assessment of a recently potentially exposed transfusion recipient, the CDC's recommendations on acute and convalescent anti-WNV serology in suspected illness may be consulted [69].

### Improving Donor Screening to Reduce Postdonation Problems

Collection facilities depend on candidate donors to reveal deferring information. In the 1990s, 1.7% to 3.0% of US blood donors did not report reasons warranting deferral, according to postdonation survey studies [70,71]. As we have seen, most of the currently estimated 0.4% of blood components discovered to be noncompliant after release come from donors who should have been deferred but were not. Donors who generated BPDs with postdonation information are more likely older, male, and more educated than deferred donors [72].

Table 7 lists several problems that have been identified with donor screening and deferral. Also shown are some recent measures that may potentially reduce the rate of falsely eligible donations. Some of these measures may be contributing to the gradual decline in BPDs in recent years. However, to date, there have been few published demonstrations of specific interventions shown to reduce “false-negative” donor history screening.

### Conclusions

Since our review in 2004, both BPDs and recalls for US blood components have declined, and the numbers of incidents involving direct infectious disease concerns have fallen even faster. Still, by our

**Table 7**

Issues affecting inaccurate or ineffective donor screening deferrals

	Reference
Problems	
Donations despite risk factors	[70,71]
Donor attitudes about risk factors	
HIV test seeking	[73,74]
Intravenous drug users	[75]
Sexual practice	[76]
Donor understanding of screening materials	[77]
Donor history questionnaire (DHQ) complex, poorly organized	[78]
Training needs of screening personnel	[79,80]
Deferral notifications confusing, upsetting, misinterpreted	[81,82]
Changes with potential impact	
Improved DHQ	[83]
Abbreviated DHQ	[84]
Computer-assisted self-interview	[85]
Maps for geographic deferrals	[86,87]

estimates, there may be more than 108 000 blood components annually in the United States—about 1 (0.4%) in 250—which, after issuance, are found to be out of compliance. Transfusion services have become accustomed to these notices, and accrediting bodies require procedures for managing them. However, familiarity should not preclude local and national efforts to improve practices and reduce problems in this arena. We offer the following suggestions for quality improvement and prevention of blood component recalls and market withdrawals.

1. *Improve data availability and analysis.* The FDA publishes weekly raw data on recalls but should also publish annual summaries, as is done for BPDs. Better yet would be an interactive database for organizing and searching public information on these and all other recalls.
2. *Improve donor screening.* Numerous problems have been identified that may contribute to false-negative deferral screening, but demonstrations of successful interventions are scarce. Better screening might even reduce unnecessary deferrals, as was observed in one malaria travel project [87].
3. *Improve processes to notify transfusion services and transfusing physicians.* The Canadian analysis indicated needs for better communications to hospitals about problems with donors or components [41]. When there are infectious disease concerns about a donor, supplying information on whether the donor was subsequently tested and the most recent results, if any, is a simple but helpful measure.
4. *Improve knowledge of the medical consequences of transfusing nonconforming blood components.* Other than HIV/HCV look-back, little information has been collected on the outcomes in transfusion recipients or the concerns of their physicians.
5. *Use outcomes knowledge from recipients to better inform the donor screening process.* This would help complete the quality improvement loop from donors to recipients and back to donors again.

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