別紙様式第2-1

No. 5

医薬品 研究報告 調査報告書

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一般的名称	人血清アルブミン		研究報告の公表状況	Dorsey K, Zou S, Schonberger L, Fang C, Dodd R. TRANSFUSION 2008-Vol. 48 Supplement	公表国 米国	
販売名(企業名)	赤十字アルブミン20(日本赤十字社) 赤十字アルブミン25(日本赤十字社)					

研究報告の概要

○古典的CJDの輸血伝播リスクは、仮にあるとしてもvCJDよりも有意に低い－USルックバック試験

背景:1995年に米国赤十字(ARC)と疾病管理予防センター(CDC)は、古典的クロイツフェルト・ヤコブ病(CJD)についてのルックバック調査による評価を開始した。これまで、ヒトにおける古典的CJDの輸血伝播の報告はない一方、変異型CJD(vCJD)の輸血伝播は英国で報告されている。

方法:供血後にCJDと診断された供血者(CJD供血者)に由来する血液成分の受血者を登録した。生存受血者については登録以降毎年バイタルサインをモニターした。受血者が死亡した場合は死因を調査し、2005年末までの死亡を網羅した。

結果:古典的CJDを発症した供血者計35名(2名を除き孤発性CJD)および受血者430名を本試験に登録した。2005年までに生存受血者88名(1,135人年)、死亡受血者326名(813.5人年)、後に追跡不能となった受血者16名(64.5人年)の合計2,013人年の輸血後追跡調査が行われた。受血者のうち、144名は5年以上生存(長期生存者)し、CJDによる死亡は確認されなかった。長期生存者については、さらに関係する製剤輸血日と供血者のCJD診断日の間隔を調査し、英国におけるvCJDの観察と比較した。CJDの輸血伝播リスクは、vCJDと比べて有意に低かった(p = 0.0117, Fisher の直接確率検定)。

結論:今回のルックバック検査の結果は、孤発性CJDの受血者への輸血伝播の証拠がないことを示しており、CJDの輸血伝播のリスクは(仮にあったとしても)vCJDと比較して有意に低いことを示すものである。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25

血液を原料とすることに由来する感染症伝播等

報告企業の意見

古典的CJDを発症した供血者計35名に由来する血液成分の受血者430名のルックバック調査の結果、孤発性CJDが輸血で伝播する証拠はなく、リスクはvCJDと比較して有意に低いとの報告である。

今後の対応

これまでの疫学研究等では、血液製剤を介して古典的CJD(孤発性、遺伝性および医原性CJD)が伝播するという証拠はない。またCJDの病原因子とされる異常プリオンがアルブミン製剤の製造工程で効果的に除去されるとの報告もあるが、輸血あるいは第Ⅷ因子製剤によりvCJDに感染する可能性が示唆されたことから、今後も引き続き情報の収集に努める。なお、日本赤十字社は、CJD、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)、CJDの既往歴(本人、血縁者)、hGH製剤投与の有無を確認し、該当するドナーを無期限に献血延期としている。

MedDRA / J Ver.11.0 J

JRC2008T-075

Disclosure of Conflict of Interest
Shadaba Asad, Leonard Mermel, Joseph Sweeney, Nothing to Disclose

S86-030K

Direct Assessment of CMV Transfusion Transmitted Risks Post Universal Leukoreduction

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Background: CMV transmission through transfusion remains a clinical concern. Two effective strategies to reduce the risks of CMV TTD have been the provision of CMV seronegative blood and leukoreduction. Even though it is still under debate, these two methods have been considered operationally equivalent in many institutional policies. For many hospitals, universal leukoreduction has become the main strategy for the prevention of CMV TTD. Direct assessment of CMV TTD risk is lacking in the era of universal leukoreduction. In this study, through prospective clinical follow-up and testing of transfusion recipients (TR) for CMV Ab and nucleic acids and CMV Ab testing of their linked donors, the risk for CMV TTD was studied.

Methods: As part of a prospective study of multiple donor exposure TRs, CMV TTD risk was assessed. Transfused units were all leukoreduced and not prospectively screened to be CMV seronegative. CMV total Ab and Nucleic Acid testing (NAT) were performed on all TRs baseline samples. For TR with negative baseline CMV testing, all follow-up TR samples were tested for CMV total Ab and NAT, and retained linked donor samples were tested for CMV total Ab. In cases when CMV TTD was suspected based on seroconversion, with or without supportive clinical evidence, donors were also tested for CMV NAT when possible. Evaluable transfusion was defined as a transfusion with TR sample(s) collected 14 to 180 days post transfusion in TR with a negative baseline CMV testing. **Results:** 46 evaluable TRs were negative for CMV at baseline. There were 1319 evaluable cellular blood component transfusions. Out of these, there were 655 RBCs for 43 TRs and 664 platelets for 31 TRs. Out of 1319 retained linked donor samples, 485 were positive for CMV total Ab. There were 19 case investigations due to changes in CMV testing results. Three appeared to be true infections or seroconversion. These may be related to transfusion; however, there was no definitive proof from donor follow-up that they were transfusion associated. Two were determined to be true infections but not transfusion related. Six were attributed to passive Ab transfer. Eight could not be determined due to inadequate information. **Conclusion:** Based on the No. of infections or seroconversions over the No. of TRs who were seronegative at baseline, the calculated CMV potential TTD rate was as high as 6.5% (3/46). Based on the No. of infection or seroconversions over the No. of transfused donor units, the calculated CMV potential TTD risks was: for leukoreduced but non-CMV screened cellular products, as high as 0.23% (3/1319); for leukoreduced and CMV seronegative (tested after transfusion) leukoreduced but non-CMV screened cellular products, as high as 0.62% (3/485). In summary, post-universal leukoreduction, CMV-transfusion-transmission, while uncommon, may still occur.

Disclosure of Conflict of Interest
Richard Cable, Shiman Zou, Kem Dorsey, Yanlin Tang, Cheryl Hapip, Russell Meimet, Jonathan Trouem-Trend, Chyang Fang, Melanie Champion, Roger Dodd: Nothing to Disclose
YanYun Wu: ARC - Grants or Research Support

S87-030K

A Linked Donor and Recipient Study of B19 Viral Transmission by Blood Component Transfusion

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Background: B19 virus (B19V) transmission by pooled plasma products has occurred from Factor VIII when DNA concentration (conc) exceeded 10^4 IU/mL and from SD plasma at a DNA conc of $>10^2$ IU/mL; this has led to "in process" screening of recovered and source plasma units for high B19V DNA conc (~10^4 IU/mL). Although several cases of B19V infection have occurred from component (cmpt) transfusion (tx), B19 screening is generally not performed for transfusable components as there has been no systematic study of this transmission rate or its association with B19 DNA conc. **Methods:** DNA positive (pos) donations (dnns) were identified by screening frozen repository plasma specimens (spms) using a previously validated sensitive kinetic PCR assay. Tx transmission was evaluated using various B19V assays to test pre- and 6-12 months post-tx specimens from adult surgical patients who received B19 DNA pos and negative (neg) control components; controls were selected in a 2:1 ratio and matched for factors influencing B19 transmission by non-tx routes. B19 transmission was inferred if either DNA, IgG, or IgM seroconversion occurred post-tx as demonstrated by replicate testing. Rates were determined in susceptible (susc) (i.e. pre-tx IgG antibody (Ab) neg) recipients and controls. **Results:** 105 of 12,529 donor specimens (0.83%) were B19 DNA pos; see the Table for plasma DNA concs. 110 components (mostly rbcs) from 103 pos donations with DNA <10^4 IU/mL (all of which were IgG Ab pos) were transfused to 105 recipients. There was no evidence of B19 infection in 21 susc case recipients (rate = 0.0%; 95% CI: 0.0-13.3) or in 43 susc control recipients (rate = 0.0%; 95% CI: 0.0-8.7). The estimated tx-transmission rate was thus 0.0% (95% CI: 0.0-13.3). Two components with >10^4 IU/mL were transfused to pre-tx B19 IgG Ab pos recipients, precluding assessment of tx transmission. **Conclusions:** Although we documented a high frequency of low conc (especially <10^4 IU/mL) B19 DNA and IgG Ab pos donations, the lack of tx transmission by these components indicates that such transmission does not occur, or if it occurs, is relatively uncommon (≤13%). These data do not support the need for real time screening of blood components with a sensitive B19 NAT assay.

TABLE. Linkage of B19 DNA pos components to recipients

B19 DNA conc (IU/mL)	# pos dnns	# DNA pos cmpts tx'd to susc recipients	# DNA pos cmpts tx'd to non-susc recipients	Total # DNA pos cmpts tx'd
<20	56	15	45	60
20-<10[2]	19	2	18	20
10^2-<10^3	23	3	22	25
10^3-<10^4	4	1	3	4
10^4-<10^5	0	0	0	0
10^5-<10^6	1	0	1	1
Subtotal	103	21	89*	110*
≥10^6	2	0	2	2
Total	105	21	91*	112*

*More than one component was tx'd for some pos donations; some recipients received more than 1 pos component.

Disclosure of Conflict of Interest
Steven Kleinman, Simone Glynn, Tzong-Hsie Lee, Leslie Tobler, Karen Schlumpf, Deborah Todd, for the NHLBI Retrovirus Epid Donor Study-II, Michael P. Busch: Nothing to Disclose

S88-030K

The Risk of Transfusion Transmission of Classic CJD is Lower Than vCJD, If not Zero – Results from US Look-Back Study

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Background: In 1995, the American Red Cross (ARC) and the Centers for Disease Control and Prevention (CDC) initiated a look-back investigation to assess the risk of transfusion transmission of classic forms of Creutzfeldt – Jakob disease (CJD), sporadic, familial and iatrogenic CJD. The presence of the infectious agent of classic CJD in blood has been documented in experimental animals, but no transfusion transmission of classic CJD in humans has been reported. In contrast, transfusion transmission of variant CJD (vCJD) has been documented in the United Kingdom. **Methods:** Blood donors who were subsequently diagnosed as having CJD (CJD donors) were identified by reports primarily from collaborating blood centers, the Food and Drug Administration (FDA), and family members. Following verification that the CJD diagnosis was made by a neurologist or confirmed by a pathologist, blood centers identified the donations made by the CJD donor and located the hospitals that received any of the blood components. The recipients of these components that were identified by hospitals were enrolled into the study. Their vital status, and cause of death, if deceased, was monitored by searching CDC's National Death Index (NDI) database at enrollment and every year thereafter for surviving recipients. The last NDI search covered deaths through the end of 2005. **Results:** A total of 35 blood donors with classic (non-variant) CJD and 430 recipients were enrolled in the study. All but 2 donors had sporadic CJD. Through 2005, recipients contributed a total of 2,013 person-years (py) of follow-up time since receipt of their blood transfusion. 1,135 py from 88 surviving recipients, 813.5 py

from 326 deceased recipients and 64.5 py from 16 recipients who were subsequently lost to follow up. Among the recipients, 144 survived 5 years or more (long-term survivors). No deaths from CJD were identified among the recipients. The most common causes of death among the recipients were cancers (followed by cardiovascular diseases. The long-term survivors were further analyzed by the interval between the date of transfusion of the implicated unit and the date of diagnosis of CJD in the donor. A comparison of observations of vCJD in the UK (TMER study) using recipients who lived 5 or more years post-transfusion and had received the unit of blood from a donor whose symptoms occurred 60 months prior to onset of symptoms. The transfusion transmission risk of CJD was statistically significantly lower than that of vCJD ($p = 0.0117$, Fishere exact test). Conclusions: The results from this look-back study continue to show no evidence of transfusion transmission of sporadic CJD to recipients. The results indicate that the risk, if any, of transfusion transmission of CJD is significantly lower that than that of vCJD.

Disclosure of Conflict of Interest
Kerri Dorsey, Shimian Zou, Lawrence Schonberger, Chyang Fang, Roger Dodd: Nothing to Disclose

S89-030K
Current Value of Serologic Test for Syphilis as a Surrogate Marker for Bloodborne Viral Infections among US Blood Donors
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Background: Routine serologic screening for syphilis has been conducted for two reasons: 1) preventing transfusion transmission of syphilis although its value has been shown to be limited; 2) serving as a surrogate marker for infections caused by other pathogens such as HIV. This study assessed the current value of the test in safeguarding the blood supply against other presently tested viral infections. **Methods:** Testing results for voluntary and directed, whole blood, repeat donors in 2005-2006 with a large US blood supplier were analyzed. All donations were tested according to standard procedures for anti-HIV, HIV RNA, anti-HCV, HCV RNA, HBsAg, antibodies against human T-lymphotropic virus (anti-HTLV), syphilis and other markers. Incidence rate was defined as the number of confirmed seroconverters or viral RNA converters over total number of person-years observed. Sensitivity referred to the number of confirmed syphilis seroconverters among all confirmed converters for another infection, such as HIV, whereas positive predictive value (PPV) was the number of confirmed HIV converters among all confirmed syphilis seroconverters. Applying the sensitivity of syphilis testing in identifying new infections of another agent to the estimated number of donors during the window-period of the other infection gave the estimated number of window-period (w-p) units removed by syphilis testing. **Results:** There were significantly higher frequencies of HIV, HCV, HBsAg and HTLV positive donations among those with positive syphilis tests although such samples would not be expected to escape detection because of the use of multiple tests for most markers. Among 3,068,320 repeat donors with confirmed testing for both syphilis and anti-HIV, 168 seroconverted for syphilis but not for anti-HIV, 57 seroconverted for anti-HIV but not for syphilis, with only 1 seroconverted for both, resulting in an incidence ratio of 331 (95% CI: 46, 2390) between syphilis seroconverters vs. non-seroconverters, a sensitivity of 1.7% and a PPV of 0.6%. There were 4 additional HIV RNA converters who did not seroconvert for syphilis, resulting in an incidence ratio of 309 (43, 2231), a sensitivity of 1.8% and a PPV of 0.6%. No syphilis seroconverters converted for HCV, HBsAg or anti-HTLV. The result for HIV represented an estimated removal by syphilis testing of 0.11 w-p units out of a total of 9.5 million repeat donations during the two-year period if only anti-HIV is tested and of 0.07 w-p units if HIV RNA is also tested. **Conclusion:** Our data show that syphilis testing has a very low sensitivity and PPV for detecting other viral infections. It presents no surrogate value for HCV, HBV and HTLV infections and could only remove approximately one HIV window-period unit out of every 95 million donations from repeat donors.

Disclosure of Conflict of Interest
Shimian Zou, Edward Notari, Chyang Fang, Susan L. Stramer, Roger Dodd: Nothing to Disclose

Transfusion Practice/Clinical Case Studies

S90-030L
Accumulation of Thrombospondin-1 (TSP-1) in Packed Red Blood Cells is Reduced by Whole Blood Leukoreduction Filters
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Background: Independent of other factors related to shock, blood transfusion is a risk factor for multiorgan failure (MOF) in trauma. The risk of organ failure, sepsis, and death correlates with increasing transfusion amount. Pathological specimens of organs of patients with MOF and disseminated intravascular coagulation (DIC) show widespread microvascular thrombosis. Multiple hemostatic changes occur in MOF leading to DIC. Degranulation of platelet α-granule glycoproteins correlates with the severity of MOF. TSP-1(thrombin sensitive protein) is one of the most abundant proteins in the platelet α-granule comprising 25%, and is part of a class of extracellular proteins which modulate cell-matrix interactions. TSP-1 is produced by platelets, megakaryocytes, endothelial cells, fibroblasts, monocytes, macrophages, and osteoblasts. TSP-1 binds to extracellular molecules including heparin, collagen, fibrinogen, fibronectin, plasminogen activator, and osteonectin. TSP-1 also binds to cells via CD36, CD47, and integrins. TSP-1 plays a role in platelet adhesion with other cells and with extracellular proteins. The accumulation of TSP-1 in PRBC was evaluated during PRBC storage as a possible contributor to MOF due to transfusion. **Methods:** Ten units of whole blood were separated into equal aliquots, one filtered with whole blood leukoreduction filters (Leukotrap-SC RC, Pall) and one unfiltered. Half units of PRBC were prepared and stored at 4°C in CPD-AS3. Aliquots from each unit were removed weekly, and plasma was separated from the cellular component and frozen at –80°C for simultaneous testing of PRBC supernatant for TSP-1 by ELISA (Pierce Searchlight). **Results:** During storage TSP-1 levels in PRBC supernatant increased to 24 times that seen on the day of collection. Filtration at collection results in maintenance of day 0 levels throughout storage. **Conclusions:** RBCs adhere to endothelium as they age. In trauma, with massive transfusion of old RBCs, the RE system is overwhelmed by rapid infusion of PS expressing cells which can occlude small vessels. The presence of molecules in PRBC supernatant which can lead to adhesion of platelets and leukocytes with further occlusion may contribute to development of MOF. This is especially important in the face of ongoing endothelial injury. The use of leukoreduction filters at collection prevents accumulation of TSP-1 during PRBC storage keeping levels similar to those in fresh PRBC units.

Day	TSP-1 pg/mL Filtered	SD	Unfiltered	SD
0	102,433	70,504	732,522	431,231
7	215,484	166,957	2,078,779	1,880,785
14	458,247	394,759	8,208,880	5,229,551
21	508,733	425,944	17,884,850	6,446,864
28	646,694	647,201	11,887,478	7,368,030
35	837,582	841,212	11,719,325	3,082,931
42	773,083	663,248	11,791,379	6,323,265

Disclosure of Conflict of Interest
Lisa Cardo, Donna Wilder: Nothing to Disclose

S91-030L
Does Leukoreduction of Blood Products Influence Outcomes? An Analysis of 842,738 Hospital Inpatients
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Background: Allogeneic leukocytes have been implicated as a cause of transfusion-related immunomodulation (TRIM) and have been associated with post-operative infection (POI) and systemic inflammatory response syndrome (SIRS) in transfused patients. Universal leukoreduction (LR) of red blood cell (RBC) units has been proposed as a means of eliminating TRIM and improving outcomes but the success of this strategy remains uncertain. We performed a retrospective analysis of 842,738 hospitalized patients from 20 hospitals treated between 2002 and 2007 included in our database (COMPARE™, Infonale/Haemonetics®, Braintree, MA) to determine the influence of LR on the incidence of POI and SIRS in hospitalized patients. **Methods:** Primary diagnosis, age, gender, race, emergency admission, any surgery, co-morbidities, severity of illness, any RBC, only LR RBCs (LR), any NON LR RBCs (NON LR), and NON LR RBCs plus

別紙様式第2

別紙(2)-3

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	厚生労働省処理欄
				2009年3月30日	該当なし	
一般的名称	乾燥 pH4 処理人免疫グロブリン		研究報告の公表状況	A recipient of immunoglobulin from a donor who developed vCJD Vox Sanguinis April 1, 2009, 96/3 (270)	公表国 英国	
販売名（企業名）	①サングロボール ②サングロボール点滴静注用 2.5g （CSL ベーリング株式会社）					

研究報告の概要

問題点（vCJD に感染した供血者のプリオン伝播のリスク）
10 年間再発性の呼吸器感染に罹患していた 61 歳女性が分類不能型免疫不全症（CVID）と診断された。抗体欠乏の診断が遅延することは、残念ながら稀なことではない。患者は 1995 年から静注用人免疫グロブリン（商品名 Vigam 、BPL 社、英国）で週 3 回の治療を受けていた。1997 年 1 月から 1998 年 2 月の期間に当該患者は、後に vCJD を発症した供血者の血漿を含有した静注用人免疫グロブリンを投与された。患者は 5g 製剤 8V（バッチナンバーVGD049）、2.5g 製剤 4V（バッチナンバーVGD050）を投与された。これらのバッチの推定 ID50/g は、それぞれ 0.0000112 と 0.0000688 であった。患者は 72 歳で内臓の腺癌の再発のため死亡した。
国立クロイツフェルト・ヤコブ病サーベイランスユニットで検死が実施された。死亡後に防腐処置を施された。この過程が体組織中のプリオン物質の検出に影響するかは不明である。脾臓とリンパ節中のプリオン蛋白をウエスタン・ブロット法で検査したが陰性であった。
組織学的、免疫化学的またはウエスタン・ブロット法による解析で、脳内にプリオン蛋白が存在するエビデンスは見出せなかった。
関与しているバッチによる治療と関連性の無い死亡との間隔が 9 年であったが、赤血球成分による vCJD 伝播症例の間隔（5-8.5 年）より長かった。そのため、もし異常プリオンが伝播していたならば、エビデンスが発見されるのは当然である。
vCJD を発症した供血者の血漿を含有した静注用人免疫グロブリンを投与されたが、当該患者は臨床的に vCJD を発症せず、組織病理学的及び分子技術によりプリオン蛋白が沈着しているエビデンスを発見できなかった。
現在まで赤血球成分によるプリオン伝播は 4 症例報告されているが、静注用人免疫グロブリンによるプリオン伝播の症例報告は無い。
静注用人免疫グロブリンなどのプール血漿の製品の安全性は、伝播する可能性を減少する製造方法での多数の工程により高まっている。
現在の静注用人免疫グロブリンの製造方法は $5\log_{10}$ までプリオン分子を削減できるので、たとえ供血にプリオン蛋白が含有されていても静注用人免疫グロブリンによる vCJD 伝播のリスクは低い。
静注用人免疫グロブリンによる vCJD 伝播の報告は無いが、伝播の可能性を避けるため予防的措置として 1997 年から英国の血漿は、血漿分画製剤の製造に使用されていない。
静注用人免疫グロブリンは多くの適応症があり、世界の需要は供給を上回っている。
現在、英国では静注用人免疫グロブリンの使用できる適応症が厳重に制限されている。世界の市場から英国の供給を賄うことが次第に困難になってきているため、血漿分画製剤の製造への英国血漿使用の禁止を継続すべきかどうか再調査するのが適切かもしれない。
このことから、現在の論争を巡る多くの問題点が浮かび上がってくると考える。

使用上の注意記載状況・その他参考事項等

報告企業の意見	今後の対応
これまで本剤によるvCJDが伝播した報告はない。製造工程において異常プリオンを低減し得るとの報告があるものの、理論的なvCJD等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与することを添付文書に記載し、注意喚起している。	今後とも新しい感染症に関する情報収集に努める所存である。

ABJ2009703

LETTER

Vox Sanguinis (2009) 96, 270

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A recipient of immunoglobulin from a donor who developed vCJD

Dear Editor,

We present the case of a female patient who at the age of 61 years was diagnosed with common variable immunodeficiency (CVID) after having suffered recurrent pulmonary infections for 10 years. A delay in the diagnosis of antibody deficiency is unfortunately not uncommon [1]. She received intravenous immunoglobulin (IVIG) replacement therapy with three weekly infusions of Vigam (BPL, Hertfordshire, UK) from 1995 onwards. During the period January 1997 to February 1998 she received batches of immunoglobulin that contained plasma from a donor who later developed variant Creutzfeldt–Jakob disease (vCJD). She received 8 × 5 g vials from batch VGD 049 and 4 × 2·5 g vials from VGD 050. The estimated ID50/g of these batches were 0·0000112 and 0·0000688, respectively. At age 72, she died of recurrence of adenocarinoma of the bowel.

Post-mortem analysis of tissues was performed by the National Creutzfeldt-Jakob Disease Surveillance Unit. She had been embalmed after death, by the introduction of formaldehyde into her femoral artery, but this process is not known to affect the detection of prion material in the body tissues. Western blotting of spleen and lymph nodes was negative for prion protein. There was no evidence of prion protein being present in the brain on histological, immunocytochemical or Western blot analysis. The time interval between treatment with the implicated batches and death from unrelated causes was 9 years, which is longer than the interval from transfusion to death in the reported cases of vCJD transmission by red cell components (5–8·5 years) [2]. Therefore, it seems reasonable to expect to find evidence of abnormal prions if transmission had occurred in this case.

Although the patient received IVIG from a batch containing plasma from a donor who developed vCJD, the patient did not develop vCJD clinically, and there was no evidence of prion protein deposition using histopathological and molecular techniques. There are no known cases of prion transmission by IVIG, in contrast to transfusions of red cell components where four cases have been reported to date [2]. The safety of pooled plasma products such as IVIG has been enhanced by adding to their manufacturing scheme multiple steps that reduce the potential for such transmission. Current IVIG manufacturing schemes are able to remove prion particles with up to a 5 log reduction [3,4] such that the risk of transmission of vCJD by IVIG may be low, even when a donation contains prion protein.

Although there have been no reports of vCJD transmission by IVIG, UK plasma has not been used for fractionation of pooled plasma products since 1997 as a (continuing) precautionary measure to avoid possible transmission. There are many indications for the use of IVIG [5], and worldwide demand exceeds supply. More stringent indications for its use are currently being drawn up and implemented in the UK (http://www.ivig.nhs.uk). Increasing difficulty in UK supply from the world market suggests that it may be appropriate to re-examine whether the ban on the use of UK plasma to make fractionated pooled plasma products should continue. We believe that this case highlights many of the issues surrounding the current debate.

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別紙様式第2-1

No. 4

医薬品　研究報告　調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2008. 12. 18	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況	Watson R. BMJ 2008 Nov; 337(7680)	公表国	
販売名（企業名）	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社)				ベルギー	

研究報告の概要	○クラミジアは2006年に欧州でもっとも多く報告された感染症であることが新しいデータで示された。欧州疾病管理予防センター（ECDC）の調査によると、クラミジア症は2006年に欧州において225,000件を上回る症例が記録され、もっとも報告頻度の高い感染疾患であった。以下、ランブル鞭毛虫症（193,000症例）、カンピロバクター症（180,000症例）、サルモネラ症（168,000症例）と続き、ストックホルム研究所に定期的に報告される47感染症のうちの上位10位を占めた他の感染症は、結核、流行性耳下腺炎、淋病、C型肝炎、侵襲性肺炎球菌疾患、HIVであった。 結核症例数はEU加盟27カ国とアイスランド、ノルウェー、リヒテンシュタインで減少傾向を示したが、英国、オランダ、スイス、ノルウェー、スウェーデンなどの移民では50%以上増加した。毎年、欧州では約90,000名が結核と診断され7,800名が死亡する。主に男性と性的な接触をもつ男性のHIV感染は増加し、毎年約30,000名がHIV / AIDSの診断を受け1,800名が死亡する。2010年までに欧州での根絶を目指している麻疹は6,279症例を記録している。 季節性インフルエンザは、年間2,500万人～5,000万人が感染し約40,000人が死亡する。また、欧州では毎年400万人ほどが院内感染し37,000名が死に至る。 メチシリン耐性黄色ブドウ球菌（MRSA）に関する状況は2002年以降ベルギー、オーストリアとスロベニアでは改善されたが、それ以外の国は横ばいまたは増加した。抗生物質の不適切な使用が公衆衛生における重大な脅威を招くこと、抗生物質の有効性を保つことは自身の責任であるとしたキャンペーンが展開されている。
報告企業の意見	今後の対応
欧州における2006年の感染症の発生報告はクラミジアが最も多く、以下、ランブル鞭毛虫症、カンピロバクター症、サルモネラ症、結核、流行性耳下腺炎、淋病、C型肝炎、侵襲性肺炎球菌疾患、HIVの順であったとの報告である。	今後も情報の収集に努める。

使用上の注意記載状況・その他参考事項等
新鮮凍結血漿「日赤」 新鮮凍結血漿-LR「日赤」 血液を介するウイルス、細菌、原虫等の感染 vCJD等の伝播のリスク

(34)

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News

Chlamydia was most often reported infection in Europe in 2006, new data show

Rory Watson

[1] Brussels

Just over 225 000 cases of chlamsydia were recorded in Europe in 2006, making it the most frequently reported infectious disease, the latest research by the European Centre for Disease Prevention and Control shows.s

The findings, which will be published in the Stockholm based centre's annual epidemiological report in a few weeks' time, also confirm that giardiasis was the second commonest disease, with 193 000 cases. This is considerably more than the 15 000 reported in 2005, but the increase is almost entirely due to the 170 000 cases that occurred in Romania.

Two other food and waterborne infections came in third and fourth place: campylobacteriosis (180 000 cases) and salmonellosis (168 000). Other infectious diseases to feature in the top 10 of the 47 that are routinely reported to the Stockholm agency were tuberculosis, mumps, gonorrhoea, hepatitis C, invasive pneumococcal disease, and HIV.

Andrea Ammon, head of the centre's surveillance unit, gave an early presentation of the report's contents at a meeting of the agency's management board in Paris last week.

She noted that although the number of cases of tuberculosis had tended to fall in the 27 European Union members and in Iceland, Norway, and Liechtenstein, increases of up to 50% or more were being found among immigrants in countries such as the United Kingdom, the Netherlands, Switzerland, Norway, and Sweden.

The report also confirms an increase in infections of HIV, mainly among men who have sex with men, and records 6279 cases of measles, a disease that Europe is committed to eradicate by 2010.

The centre says that some four million people in Europe are infected every year while being treated in hospitals or clinics, of whom 37 000 die as a result. Seasonal flu affects between 25 and 50 million people a year, killing around 40 000.

Each year some 90 000 diagnoses of tuberculosis are made, a disease that kills 7800 people, while HIV or AIDS is identified in about 30 000 people, 1800 of whom die from the disease.

Although the situation regarding meticillin resistant *Staphylococcus aureus* (MRSA) had improved in Belgium, Austria, and Slovenia since 2002, in all other countries the levels of resistance to MRSA had either remained the same or grown. Data presented by Dominique Monnet, programme coordinator for antimicrobial resistance, showed that a threefold gap exists between countries that prescribe antibiotics to outpatients the most and those that do so the least.

Drawing on the high profile information campaigns that have helped to reduce use of antibiotics in France and Belgium, the Stockholm centre has helped more than 30 countries throughout Europe to run antibiotic awareness events in recent weeks. The common messages at the different events are that inappropriate use of antibiotics poses a serious threat to public health and that ensuring that antibiotics remain effective is everyone's responsibility.

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More information is at www.ecdc.europa.eu.

別紙様式第2-1

No. 5

医薬品 研究報告 調査報告書

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				2008. 12. 19	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況	FDA, CBER. Available from: http://www.fda.gov/cber/blood/fatal07.pdf.	公表国 米国	
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社)					

研究報告の概要

○FDAに報告された供血後及び輸血後の死亡例 2007年度概要

2005年度から2007年度にかけて米国食品医薬品局(FDA)に報告された供血後及び輸血後の死亡例の概要である。

2007年度に、FDAは受血者76件、供血者17件の死亡報告を受領した。受血者死亡例の内訳は、52件が輸血に関連したもの、11件が死亡原因として輸血を排除できないもの、13件が輸血と関連しないものであった。

過去3年間の合計は177例で、内訳はTRALIが98件(55%)で最も高く、微生物感染は21件(12%)であった。微生物感染の内5件(24%)をバベシア症が占め、ついで*Staphylococcus aureus*が4件(19%)となった。

アフェレーシス血小板に関連した致死性の微生物感染報告は、2005年度から2006年度にかけて減少が見られ、2007年度も低いままであった。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
2005年度から2007年度にかけて米国食品医薬品局に報告された供血後及び輸血後の死亡例の概要である。	日本赤十字社では、薬事法及び関連法令に従い輸血副作用・感染症情報を収集し、医薬品医療機器総合機構を通じて国に報告している。今後も引き続き輸血副作用・感染症に関する情報の収集に努める。

Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2007

I. Background

As previously mentioned in the annual summary of fatalities reported to the FDA in Fiscal Years (FY) 2005 and FY2006, the blood supply is safer today than at any time in history. Due to advances in donor screening, improved viral marker tests, automated data systems, and changes in transfusion medicine practices, the risks associated with blood transfusion continue to decrease. Overall, the number of transfusion related fatalities reported to the FDA remains small in comparison to the total number of transfusions. In 2006 there were approximately 30 million components transfused.[1] During the proximate period of FY2006, there were 73 reported transfusion related and potentially transfusion related fatalities, with a decrease to 63 in FY2007.

CBER is distributing this summary of transfusion fatality reports received by the FDA to make public the data received in FY2007, to provide the combined data received over the last three fiscal years, and to compare the FY2007 reports to the fatality reports received in FY2006 and FY2005. We also include information on the infrequent reports of post-donation fatalities. Throughout this report we note changes over time, but the reader should interpret these changes cautiously, given the small numbers of reports and inherent variations in reporting accuracy. The significance of shifts in numbers derived from small populations may appear to be greater than they really are.

Refer to Sections 606.170(b) and 640.73 of Title 21, Code of Federal Regulations (21 CFR 606.170(b) and 21 CFR 640.73), for fatality reporting requirements. For information regarding the notification process, see our web page, Notification Process for Transfusion Related Fatalities and Donation Related Deaths, http://www.fda.gov/cber/transfusion.htm. For further information, see our *Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion*, September 2003.[2]

1 Whitaker BI, Green J, et al. The 2007 Nationwide Blood Collection and Utilization Survey Report. Washington (DC): Department of Health and Human Services; 2008.

2 Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion, September, 2003. http://www.fda.gov/cber/gdlns/bldfatal.htm.

If you have questions concerning this summary, you may contact us using any of the three following options.

1. Email us at fatalities2@fda.hhs.gov,
2. Call us at 301-827-6220, or
3. Write us at:
   FDA/Center for Biologics Evaluation and Research
   Office of Compliance and Biologics Quality
   Division of Inspections and Surveillance (HFM-650)
   1401 Rockville Pike, Suite 200 North
   Rockville, Maryland 20852-1448

II. Results

During FY2007 (October 1, 2006, through September 30, 2007), we received a total of 93 fatality reports. Of these reports, 76 were transfusion recipient fatalities and 17 were post-donation fatalities.

Of the 76 transfusion recipient fatality reports, we concluded:
a) 52 of the fatalities were transfusion-related,
b) in 11 cases we were unable to rule out transfusion as the cause of the fatality,
c) 13 of the fatalities were unrelated to the transfusion.

We summarize the results of our review in the following sections. Sections A through D of this document present the transfusion-related fatalities. Sections E and F and Table 4 present the fatality reports which were unrelated to the transfusion, or in which we could not rule out the transfusion as the cause of death. Section G presents the post-donation fatality reports.

A. Overall Comparison of Transfusion-Related Fatalities Reported in FY2005, FY2006, and FY2007

In combined FY2005, FY2006, and FY2007, Transfusion Related Acute Lung Injury (TRALI) caused the highest number of reported fatalities (55%), followed by hemolytic transfusion reactions (22%) due to non-ABO (15%) and ABO (7%) incompatibilities. Complications of

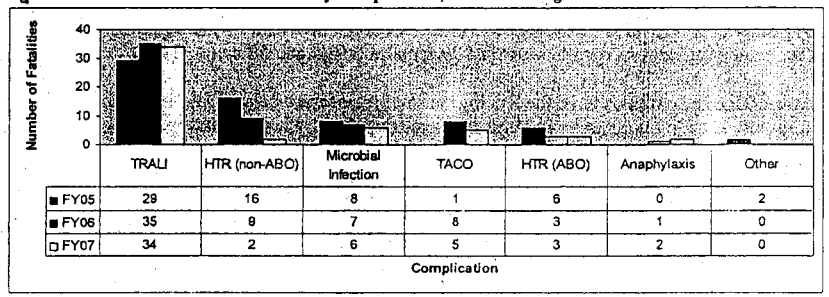
microbial infection, Transfusion Associated Circulatory Overload (TACO), and anaphylactic reactions each accounted for a smaller number of reported fatalities (Table 1and Figure 1).

Table 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2007

	FY05		FY06		FY07		Total (FY05+06+07)	
Complication	No.	%	No.	%	No.	%	No.	%
TRALI	29	47%	35	56%	34*	65%	98	55%
HTR (non-ABO)	16	26%	9	14%	2	4%	27	15%
Microbial Infection	8	13%	7	11%	6	12%	21	12%
TACO	1	2%	8	13%	5	10%	14	8%
HTR (ABO)	6	10%	3	5%	3	6%	12	7%
Anaphylaxis	0	0%	1	2%	2	4%	3	2%
Other	2**	3%	0	0%	0	0%	2	1%
Totals	62	100%	63	100%	52	100%	177	100%

*In FY2007, our review committee began using the Canadian Consensus Conference criteria[3,4] for evaluating TRALI cases – this number includes both "TRALI" and "possible TRALI" cases
**Other: Includes one case of Graft vs. Host Disease (GVHD) and one therapeutic plasma exchange (TPE) error (use of a treatment column contraindicated due to patient's medical history)

Figure 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2007



B. Transfusion Related Acute Lung Injury (TRALI)

In FY2007, as in the previous two fiscal years, TRALI continued to be the leading cause of transfusion related fatalities reported to CBER, representing 65% of confirmed transfusion related fatalities. Over the last three fiscal years, TRALI represented 55% of confirmed transfusion related fatalities. While the number of TRALI fatalities associated with receipt of Fresh Frozen Plasma (FFP) decreased from 22 (63% of TRALI cases) in FY2006 to 12 (35% of

[3] Goldman M, Webert KE, Arnold DM. et al. Proceedings of a consensus conference: towards an understanding of TRALI. Transfus Med Rev 2005;19:2-31.
[4] Kleinman S, Caulfield T, Chan P, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 2004;44:1774-1789

TRALI cases) in FY2007 (Figure 2), the number was comparable to that reported in FY2005 (13 cases). For the same three years there was an increase in reports of TRALI fatalities from Red Blood Cells (RBC) with 5 cases reported in each of FY2005 and FY2006 compared with 12 cases reported in FY2007.

When compared to the proportions of all transfused products, plasma products continue to be associated with a disproportionate share of TRALI cases. In Calendar Year 2006, for example, transfused plasma products accounted for approximately 13% of all transfused components, apheresis platelets (using platelet concentrate equivalent units) – approximately 30%, and red blood cell-containing products – approximately 49%.[5] In comparison, for the combined fiscal years 2005-2007, FFP and other plasma accounted for 52% (51/98) of reported TRALI fatalities, apheresis platelets accounted for 7% (7/98), and RBC's accounted for 22% (22/98).

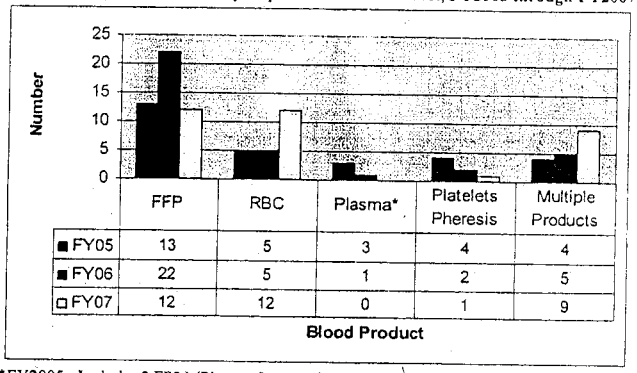
In FY2007, there were 34 TRALI cases temporally associated with products from 162 donors. Of these donors, 104 (64%) were tested for white blood cell (WBC) antibodies (Table 2). Antibody tests were negative in 41% of those tested. Of those tested, Human Leukocyte Antibodies (HLA) were present in 43% of donors. Human Neutrophil Antibodies (HNA) were present in 22% of donors, but most of these reactions (12/17) were weak and non-specific. Many donors had multiple antibodies. Reporters who included patient testing data were able to match donor antibodies with recipient cognate antigens in 7 of the 34 cases, implicating 11 donors (In 2 of these cases, there were recipient matches with 3 donors).

The gender of 25 (15%) of the donors was unknown or not provided by the reporting facilities. Of the remaining donors, reports identified 79 females (49%) and 58 males (36%).

Because TRALI continues to be the leading cause of transfusion-related fatalities, the transfusion community is taking voluntary measures to reduce this risk. Data show that the largest percentage of fatal TRALI cases are associated with female donors with white blood cell antibodies, and recent literature describes efforts to selectively use plasma from male donors for transfusion.[6,7,8] In November, 2006, the American Association of Blood Banks (AABB) issued an Association Bulletin, which included a recommendation that blood collection and transfusion facilities begin implementation of TRALI risk reduction measures for all high plasma-volume components. The measures include interventions to minimize the preparation of these components from donors known to have white blood cell antibodies or who are at increased risk for developing these antibodies.[9]

[5] Whittaker BI, op.cit. Tables 4-1 and 4-2.
[6] Curtis, BR, Mcfarland JG. Mechanisms of transfusion-related acute lung injury (TRALI): anti-leukocyte antibodies. Crit Care Med 2006;34(5 Suppl):S118-S123.
[7] Eder AF, Herron R, Strupp A, et al. Transfusion-related lung injury surveillance (2003-2005) and the potential impact of the selective use of plasma from male donors in the American Red Cross. Transfusion 2007;47:599-607.
[8] Chapman CE, Williamson LM, Cohen H, et al. The impact of using male donor plasma on hemovigilance reports of transfusion-related acute lung injury (TRALI) in the UK (abstract). Vox Sang 2006;91(Suppl 3):227.
[9] Transfusion-related acute lung injury. AABB Association Bulletin. Bethesda: American Association of Blood Banks;2006 Nov 3.

Figure 2: Reports of TRALI by Implicated Blood Product, FY2005 through FY2007



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

Table 2: Donor Antibodies Identified in Association with TRALI, FY2007

FY07 Donor Leukocyte Antibodies	No.	%
HLA Class I	18	17%
HLA Class II	6	6%
HLA Class I and II	15	14%
HNA	17	16%
HLA and HNA	6	6%
Negative	42	41%
Total Donors Tested	104	100%

This table does not include the 59 donors that were not tested for WBC antibodies

C. Hemolytic Transfusion Reactions

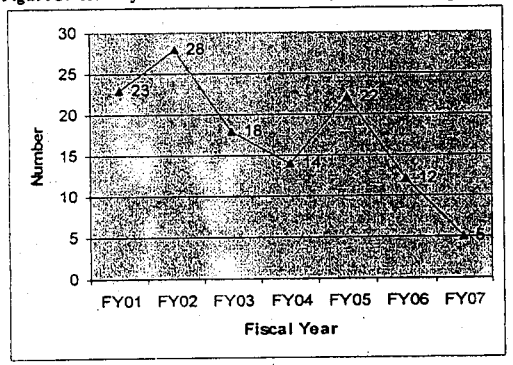
In FY2007, there was a continued decline in the number of reported fatal hemolytic transfusion reactions, with a total of five, as compared to 12 in FY2006, and 22 in FY2005. The recent decrease is due to a decline in reports of non-ABO hemolytic reactions, with reports of 16 fatalities in FY2005, 9 in FY2006 and 2 in FY2007 (Figure 1 and Table 3). We have seen an overall decrease in the number of reported fatal hemolytic transfusion reactions since FY2001 (Figure 3).

Table 3: Hemolytic Transfusion Reactions by Implicated Antibody, FY2005 through FY2007

	FY05		FY06		FY07		Total (FY05+06+07)	
Antibody	No.	%	No.	%	No.	%	No.	%
ABO	6	27%	3	25%	3	60%	12	31%
Multiple Antibodies*	6	27%	4	33%	1	20%	11	28%
Other**	3	14%	0	0%	0	0%	3	8%
Jk^b	3	14%	0	0%	0	0%	3	8%
Jk^a	1	5%	1	8%	1	20%	3	8%
K	1	5%	1	8%	0	0%	2	5%
Fy^a	0	0%	1	8%	0	0%	1	3%
Fy^b	0	0%	1	8%	0	0%	1	3%
E	1	5%	0	0%	0	0%	1	3%
I	1	5%	0	0%	0	0%	1	3%
Js^a	0	0%	1	8%	0	0%	1	3%
Totals	22	100%	12	100%	5	100%	39	100%

*FY2005 antibody combinations included E+c, Fy^a+K, Fy^a+Jk^b, E+I+A_1, possible C+E+K, Wr^a+warm autoantibody.
*FY2006 antibody combinations included E+c, S+K, Jk^b+cold agglutinin, unidentified auto- and alloantibodies.
*FY2007: anti-M+C
**Includes one report of non-immune hemolysis, one report of an unidentified antibody to a low incidence antigen, and one report of Cold Agglutinin Syndrome due to *Mycoplasma pneumonia* or Lymphoma.

Figure 3: Hemolytic Transfusion Reactions, FY2001 through FY2007



In FY2007, there were three reports of fatal hemolytic transfusion reactions due to ABO-incompatible blood transfusions:

- 1 case: recipient identification error at the time of transfusion
- 1 case: blood bank clerical error (incorrect sample used for testing)
- 1 case: initial recipient ABO/Rh typing results switched with another patient; ABO incompatible FFP issued prior to completion of required second typing

D. Microbial Infection

In FY2007, there were 6 reported fatalities attributed to microbial infection compared with 7 reported in FY2006 and 8 reported in FY2005. Three different bacteria were implicated in three fatalities, and three other fatalities resulted from Babesia transmission following Red Blood Cell transfusions from donors who subsequently tested positive for *Babesia microti*. The babesiosis cases accounted for 50% (3/6) of the microbial infections associated with transfusion fatalities in FY2007. Babesia accounted for 24% (5/21) of reported cases over the last three fiscal years, followed by Staphylococcus aureus, which accounted for 19% (4/21) (Table 4).

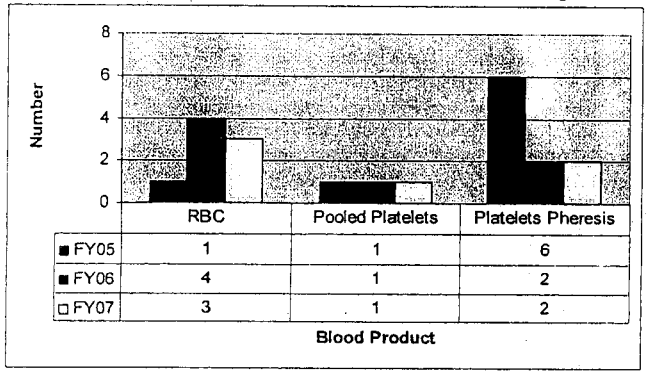
There was one strict anaerobe, *Eubacterium limosum*, implicated in a fatal bacterial infection during the 3-year reporting period; this fatality occurred in FY2005. The remaining bacteria are facultative anaerobes.

In FY2007, the decrease in reports of fatal microbial infections associated with apheresis platelets seen between FY2005 and FY2006 persisted (Figure 4). This finding is consistent with an overall decrease in the number of bacterial infections associated with apheresis platelets since FY2001 (Figure 5).

Table 4: Microbial Infection by Implicated Organism, FY2005 through FY2007

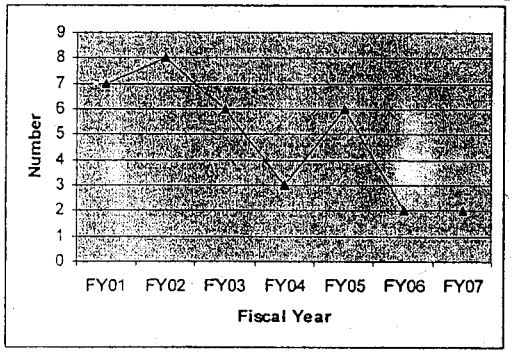
	FY05		FY06		FY07		Total (FY05+06+07)	
Organism	No.	%	No.	%	No.	%	No.	%
Babesia microti	0	0%	2	29%	3	50%	5	24%
Staphylococcus aureus	3	37%	0	0%	1	17%	4	19%
Escherichia coli	0	0%	3	43%	0	0%	3	14%
Serratia marcescens	2	24%	0	0%	0	0%	2	10%
Staphylococcus lugdunensis	1	13%	0	0%	0	0%	1	5%
Staphylococcus epidermidis	1	13%	0	0%	0	0%	1	5%
Eubacterium limosum	1	13%	0	0%	0	0%	1	5%
Morganella morganii	0	0%	1	14%	0	0%	1	5%
Yersinia enterocolitica	0	0%	1	14%	0	0%	1	5%
Streptococcus dysgalactiae	0	0%	0	0%	1	17%	1	5%
Klebsiella oxytoca	0	0%	0	0%	1	17%	1	5%
Total	8	100%	7	100%	6	100%	21	100%

Figure 4: Microbial Infection by Implicated Blood Product, FY2005 through FY2007



Red Blood Cells microorganisms: *S. marcescens (1), E. coli (1), Y. enterocolitica (1), B. microti (5)*
Pooled Platelets microorganisms: *S. aureus (1), E. coli (1), Streptococcus dysgalactiae (1)*
Platelets Pheresis microorganisms: *S. aureus (3), S. marcescens (1), S. lugdunensis (1), S. epidermidis (1), E. limosum (1), E. coli (1), M. morganii (1), K. oxytoca (1)*

Figure 5: Bacterial Infection by Apheresis Platelets, FY2001 through FY2007



E. Transfusion Not Ruled Out as Cause of Fatality

In these reported fatalities, the reporting facilities were unable to identify a specific complication of transfusion as the cause of death. Often, these patients had multiple co-morbidities, and after review of the investigation documentation, our medical reviewers could neither confirm nor rule out the transfusion as the cause of the fatality (Table 5). We did not include these reported fatalities in the analysis in Sections II.A through II.D (transfusion-related fatalities), above.

Combining the transfusion related fatalities with those that our medical officers could not rule out, there was a decrease in total reported fatalities from 73 in FY2006 to 63 in FY2007.

F. Not Transfusion Related

After reviewing the initial fatality reports and the investigation documentation, we categorized a number of reported fatalities as "Not Transfusion Related." Our medical reviewers concluded that, while there was a temporal relationship between transfusion and subsequent death of the recipient, there was no evidence to support a causal relationship (Table 5). Thus, we did not include these reported fatalities in the analysis in Sections II.A through II.D (transfusion-related fatalities), above.

Table 5: Fatalities Not Related to Transfusion or Transfusion Not Ruled Out, FY2005 through FY2007

	FY05	FY06	FY07
Not Transfusion Related	21	8	13
Not Ruled Out	14	10	11
Totals	35	18	24

G. Post-Donation Fatalities

There was a small increase in the number of fatalities following Source Plasma donation, and two fatalities following donation of Apheresis Platelets (Table 6). In two cases (both Source Plasma donors), our medical reviewers determined that clear medical evidence supported a cause of death that was not donation related. For the remaining 13 of the 15 FY2007 fatalities following Source Plasma and Apheresis Platelet donations, our medical reviewers concluded that, while there was a temporal link between the donations and the fatalities, there was no evidence to support a causal relationship between the Source Plasma or Apheresis Platelet donations and subsequent death of the donors. This was also the case for the 12 fatalities following Source Plasma donation in FY2005 and FY2006.

In FY2007, we received reports of two fatalities following Whole Blood donation, both autologous, collected by manual methods. In both cases, our medical reviewers found no evidence to support a causal relationship between the donation and subsequent death of the donor. For eight of the nine Whole Blood donations (includes two autologous donations) reported in FY2005 and FY2006, our medical reviewers found no evidence to support a causal relationship between the donation and subsequent death of the donor. In one FY2006 case, an autologous donation, our medical reviewers could neither confirm nor rule out the donation as contributing to the donor's death.