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
				2010. 3. 30	該当なし	

一般的名称	解凍人赤血球濃厚液	研究報告の公表状況		公表国
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社)		CDC,Outbreak Notice. 2010 Mar 16; Available from: http://wwwnc.cdc.gov/travel/content/outbreak-notice/dengue-tropical-sub-tropical.aspx	米国

研究報告の概要

○米国疾病対策センター(CDC)によるアウトブレイク情報 熱帯・亜熱帯地域におけるデング熱
現状:デング熱は熱帯・亜熱帯地域への旅行者における発熱の最も一般的な原因の1つであり、ウイルスは蚊によって媒介される。感染は都市部で発生することが多い。
2009年から、デングの症例数の増加が世界各地で報告されている。アフリカのカーボベルデでは、2009年に21,000例の疑い症例と6例の死亡例が報告された。南太平洋地域では、マレーシア、インドネシア、スリランカなど広範囲で感染が起こっている。中南米では、ブラジル、コロンビア、グアテマラ、ホンジュラス、ニカラグア、プエルトリコ、サン・バルテルミー島、サン・マルタン島などでデング熱が報告されている。中東では、サウジアラビアのジッダやメッカなどの観光地でも感染が起こっている。
渡航者向け勧告:蚊に刺されないようにすることで、デング熱感染のリスクを減らすことができる。デング熱の媒介蚊は朝夕だけでなく日中を通して活動し、特に室内、日陰、曇りの日に刺すことが多い。蚊帳や虫除けを使用し、屋外では長袖を着用することで、蚊に刺されないようにすること。
症状と治療:デング熱の症状には、発熱、重い頭痛、目の奥の痛み、関節痛・筋肉痛、紅斑、嘔気・嘔吐、出血症状などがある。通常は軽症だが、重症となりデング出血熱(DHF)を発症することもある。デング熱にかかったことのある人は、DHFのリスクが高い。
デングのワクチンや治療薬はないため、治療としては発熱に対する対症療法と水分補給、重症例に対しては血圧を維持する治療が行われる。外国から帰国後に発熱した場合は医師の診察を受け、最近の渡航歴について伝えること。

報告企業の意見	今後の対応
2009年からデングの症例数の増加が世界各地で報告され、米国疾病対策センター(CDC)が渡航者向けに蚊に刺されないよう注意喚起する情報を発表したとの報告である。日本においても、海外で感染して帰国される方の報告があることから、海外旅行者向けに情報提供が実施されている。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国(入国)後4週間は献血不適としている。また、発熱などの体調不良者を献血不適としている。今後も引き続き、新興・再興感染症の発生状況等に関する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

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「日赤」
解凍赤血球-LR「日赤」
照射解凍赤血球-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

④

Centers for Disease Control and Prevention
Your Online Source for Credible Health Information

Outbreak Notice
Update: Dengue, Tropical and Subtropical Regions
This information is current as of today, April 19, 2010 at 21:22 EDT

Updated: March 16, 2010

Situation Information

Dengue fever is the most common cause of fever in travelers returning from the Caribbean, Central America, and South Central Asia.[1] This disease is caused by four similar viruses (DENV-1, -2, -3, and -4) and is spread through the bites of infected mosquitoes.

Dengue infections are frequently reported from most tropical countries of the South Pacific, Asia, the Caribbean, the Americas, and Africa. Although dengue transmission often occurs in both rural and urban a dengue infections are most frequently reported from urban settings.

Since early 2009, an increased number of dengue cases have been reported from countries throughout several regions of the world.

Africa

Cape Verde: In 2009, more than 21,000 suspected cases and 6 deaths (as of December 6, 2009) were reported. Approximately 60 cases were reported in nearby Senegal, according to the UN Office for the Coordination of Humanitarian Affairs.

South Pacific

Dengue activity continues to circulate throughout this region. Examples of outbreaks include the followi

- Malaysia: In the first 6 weeks of 2010, more than 6200 cases and 23 deaths were reported throughout the country, especially in Selangor and Sarawak.
- Indonesia: Dengue activity is ongoing. From January–October 2009, more than 100 deaths were attributed to dengue hemorrhagic fever. In December 2009, the Ministry of Health issued an alert about heightened dengue hemorrhagic fever transmission during this rainy season.
- Sri Lanka: As of February 23, 2010, 7500 cases have been reported throughout the country, including in the Colombo capital district.

Central and South America and the Caribbean

Certain countries in Central and South America as well as in the Caribbean, are reporting dengue activity. These areas include Brazil, Colombia, Guatemala, Honduras, Nicaragua, Puerto Rico, St. Barthelemy, and Saint Martin.

Middle East

Dengue activity has been reported in recent months in this region, including areas popular among travelers such as Jeddah and Mecca in Saudi Arabia.

To view areas where cases have been reported in previous years, see the Distribution of Dengue maps. For more information on dengue and updates on worldwide activity, see CDC's Dengue website and WHO's Dengue webpage.

Advice for Travelers

Travelers can reduce their risk of getting dengue fever by protecting themselves from mosquito bites. The mosquitoes that spread dengue usually bite at dusk and dawn but may bite at any time during the day, especially indoors, in shady areas, or when the weather is cloudy.

Travelers should follow the steps below to protect themselves from mosquito bites:

- Where possible, stay in hotels or resorts that are well screened or air conditioned and that take measures to reduce the mosquito population. If the hotel is not well screened, sleep under bed nets to prevent mosquito bites.
- When outdoors or in a building that is not well screened, use insect repellent on uncovered skin. If sunscreen is needed, apply before insect repellent.
    - Look for a repellent that contains one of the following active ingredients: DEET, picaridin (KBR 3023), Oil of Lemon Eucalyptus/PMD, or IR3535. Always follow the instructions on the label when you use the repellent.
    - In general, repellents protect longer against mosquito bites when they have a higher concentration (percentage) of any of these active ingredients. However, concentrations above 50% do not offer a marked increase in protection time. Products with less than 10% of an active ingredient may offer only limited protection, often no longer than 1-2 hours.
    - The American Academy of Pediatrics approves the use of repellents with up to 30% DEET on children over 2 months old.
    - Protect babies less than 2 months old by using a carrier draped with mosquito netting with an elastic edge for a tight fit. For more information about the use of repellent on infants and children, please see the "Insect and Other Arthropod Protection" section in Traveling Safely with Infants and Children and the "Children" section of CDC's Frequently Asked Questions about Repellent Use.
    - For more information on the use of insect repellents, see the information on the Mosquito and Tick Protection webpage.
- Wear loose, long-sleeved shirts and long pants when outdoors.
    - For greater protection, clothing may also be sprayed with repellent containing permethrin or another EPA-registered repellent. (Remember: don't use permethrin on skin.)

Symptoms and Treatment

Symptoms of dengue include:

- fever
- severe headache
- pain behind the eyes
- joint and muscle pain
- rash
- nausea/vomiting
- hemorrhagic (bleeding) manifestations

Usually dengue fever causes a mild illness, but it can be severe and lead to dengue hemorrhagic fever (DHF), which can be fatal if not treated. People who have had dengue fever before are more at risk of getting DHF.

No vaccine is available to prevent dengue, and there is no specific medicine to cure illness caused by dengue. Those who become ill with dengue fever can be given medicine to reduce fever, such as acetaminophen, and may need oral rehydration or intravenous fluids and, in severe cases, treatment to support their blood pressure. Aspirin (acetylsalicylic acid), aspirin-containing drugs, and other nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) should be avoided because of the possibility of bleeding. Early recognition and treatment of severe dengue (e.g., signs and symptoms consistent with impending blood pressure failure) can reduce the risk of death.

If you return from a trip abroad and get sick with a fever, you should seek medical care. Be sure to tell the doctor or other health-care provider about your recent travel.

Information for Health-Care Providers

Proper diagnosis of dengue is important, as many other diseases may mimic dengue. Health-care providers should consider dengue, malaria, and (in south Asia and countries bordering the Indian Ocean) chikungunya in the differential diagnosis of patients who have fever and a history of travel to tropical areas during the 2 weeks before symptom onset.

See the Clinical & Laboratory Guidance on the CDC Dengue website for information regarding reporting dengue cases and instructions for specimen shipping. Serum samples obtained for viral identification and serologic diagnosis can be sent through state or territorial health departments to:

CDC Dengue Branch
Division of Vector-Borne Infectious Diseases
National Center for Zoonotic, Vector-Borne and Enteric Diseases
1324 Calle Cañada
San Juan, Puerto Rico 00920-3860
Telephone: 787-706-2399; fax, 787-706-2496.

More Information

For more information about dengue and protection measures, see the following links:

- Dengue Fever in *CDC Health Information for International Travel 2010*
- Mosquito and Tick Protection
- Questions and Answers: Insect Repellent Use and Safety
- CDC Dengue website

For more information about dengue in travelers, see

- Travel-Associated Dengue—United States, 2005 [*MMWR* 2006, 55 (25)].
- Travel-Associated Dengue Infections—United States, 2001-2004 [*MMWR* 2005, 54 (22)]

[1]Freedman DO, Weld LH, Kozarsky PE, Fisk T, Robins R, von Sonnenburg F, et al., for the GeoSentinel Surveillance Network. Spectrum of disease and relation to place of exposure among ill returned travelers. N Engl J Med 2006;354:119-130.

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National Center for Preparedness, Detection, and Control of Infectious Diseases

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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 2010年6月24日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	人 C1-インアクチベーター	研究報告の公表状況	Parvovirus B19 Is Inactivated by Pasteurization, a Dedicated Virus Inactivation Step in the Manufacturing Process of Plasma-Derived Products Blood　114 (22): p1224 NOV 20 2009	公表国 ドイツ	
販売名（企業名）	①ベリナート P ②ベリナート P 静注用 500 （CSL ベーリング株式会社）				

研究報告の概要

ヒトパルボウイルス B19（B19V）は、エンベロープを持たない小型のウイルスで、小児の伝染性紅斑の病原体である。しかし成人期に発症すると関節痛、関節炎、（一過性）骨髄無形成クリーゼ、貧血、胎児水腫（妊娠時）などの臨床症状を呈する。
B19V は、飛沫感染が一般的であるが、血液または血液成分、血漿分画製剤を介して非経口感染する。
B19V に関して血漿分画製剤の安全性を証明するために、通常 B19V のモデルウイルスとして動物のパルボウイルスを使用してウイルスバリデーション試験を実施するが、このウイルスは一般に加熱などの不活化に強い抵抗性を有している。
CSL ベーリングのウイルス研究所で開発した B19V 細胞培養感染性試験により、B19V は動物パルボウイルス CPV（イヌパルボウイルス）と比較してパスツリゼーション（60℃10 時間の液状加熱）に比較的高い感受性を示すことがわかった。
B19V は、安定化されていない製品中間体で熱に感受性を示すばかりでなく、高濃度のショ糖やグリシンの安定剤を含有する血漿分画製剤の中間体の研究でも熱に感受性を示した。これらのたん白安定剤は B19V に安定化効果を有するが、このウイルスは CPV よりパスツリゼーションに対して高い感受性を示した。
パスツリゼーションは広範囲な血漿分画製剤において B19V を効果的に不活化できることが示された。

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
今回の研究で、本剤の製造工程で B19V が大幅に減少していることがわかった。 また、当社製品の添付文書に B19V の不活化に関して以下の内容を記載し、注意喚起している。 ・製造する原料血漿は、ヒトパルボウイルス B19 について NAT によるスクリーニングを実施し、適合した血漿を用いている。 ・血漿分画製剤の現在の製造工程では、ヒトパルボウイルスB19等のウイルスを完全に不活化・除去することが困難であるため、本剤の投与によりその感染の可能性を否定できないので、投与後の経過を十分に観察すること。	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。

Methods: Forty-three patients were included in our study (MDS=16, chronic myeloid leukemia (CML)=12, AML=4, polycythemia vera (PV)=3, essential thrombocythemia (ET)=3, chronic myelomonocytic leukemia (CMML)=3, myelofibrosis (MF)=1 and chronic neutrophilic leukemia (CNL)=1). Forty-one patients were evaluated according to their ABO group using serological immunohematological tests (Diamed Inc., Brazil). ABH secreted antigens were investigated in saliva and a PCR-based ABO genotyping using restriction enzyme digestion (*Alu* and *Kpn*) was performed to confirm the ABO blood type. In addition, the expression of the A, B and H antigens was analyzed by flow cytometry in 26 patients (median age=63 yrs; 6M/17F) and 81 healthy controls (median age=33 yrs; 38M/43F). Methylation of CpG islands was investigated in 45 bone marrow samples using methylation specific PCR (MSP) technique with methylated and unmethylated primer sets for region from -200 to +26 sequence of the *ABO* gene.

Results: The investigation of the secreted antigens in saliva and the genotyping studies confirmed the results of the ABO serological tests in 40 patients, but we found that the RBCs of one patient were not agglutinated by anti-B while his genotype result was compatible with BO indicating loss of the B antigen in his RBCs. Overall, loss of A, B or H antigen was detected by flow cytometry in 11/26 (42%) patients. Hypermethylation of the ABO promoter gene was detected in 51% (23/45) of the analyzed bone marrow samples. Among patients with hypermethylation in the ABO promoter gene, 44% had loss of A or B antigens confirmed by serological or flow cytometric tests compared with 28% in the group of patients with unmethylated ABO promoter gene (p=0.632).

Conclusions: Epigenetic changes including methylation of cytosine residues are recognized as major contributors to gene silencing, disease progression and worse outcome in several cancer patients. Our data showed that the hypermethylation of the *ABO* gene is frequent in patients with myeloid malignancies corresponding to the pathogenesis already described for AML and MDS. However, not all patients showing loss of RBCs antigens had *ABO* methylation evidence, suggesting that other mechanisms may take place. Patients with myeloid malignancies often need blood transfusion support and loss of RBCs antigens can lead to changing in ABO blood group increasing the risk of serious blood transfusion reactions. The relatively high rate (42%) of loss of ABH antigens found in this study demonstrated that these patients have to be carefully managed to avoid such severe transfusion reactions. (Grants supported by CNPq, 478814/2006-2).

Disclosures: No relevant conflicts of interest to declare.

Abstract 3152 **Poster Board III-89**

Parvovirus B19 Is Inactivated by Pasteurization, a Dedicated Virus Inactivation Step in the Manufacturing Process of Plasma-Derived Products.

ALBRECHT GROENER, Thomas Nowak* and Wolfram Schäfer*, *Virology, CSL Behring, Marburg, Germany*

Human parvovirus B19 (B19V), a small non-enveloped virus, is the causative agent of the childhood disease erythema infectiosum (fifth disease) but causes, especially when the disease occurs during adulthood, a number of clinical symptoms as arthralgia, arthritis, (transient) aplastic crisis, anaemia, and hydrops fetalis (during pregnancy). B19V is normally spread via the respiratory route, however, parenteral transmission can occur through blood or blood components and plasma-derived products. In order to demonstrate the safety of plasma-derived products regarding B19V, virus validation studies are performed, using usually animal parvoviruses as models for B19V which indicate that this virus is highly resistant to commonly used inactivation methods as heat. Employing a cell culture infectivity assay for B19V, established at CSL Behring's virology laboratory, a considerable higher sensitivity of B19V to pasteurization (heat treatment in aqueous solution at 60°C for 10 hours) could be demonstrated for B19V in contrast to the animal parvovirus CPV (canine parvovirus). B19V was not only very sensitive to heat in unstabilised product intermediates but also heat sensitive when studying intermediates of various plasma products containing high concentrations of the stabilizers sucrose and glycine. Although these protein stabilizers had also a stabilizing effect on B19V this virus was nevertheless considerably more sensitive to pasteurization than CPV. As shown below, pasteurization results in an effective inactivation of B19V in a wide range of plasma-derived products.

Product	Mean Virus Reduction Factor [log_{10}] due to Pasteurization	
	B19V	CPV
VWF / FVIII (Humate-P)	≥3.9	1.1
FVIII (Beriate P) [a]	≥3.8	0.7
Fibrinogen (RiaSTAP) [b]	≥4.5	1.6
PCC (Beriplex P/N) [a]	3.5	0.5
C1-INH (Berinert P) [a]	3.9	1.4
Human Thrombin [a]	3.5	0.5
FXIII (Fibrogammin P) [a]	≥4.0	1.0
scIG (Vivaglobin)	≥5.0[c]	2.3
Human albumin (different products)	≥4.3	1.6

[a] product not licensed in USA

[b] Pasteurization time 20 hours

[c] studied in a porcine immunoglobulin intermediate to avoid neutralization by human IgG

Based on these experimental data on inactivation of B19V by pasteurization and a plasma pool for fractionation not exceeding 10^4 IU B19V DNA/ml, the virus safety of plasma-derived products regarding B19V can be assessed more correctly demonstrating an appropriate margin of safety.

Disclosures: Groener: *CSL Behring:* Employment. **Nowak:** *CSL Behring:* Employment. **Schäfer:** *CSL Behring:* Employment.

Abstract 3153 **Poster Board III-90**

Phage-Displayed Peptide-Q Dot Nanocrystal Combo for High-Sensitivity Bacterial Detection in Plasma.

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Introduction: Despite improved phlebotomy practices, refrigeration of red cells, freezing of plasma and improved materials for transfusion product collection and storage, bacterial contamination of transfusion products is still a longstanding problem. Current bacterial detection tests relevant to transfusion medicine, especially for stored platelets have limitations with regard to time, specificity and sensitivity. There is a need for new and improved cost-effective high-affinity detection probes to fill this gap. In this study, using plasma spiked with *Bacillus cereus* 4342 and *B. anthracis*-Sterne as an experimental system, we identified peptides from a bacteriophage-displayed random peptide library that selectively bind and detect the *Bacillus* strains. By labeling the peptides with Q dot-liquid nanocrystals, the detection sensitivity of the peptides was further enhanced.

Methods: A commercially available bacteriophage-displayed random peptide library was screened using *B. cereus* 4342 as bait, using appropriate controls under stringent conditions. The screening and subsequent sequencing of the phage DNA identified two phages each containing a coding sequence for 12-amino acid peptide that are selectively capable of binding to the *Bacillus*. Based on the nucleic acid sequence, the two synthetic peptides with biotin tag were prepared for detection assays and to enhance the detection sensitivity further, the peptides were labeled with streptavidin-conjugated fluorescent quantum-dots (Q dots). Fluorescence was measured either by a plate reader or using a fluorescence microscope.

Results: The two synthetic peptides selectively bound to the *Bacillus* strains in both dot blot and ELISA assays. The membrane-based dot blot assay demonstrated an assay sensitivity of 10^3 colony forming units/ml (CFU/ml), whereas ELISA demonstrated a sensitivity of 10^2 CFU/ml detection limit. Fluorometry analysis of spiked plasma samples revealed that the two peptides were able to bind to *B. cereus* 4342 and *B. anthracis* Sterne and detect these bacteria in plasma at 10^2 CFU/ml concentrations. The peptide-Qdot combo even detected a single bacterium in fluorescence microscopy.

Conclusion: Overall, the results reported here validate the usefulness of affinity-selected recombinant filamentous phage-derived peptides in combination with Qdot-liquid nanocrystals as high sensitivity detection probes for bacteria in various platforms and settings relevant to the blood safety and transfusion medicine.

The findings and conclusions in this abstract have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.

Disclosures: No relevant conflicts of interest to declare.

Abstract 3154 **Poster Board III-91**

Rate of Inhibitor Development in Hemophilia A Patients Treated with Plasma Derived or Recombinant Factor VIII Concentrates. A Systematic Review of the Literature.

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Background. The development of alloantibodies that inhibit the coagulant activity of factor VIII (FVIII) is currently the most challenging complication of treatment in persons with hemophilia. Among other factors known to influence inhibitor development, several reports in the literature claimed for a different rate of inhibitor development in hemophilia A (HA) patients after plasma derived (pd-) or recombinant (r-) FVIII administratioo. Aim of

医薬品 研究報告 調査報告書

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				2010. 3. 24	該当なし	

一般的名称	解凍人赤血球濃厚液	研究報告の公表状況		公表国
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社)		Szelei J, Liu K, Li Y, Fernandes S, Tijssen P. Emerg Infect Dis. 2010 Mar;16(3):561-4.	カナダ

研究報告の概要

○血液製剤中のパルボウイルス4様ウイルス
PARV4様ウイルスは中国のウシやブタで見つかり、ヒトPARV4ウイルスと60－65%の相同性を持つ。英国でブタの血漿およびブタ血漿由来第VIII因子製剤のパルボウイルス(PARV)4様ウイルスをスクリーニングした。血漿検体中のPARV4様ウイルスの保有率は比較的低かったが、ウイルスはブタ血漿由来第VIII因子の製造時に濃縮されるとみられた。

報告企業の意見	今後の対応
ブタの血漿およびブタ血漿由来第VIII因子製剤のパルボウイルス4様ウイルスをスクリーニングしたところ、血漿検体中のPARV4様ウイルスの保有率は比較的低かったが、ウイルスはブタ血漿由来第VIII因子の製造時に濃縮されると見られたとの報告である。	本報告のパルボウイルス4様ウイルスの病原性は不明であり、対策の必要性を検討するため、引き続き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

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「日赤」
解凍赤血球-LR「日赤」
照射解凍赤血球-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

⑥

Parvovirus 4–like Virus in Blood Products

Jozsef Szelei, Kaiyu Liu, Yi Li, Sandra Fernandes, and Peter Tijssen

Porcine plasma and factor VIII preparations were screened for parvovirus 4 (PARV)–like viruses. Although the prevalence of PARV4-like viruses in plasma samples was relatively low, viruses appeared to be concentrated during manufacture of factor VIII. PARV4-like viruses from human and porcine origins coevolved likewise with their hosts.

In 2005, a previously unknown virus, parvovirus 4 (PARV4), was detected in a plasma sample from a hepatitis B–positive injection drug user (IDU) (*1*). Although PARV4 was subsequently detected in plasma from healthy donors, its prevalence is higher in samples from IDUs, AIDS patients, and hepatitis C virus–infected persons (*2,3*). In recent serologic studies, 67% of HIV-infected IDUs had antibodies to PARV4, whereas non-IDU controls were seronegative (*4*) This increased prevalence in IDUs and persons with hemophilia most likely reflects parenteral transmission of the virus (*4,5*). Furthermore, PARV4 was frequently detected in human coagulation factor concentrates prepared from older plasma samples (*6*). The lower detection frequency in current concentrates may be due to exclusion of high-risk batches, e.g., from IDU or hepatitis C virus–infected persons during plasma collection, and to improved purification methods. The presence of PARV4 in plasma suggests a viremic phase enabling spread of the virus to different organs. Even though recent studies by Kleinman et al. indicate that parvovirus B19 is not readily transmitted to susceptible hosts by blood component transfusion, similar evaluation of PARV4 transmission will be invaluable in assessing the need to routinely screen for this emerging virus (*7*).

PARV4 contains a 5-kb single-stranded DNA genome with inverted terminal repeats and a large open reading frame (ORF) in each half of the genome coding for nonstructural (NS) protein and structural protein, respectively. PARV4-like viruses form a separate cluster among the parvoviruses (*1,8*). Three genotypes of human PARV4 parvoviruses with ≈93% nucleotide sequence identity have been described. The sequence of genotype 1 (PARV4-g1) is highly conserved, whereas that of genotype 2 (PARV4-g2 [formerly PARV5]) is somewhat more diverse. PARV4-g2 is found mostly in older coagulation factor concentrates (1960s–1980s), suggesting that genotype 1 emerged recently (*6,8*). A third genotype (PARV4-g3) was isolated from persons in sub-Saharan Africa (*9*). Additionally, PARV4-like viruses with a 60%–65% nucleotide identity were recently identified at high frequencies in porcine and bovine tissue samples in People's Republic of China (*10*).

In this study, porcine plasma samples and factor VIII (FVIII) concentrates used by persons with hemophilia who have autoimmune antibodies against human FVIII were investigated for PARV4-like viruses. We then determined the degree of identity of these isolates with the human virus.

The Study

Plasma samples from healthy pigs were collected in Great Britain in 2001. Initially, these samples were tested for PARV4-like viruses by using previously described degenerate PCR primers (*10*). DNA was extracted from samples by using the High Pure DNA Isolation

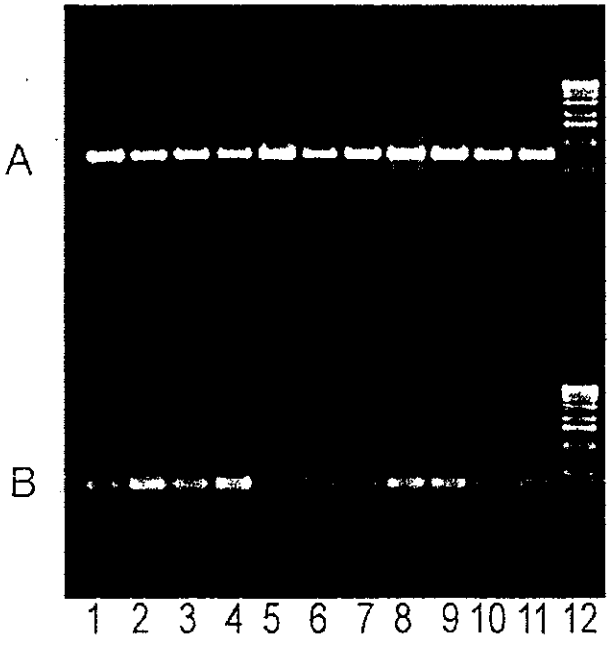

Figure 1. Parallel PCR amplification of PARV4-like (A) and PPV (B) by using purified DNA from clotting FVIII preparations. The results of this PCR usually suggested a higher PARV4 load despite the higher efficiency of the PPV PCR (J. Szelei and P. Tijssen, unpub. data). This finding was confirmed with the quantitative MIMIC PCR method for PPV (*11*). Numbers indicate different lots of FVIII prepared in 1:1994A, 2:1994B, 3:1996A, 4:1996B, 5:1999, 6:2000A, 7:2000B, 8:2001A, 9:2001B, 10:2001C, 11:2001D, and 12: DNA marker (1-kb ladder; Invitrogen, Carlsbad, CA USA). PARV4, parvovirus 4; PPV, porcine parvovirus; FVIII, factor VIII.

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Table 1. Percentage diversity of genome sequences of PARV4-like viruses*†

Genotype	PARV4-p	PHoV	BHoV	PARV4-g1	PARV4-g2
PARV4-p	98–99				
PHoV	97–98	98–99			
BHoV	62	62	99		
PARV4-g1	58	58	60	98–100	
PARV4-g2	58–59	58	59–60	91–92	96–99
PARV4-g3	58	58	60	92	91–92

*PARV4, parvovirus type 4; PARV4-p, porcine PARV-4; PHoV, porcine hokovirus; BHoV, bovine hokovirus; PARV4-g1, PARV4 genotype 1; PARV4-g2, PARV4 genotype 2; PARV4-g3, PARV4 genotype 3.
†Pairwise sequence comparisons were performed by using the ClustalW program (www.ebi.ac.uk/Tools/clustalw) as described in Figure 2 and percentages of sequence identities were calculated. Nucleotide sequences representing the equivalent regions (position 248–5088, numbered according to the PARV4 sequence NC_007018) were used to align the DNA fragments.

Kit (Roche Applied Science, Roche Diagnostics Canada; Laval, Quebec, Canada). Only 3 of the 98 plasma samples contained detectable amounts of PARV4-like viruses. To further study these porcine viruses, we obtained nearly full-length genomes from overlapping PCR fragments. Primers designed for these PCRs were PrS1: 5′-CCACACCTACCTCGCCTATAAGAATCAG-3′; PrAS1: 5′-CTCCACTTGTTCAGCACGGGATCC-3′; PrS2: 5′-CCACGAGCTGGAAGTCTTTA-3′; PrAS2: 5′-GGAGTCCGCATACCCATAACAGGCTG-3′; PrS3: 5′-GTGTACCGCAGTGGGAGCCATG-3′; and PrAS3: 5′-TTCTGGGCAACCCACTGATCAGAAGG-3′. The nearly full-length clones were sequenced by primer-walking. Genomic analysis confirmed that these viruses were related to the PARV4 viruses and were close relatives of the recently identified porcine hokoviruses (PHoVs) (*10*).

We also confirmed the moderate frequency of PARV4-like viremia in the previously tested pig plasma samples with a more sensitive PCR assay by using specific primers PrS4 (5′-AGTTACGGGGGACCGCTACAGTG-3′) and PrAS3. In contrast, examination of 11 commercial clotting FVIII preparations showed that all of these independent lots contained substantial amounts of PARV4-like parvovirus, whereas the level of porcine parvovirus DNA was generally lower in the corresponding samples (Figure 1). Similar to the plasma samples, long overlapping PCR frag-

Table 2. Analysis of relationships among the protein sequences of PARV4-like viruses*†

Sequence	PARV4-p	PHoV	BHoV	PARV4-g1	PARV4-g2	PARV4-g3
PARV4-p						
NS	99–100	(99)	(80)	(68)	(68)	(68)
VP	99–100	(99)	(79)	(77)	(78)	(77)
SAT	100					
PHoV						
NS	97–98	98–99	(79)	(68)	(68)	(68)
VP	99	99	(79)	(77)	(77)	(77)
SAT	98–100	98–100				
BHoV						
NS	67–68	67	99	(70)	(70)	(70)
VP	66	66	NA	(78)	(78)	(78)
SAT	79	79	100			
PARV4-g1						
NS	53–55	53–54	56–57	96–99	(99)	(98)
VP	65	65	65	99	(99)	(98–99)
SAT	59	59	59	100		
PARV4-g2						
NS	54–55	53–54	56	96–97	98–99	(98)
VP	65	65	64–65	98	98–99	(98)
SAT	59	59	59	100	100	
PARV4-g3						
NS	54	53–54	56	96–97	96–97	NA
VP	65	65	64	98	97–98	NA
SAT	59	59	59	100	100	

*PARV4, parvovirus type 4; PARV4-p, porcine PARV-4; PHoV, porcine hokovirus; BHoV, bovine hokovirus; PARV4-g1, PARV4 genotype 1; PARV4-g2, PARV4 genotype 2; PARV4-g3, PARV4 genotype 3; NS, nonstructural protein; VP, viral protein; NA, no alignment; SAT, small alternatively translated proteins.
†Numbers indicate percentages of amino acid sequence identity; numbers in parentheses indicate percentages of amino acid similarity (preserved physicochemical properties). Sequence similarity was not calculated for the SAT proteins, because of their relatively smaller size. When only 1 sequence was available (e.g., VP of BHoV), no alignment was performed.

ments were amplified from the FVIII preparations to obtain nearly full-length sequences. Their analysis provided information about the evolution of PARV4-like viruses, during nearly a decade, in pigs. Sequence data were registered by GenBank (accession nos. Cl2001A: FJ982246; Cl2001B: FJ982247; Cl2001C: FJ982248; F8–1994A: FJ982249; F8–1994B: FJ982250; F8–1996A: FJ982251; F8–1996B: FJ982252; F8–1999: FJ982253; F8–2000A: FJ982254; and F8–2000B: FJ982255). Phylogenetic and molecular evolutionary analyses were conducted by using MEGA version 4 (*12*).

The genomes of these newly isolated PARV4-like viruses were similar to the PHoVs previously identified in Hong Kong Special Administrative Region, People's Republic of China. Although, these new isolates showed some diversity (98%–99% identity), they differed somewhat more from the PHoVs (97%–98% identity). The viral protein (VP)-ORF was highly conserved (99%), whereas the NS-ORF showed more diversity (97%–98%). Genomic and protein-coding sequences were also compared with other PARV4-like viruses (Tables 1, 2). Phylogenic analysis using neighbor-joining and maximum parsimony methods demonstrated that PHoVs grouped together, whereas PARV4-like sequences from FVIII prepared at different times were less uniform (Figure 2). Older FVIII PARV4 contaminants (especially from 1994) were related more closely to the bovine hokoviruses (BHoVs) and to PARV4-g2. Finally, analysis of the newly identified virus genomes

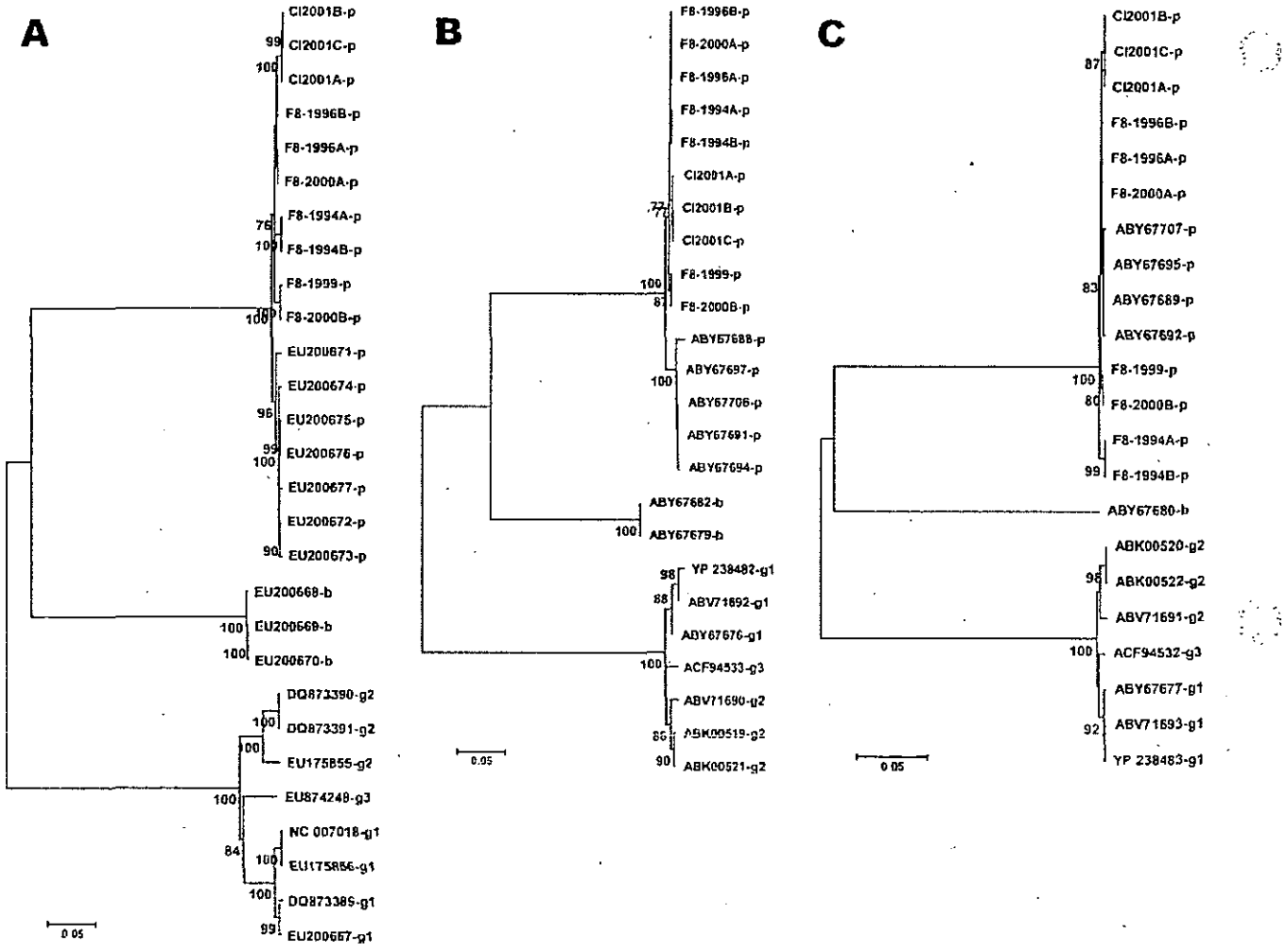

Figure 2. Construction of phylogenic trees for newly identified porcine viruses and comparison with previously identified prototype parvovirus 4 (PARV4)–like sequences. Sequences of other PARV4-like viruses indicated by the accession numbers were obtained from GenBank, and their origins are marked by letters (p, porcine; b, bovine; PARV4-g1, g2, g3, human parvovirus 4 genotypes 1, 2, and 3). ClustalW-aligned genomes (A) and nonstructural (NS) protein (B) and viral protein (VP) (C) were all trimmed to obtain sequences with similar lengths. All computer analysis was performed by using the neighbor-joining method. Branches corresponding to partitions reproduced in <70% bootstrap replicates are collapsed. The tree is drawn to scale, and the percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1,000 replicates) are shown below the branches. F8-year, year of the factor VIII lot; Cl-year, plasma samples and year of collection. Scale bar represents the number of nucleotide (A) or amino acid (B, C) substitutions per site.

showed an alternative coding sequence inside of the VP gene with a recognizable relationship to small alternatively translated proteins (SAT) (*13*). In the porcine PARV4-like viruses, the start codon for the SAT protein was 3 nt downstream relative to the position of SAT-ATG in the human and bovine PARV4 viruses. Although the SAT protein was 67 aa in all the characterized human PARV4 viruses, porcine and bovine PARV-like viruses contained SAT proteins with 84 aa. The amino acid sequences of the SAT proteins were highly conserved in each PARV4 virus group; however, they differed greatly between PARV4 viruses belonging to different host species (Table 2).

Conclusions

Improved virus detection methods have facilitated the discovery of new viruses and have provided insight into the existence of a wide variety of potentially pathogenic strains in biopharmaceutical products. Plasma samples, collected from individual pigs in 2001–2002, and FVIII samples, prepared during 1994–2001, were tested for PARV4-like viruses.

Sequence analysis showed that PARV4-like viruses may have undergone some degree of selective pressure during this time because the genomes sequenced showed a greater variability than the porcine parvovirus NS sequences isolated from the same samples (J. Szelei and P. Tijssen, unpub. data). In the current study, comparison of the genomic and NS protein coding sequences indicated that viruses in the older samples were more closely related to BHoV and PARV4-g2 (Figure 2). Fewer changes were observed in the VP coding sequence (Table 2). Because VPs are responsible for the entry of parvoviruses, they usually adapt to host-specific receptor(s). The presence of PARV4-g2–like isolates in older samples and the omnipresenec of PARV4-like viruses in more recent samples suggested that the porcine PARV4-like virus and human PARV4 may have similarly evolved (*8*). These new parvovirus isolates from Great Britain would belong to a different cluster of porcine PARV4-like viruses than the hokoviruses from Hong Kong Special Administrative Region.

Although older isolates shared more identity with BHoV and PARV4-g2, the substantial differences in the DNA sequences of PARV4-like viruses from different species (human, bovine, pig) suggested that they would have diverged a long time ago. This hypothesis was also supported by the sequence stabilization of the SAT proteins, which may play important host-specific roles in the viral exit (*13*). Nevertheless, the existence of a wide variety of different PARV4 strains, most of which result in chronic infections, could provide a basis for an evolutionary jump and recombination and should raise major concerns about the dangers of parenteral transmission.

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Dr Szelei is senior research associate at the Institut National de la Recherche Scientifique–Institut Armand-Frappier. His work focuses on the molecular biology of parvoviruses.

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医薬品
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識別番号・報告回数			報告日	第一報入手日 2010 年 4 月 23 日	新医薬品等の区分 該当なし	厚生労働省処理欄

一般的名称	①②③ポリエチレングリコール処理抗破傷風人免疫グロブリン ④⑤乾燥抗破傷風人免疫グロブリン	研究報告の公表状況	Eurosurveillance 2010; 15(16)	公表国 スコットランド
販売名 (企業名)	①テタノブリン IH 静注 250 単位　(ベネシス) ②テタノブリン IH 静注 1500 単位　(ベネシス) ③テタノブリン-IH　(ベネシス) ④テタノブリン筋注用 250 単位　(ベネシス) ⑤テタノブリン　(ベネシス)			

研究報告の概要

キランダー等の報告では、重篤や致命的なパンデミックインフルエンザ A(H1N1)の症例の一部で、赤血球凝集素(HA)の HA1 サブユニットのポジション 222(D222G)でアスパラギン酸からグリシンへのアミノ酸置換が起こっているということを報告した。この研究では重症症例 61 人のうち 11 人(18%)にこの変異があり、一方、軽い疾患症例では 205 人のうちこの変異は 0 人だった。
この最初の報告以来、数か国でこの変異が検出された。このデータは、最近の世界保健機関(WHO)概説でも要約され、全体での D222G の変異率は 1.8%未満であり、一方、致命的な症例の D222G 変異率は 7.1%であるとの報告だった。WHO の論文は他のアミノ酸の変異 (D222E と D222N) が起こっていると報告したが、この意義は不明である。香港のグループは新型インフルエンザで重篤症例と非重篤症例でこのアミノ酸を解析した。この研究では新型インフルエンザの重篤症例や死亡症例 219 人のうち 9 人(4.1%)にこの D222G 変異があり、一方、非重篤症例 239 人のうち D222G 変異は 0 人だった。
我々は、西スコットランドの症例 (community 症例と重症症例の両方) の多くから HA 遺伝子の HA1 サブユニットの配列を決定した。さらに、重症症例を死亡患者と入院後に回復した症例に区別した。我々は、community 症例と入院患者の両方(0/35、0%)と比べて死亡患者 (2/23、 8.7%) で D222G の変異率が高いことが分かった。我々は、重症症例と死亡症例では D222N(アスパラギン酸からアスパラギンへ)の変異率が高い (2/32、6.2%。対照は 0/26、0%)ことを検出した。この変異の意義は不明である。重症症例と community 症例の両方で D222E(アスパラギン酸からグルタミン酸)が低レベルあり、両者とも重大な違いはなかった。
興味深いことに、死亡し D222G 変異があった患者の 1 人で元の配列はコドン D222 において D222D/G の混合塩基であった。この患者から更に 2 つのサンプルを再びシーケンスを行うと、一つは純粋な D222G で他方は純粋な野生型 D222 であり、この患者は異なる集団のウイルスが混合していることを示した。これは突然変異と野生型のウイルスの共存についてのキランダーらの論文でも同様に確認できる。

報告企業の意見	今後の対応
新型インフルエンザの重篤症例や死亡例で D222G 変異の検出が目立ち、非重篤症例では D222G 変異は見られなかったことについての報告である。 インフルエンザA(H1N1)はオルソミクソウイルス科に属するビリオンは球形で、直径80～120nmの脂質エンベロープを有する比較的大きなRNAウイルスである。万一、インフルエンザA(H1N1)が原料血漿に混入したとしてもBVDをモデルウイルスとしたウイルスバリデーション試験成績から、製造工程にて十分に不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないものと考えるので、特段の措置はとらない。

使用上の注意記載状況・その他参考事項等

代表としてテタノブリン IH 静注 250 単位の記載を示す。
2. 重要な基本的注意
(1) 本剤の原材料となる血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体陰性であることを確認している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査 (NAT) を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した高力価の破傷風抗毒素を含有する血漿を原料として、Cohn の低温エタノール分画で得た画分からポリエチレングリコール 4000 処理、DEAE セファデックス処理等により抗破傷風人免疫グロブリンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理及びウイルス除去膜によるろ過処理を施しているが、投与に際しては、次の点に十分注意すること。

LETTERS

Occurrence of haemagglutinin mutation D222G in pandemic influenza A(H1N1) infected patients in the West of Scotland, United Kingdom, 2009-10

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To the editor: Kilander *et al.* (2010) [1] have previously reported that in some cases of patients with severe or fatal pandemic influenza A(H1N1), an amino acid substitution from aspartic acid to glycine occurs at position 222 (D222G) of the HA1 subunit of haemagglutinin (HA). In their study 11 (18%) of 61 patients with severe disease had the mutation, in contrast to 0 of 205 patients with mild disease.

Since the original report [1] several countries have detected this mutation [2]. This data has been summarised in a recent World Health Organization (WHO) review, which reported that the overall prevalence of D222G was <1.8% in contrast to a rate of 7.1% in fatal cases [2]. The WHO paper also reports on the occurrence of other mutations at this amino acid, D222E and D222N, although their significance is unclear. A group in Hong Kong have also analysed this amino acid in severe and non-severe cases of pandemic influenza A(H1N1) [3]. In this study nine (4.1%) of 219 severe or fatal cases of pandemic influenza A(H1N1) had the D222G mutation, in contrast to 0 of 239 non-severe cases.

We sequenced the HA1 subunit of the HA gene from a number of West of Scotland cases, both community cases and severely ill. Furthermore we subdivided the severely ill into those who had died and those who recovered after hospitalisation. We found an increased incidence of D222G in those patients who died (2/23 - 8.7%) compared to both community and hospitalised patients (0/35 - 0%). We also detected an increased incidence (2/32 - 6.2% cf 0/26 - 0%) of D222N (aspartic acid to asparigine) in severely ill patients and those who had died. The significance of this mutation is unclear. There was a low level of D222E (aspartic acid to glutamic acid) present in both severely ill and community cases with no significant difference between the two. The results are summarised in the Table.

Interestingly, in one of the patients who died and had the D222G mutation, the original sequence had a mixed base in the D222 codon giving D222D/G. On resequencing two more samples from this patient, we obtained a pure D222G on one occasion and a pure wildtype D222 on the other, showing that this patient had a mixed population of virus. This confirms the finding in Kilander's paper [1] of the co-existence of mutant and wildtype virus.

TABLE

Prevalence of mutations at amino acid D222 of haemagglutinin of influenza A(H1N1), Scotland, United Kingdom, 2009-2010

	Number of patients	D222G	D222N	D222E
All cases	58	2 (3.4%)	2 (3.4%)	4 (6.9%)
Patients who died	23	2 (8.7%)	0	1 (4.3%)
Seriously ill patients	9	0	2 (22%)	1 (11%)
Community patients	26	0	0	3 (11%)

References

1. Kilander A, Rykkvin R, Dudman S, Hungnes O. Observed association between the HA1 mutation D222G in the 2009 pandemic influenza A(H1N1) virus and severe clinical outcome, Norway 2009-2010. Euro Surveill. 2010;15(9) pii=19498. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19498
2. World Health Organization. Preliminary review of D222G amino acid substitution in the haemagglutinin of pandemic influenza A(H1N1) 2009 viruses. Wkly Epidemiol Rec. 2010;85(4):21-2.
3. Mak GC, Au KW, Tai LS, Chuang KC, Cheng KC, Shiu TC, Lim W. Association of D222G substitution in haemagglutinin of 2009 pandemic influenza A (H1N1) with severe disease. Euro Surveill. 2010;15(14). pii=19534. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19534

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
				2010. 3. 30	該当なし	

一般的名称	解凍人赤血球濃厚液	研究報告の公表状況	FDA, CBER. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM205620.pdf	公表国
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社)			米国

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 2009年度概要
2005年度から2009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。
2009年度(2008年10月1日～2009年9月30日)に、FDAは受血者74件、供血者6件の死亡報告を受領した。受血者死亡例の内訳は、44件が輸血に関連したもの、22件が死亡原因として輸血を排除できないもの、8件が輸血と関連しないものであった。
2005年度から2009年度の統合データ267件において、輸血関連急性肺障害(TRALI)による死亡報告がもっとも多く(48%)、次が溶血性反応(26%)だった。微生物感染、輸血関連循環過負荷(TACO)、アナフィラキシー様反応は少なかったが、TACOに関しては2008年の3件から2009年は12件に増加した。
2008年度の微生物感染は細菌感染5件で、このうち*Staphylococcus aureus*が2件であった。2006年度から2008年度にバベシア感染10件が報告されたが、2009年度は1件も報告がなかった。製剤別ではアフェレーシス血小板が4件、プール血小板が1件で、赤血球製剤による死亡報告はなかった。また、供血後の死亡報告6件について、供血との因果関係は認められなかった。

報告企業の意見	今後の対応
2005年度から2009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。	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。

使用上の注意記載状況・その他参考事項等

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「日赤」
解凍赤血球-LR「日赤」
照射解凍赤血球-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

Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2009

I. Background

As previously mentioned in the annual summary of fatalities reported to the FDA in Fiscal Years (FY) 2005 through FY2008, 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, for example, there were approximately 30 million components transfused.[1] During the proximate period of FY2006, there were 73 reported transfusion related and potentially[2] transfusion related fatalities, with subsequent reports of 63 in FY2007, 54 in FY2008, and 66 in FY2009.

CBER is distributing this summary of transfusion fatality reports received by the FDA to make public the data received in FY2009, to provide the combined data received over the last five fiscal years, and to compare the FY2009 reports to the fatality reports received in the previous four fiscal years. 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/biologicsbloodvaccines/safetyavailability/reportaproblem/transfusiondonationfatalities/default.htm. For further information, see our *Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion*, September 2003.[3]

A team of CBER medical officers reviews the documentation submitted by the reporting facilities and obtained by FDA investigators, to assess the relationship, if any, between the blood donation or transfusion and the reported fatality.

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[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] Transfusion could not be ruled out as the cause of the fatality.

[3] Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion, September, 2003. http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/blood/ucm074947.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 FY2009 (October 1, 2008, through September 30, 2009), we received a total of 80 fatality reports. Of these reports, 74 were transfusion recipient fatalities and 6 were post-donation fatalities.

Of the 74 transfusion recipient fatality reports, we concluded:

a) 44 of the fatalities were transfusion-related,
b) 22 of the fatalities were cases that transfusion could not be ruled out as the cause of the fatality,
c) 8 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 5 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 from FY2005 through FY2009

In combined Fiscal Years (FY) 2005 through 2009, Transfusion Related Acute Lung Injury (TRALI) caused the highest number of reported fatalities (48%), followed by hemolytic transfusion reactions (26%) due to non-ABO (16%) and ABO (10%) incompatibilities.

Complications of microbial infection, Transfusion Associated Circulatory Overload (TACO), and anaphylactic reactions each accounted for a smaller number of reported fatalities (Table 1 and Figure 1). Over the last five fiscal years, we have seen an overall increase in reports of transfusion related TACO fatalities – from three reports in FY2008 to 12 reports in FY2009.[4] The number of transfusion related deaths due to anaphylaxis has remained very small over the last 5 years.

Table 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2009

Complication	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	FY09	FY09	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
TRALI	29	47%	35	56%	34*	65%	16*	35%	13*	30%	127	48%
HTR (non-ABO)	16	26%	9	14%	2	4%	7	15%	8	18%	42	16%
HTR (ABO)	6	10%	3	5%	3	6%	10	22%	4	9%	26	10%
Microbial Infection	8	13%	7	11%	6	12%	7	15%	5	11%	33	12%
TACO	1	2%	8	13%	5	10%	3	7%	12	27%	29	11%
Anaphylaxis	0	0%	1	2%	2	4%	3	7%	1	2%	7	3%
Other	2**	3%	0	0%	0	0%	0	0	1***	2%	3	1%
Totals	62	100%	63	100%	52	100%	46	100%	44	100%	267	100%

*In FY2007, our review committee began using the Canadian Consensus Conference criteria[5,6] for evaluating TRALI cases – these numbers 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)

***Other: Hypotensive Reaction[7]

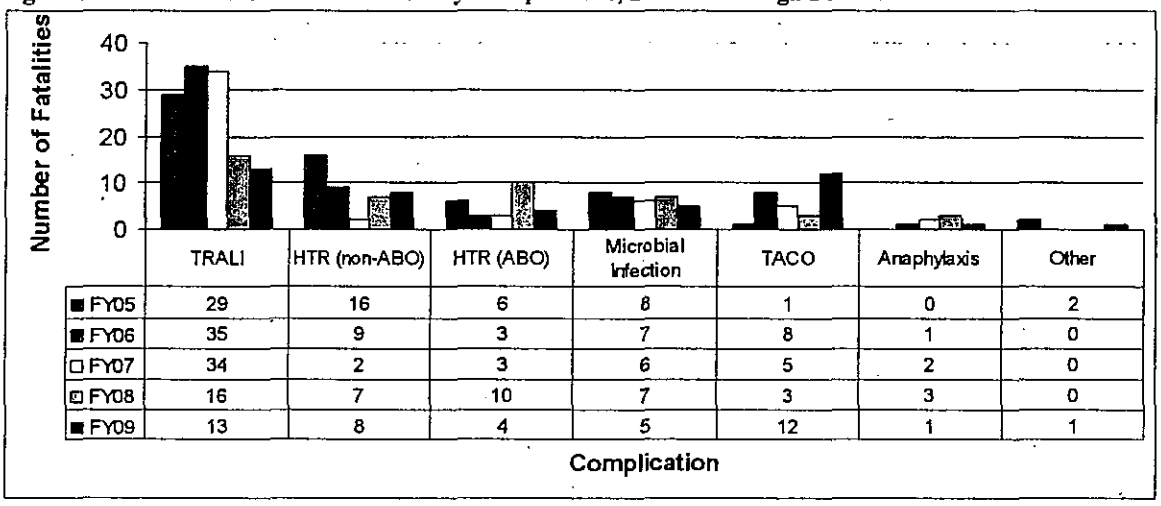
[4] Popovsky MA. Transfusion associated circulatory overload: the plot thickens. Transfusion 2009;49:2-4.

[5] 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.

[6] 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.

[7] Centers for Disease Control and Prevention. The National Healthcare Safety Network (NHSN) Biovigilance Component protocol. 2009:17.

Figure 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2009



	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY05	29	16	6	8	1	0	2
FY06	35	9	3	7	8	1	0
FY07	34	2	3	6	5	2	0
FY08	16	7	10	7	3	3	0
FY09	13	8	4	5	12	1	1

B. Transfusion Related Acute Lung Injury (TRALI)

While TRALI represented 48% of confirmed transfusion related fatalities reported to CBER over the last five fiscal years, fatalities due to TRALI have continued to decrease - to 30% of confirmed transfusion related fatalities in FY2009, compared to 35% in FY2008, and 65% in FY2007. The number of TRALI fatalities associated with receipt of Plasma products decreased from 12 (35% of TRALI cases) in FY2007, to 4 (25% of TRALI cases) in FY2008, to 3 in FY2009 (23% of TRALI cases) (Figure 2). TRALI fatalities associated with receipt of Apheresis Platelets decreased from 5 (31% of TRALI cases) in FY2008 to 2 (15% of TRALI cases) in FY2009.

In Calendar Year 2006, 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%.[8] In comparison, for the combined fiscal years 2005-2009, Fresh Frozen Plasma (FFP) and other plasma accounted for 46% (58/127) of reported TRALI fatalities, apheresis platelets accounted for 11% (14/127), and RBC's accounted for 26% (33/127).

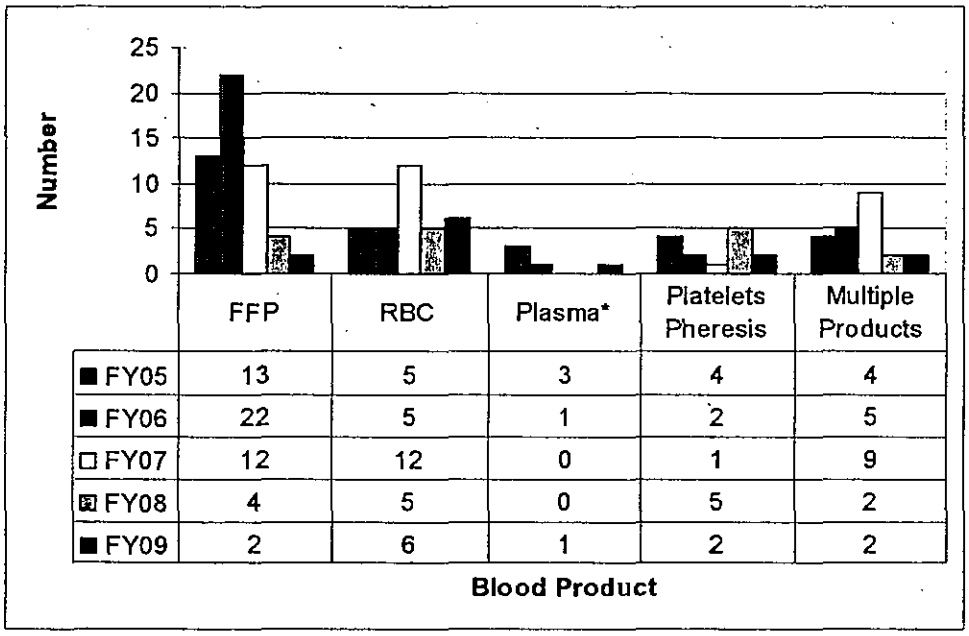
In FY2009, the 13 TRALI cases were temporally associated with products from 38 donors. Of the 38 implicated donors, 19 (50%) were tested for white blood cell (WBC) antibodies (Table 2). Antibody tests were negative in 42% of those tested. Of those tested, Human Leukocyte Antibodies (HLA) were present in 53% of donors. Human Neutrophil Antibodies (HNA) were present in 26% of donors (in two of these donors, no HNA specificity was determined). Some of the donors had multiple antibodies. Reporters who included patient testing data were able to match donor antibodies with recipient cognate antigens in 6 of the 13 cases, implicating 5 female donors and one male.

[8] Whittaker BI, op.cit. Tables 4-1 and 4-2.

Of the 38 implicated donors, reports identified 16 females (42%) and 22 males (58%). Of the 19 donors that were tested, 12 were females (10 with a history of pregnancy; 2 with unknown pregnancy history) and 7 were males (one with a history of transfusion; 6 with no reported history of transfusion or transplant). Nine of the 12 females tested positive for antibodies, implicating 6 RBC's, 1 FFP, and 2 Apheresis Platelets. Two of the 7 males tested positive for antibodies, implicating 1 FFP and 1 Plasma frozen within 24 hours after collection (FP24).

Although the transfusion community has taken voluntary measures to reduce the risk of TRALI, this complication of transfusion continues to be one of the leading causes of transfusion-related fatalities reported to the FDA. Current literature describes the results of continued international efforts to reduce the use of plasma for transfusion prepared from female donors.[9,10,11,12,13]

Figure 2: Reports of TRALI by Implicated Blood Product, FY2005 through FY2008



	FFP	RBC	Plasma*	Platelets Pheresis	Multiple Products
FY05	13	5	3	4	4
FY06	22	5	1	2	5
FY07	12	12	0	1	9
FY08	4	5	0	5	2
FY09	2	6	1	2	2

*FY2005: Includes 2 FP24 (Plasma frozen within 24 hours after collection) and 1 Liquid Plasma
*FY2006: Includes 1 FP24
*FY2009: Includes 1 FP24

[9] Eder AF, Benjamin RJ. TRALI risk reduction: donor and component management strategies. J Clin Apher 2009;24(3):122-9.
[10] Murphy MF, Navarete C, Massey E. Donor screening as a TRALI risk reduction strategy. Transfusion 2009;49:1779-82.
[11] Stillman CC, Fung YL, et al. Transfusion-related acute lung injury (TRALI): Current concepts and misconceptions. Blood Reviews 2009;23:245-255.
[12] Chapman CE, Stainsby D, et al. Serious Hazards of Transfusion Steering Group. Ten years of hemovigilance reports of transfusion related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. Transfusion 2009;49:440-52.
[13] Keller-Stanislawski B, Riel A, et al. Frequency and severity of transfusion-related acute lung injury – German haemovigilance data [2006-2007]. Vox Sang 2010;98:70-77.

Table 2: Donor Antibodies Identified in Association with TRALI, FY2007 through FY2009

Donor Leukocyte Antibodies	FY07 No.	FY07%	FY08 No.	FY08%	FY09 No.	FY09 %
HLA Class I	18	17%	3	18%	1	5%
HLA Class II	6	6%	2	12%	0	0%
HLA Class I and II	15	14%	6	35%	5	26%
HNA	17	16%	2	12%	1	5%
HLA and HNA	6	6%	2	12%	4	21%
Negative	42	41%	2	12%	8	42%
Total Donors Tested	104	100%	17	100%	19	100%

This table does not include the 59 donors that were not tested for WBC antibodies in FY07, the 3 donors that were not tested in FY08, and the 19 donors that were not tested in FY09.

C. Hemolytic Transfusion Reactions

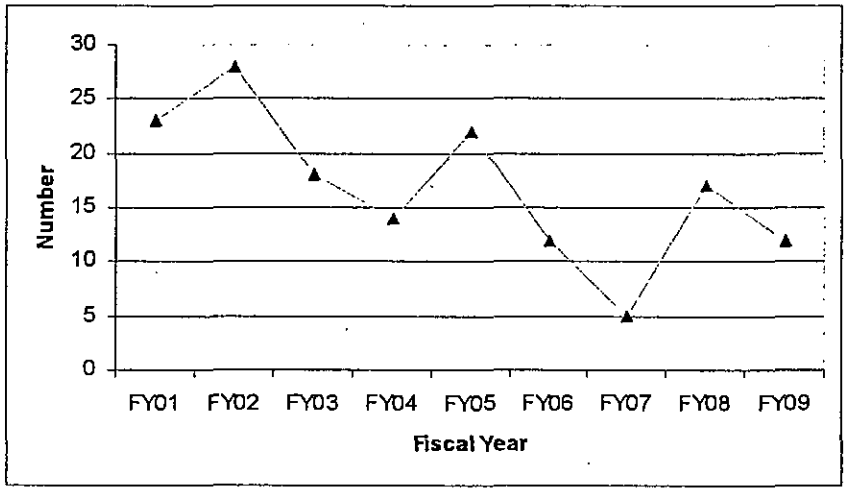
In FY2009, hemolytic transfusion reactions and TACO were the second leading causes of transfusion related fatalities reported to CBER, each representing 27% of confirmed transfusion related fatalities. The number of reported fatal hemolytic transfusion reactions decreased from 17 in FY2008 to 12 in FY2009, due to a decrease in reports of ABO hemolytic reactions, from 10 (59%) in FY2008, to 4 (33%) in FY2009 (Figure 1 and Table 3). We continue to see an overall decrease in the number of reported fatalities due to hemolytic transfusion reactions since FY2001 (Figure 3).

Table 3: Hemolytic Transfusion Reactions by Implicated Antibody, FY2005 through FY2009

	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	FY09	FY09	Total	Total
Antibody	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
ABO	6	27%	3	25%	3	60%	10	59%	4	33%	26	38%
Multiple Antibodies*	6	27%	4	33%	1	20%	1	6%	2	17%	14	21%
Jk^b	3	14%	0	0%	0	0%	2	12%	0	0%	5	7%
Other**	3	14%	0	0%	0	0%	0	0%	2	17%	5	7%
Kell	1	5%	1	8%	0	0%	2	12%	0	0%	4	6%
Jk^a	1	5%	1	8%	1	20%	0	0%	2	17%	5	7%
Fy^a	0	0%	1	8%	0	0%	2	12%	1	8%	4	6%
Fy^b	0	0%	1	8%	0	0%	0	0%	0	0%	1	1%
E	1	5%	0	0%	0	0%	0	0%	0	0%	1	1%
I	1	5%	0	0%	0	0%	0	0%	0	0%	1	1%
Js^a	0	0%	1	8%	0	0%	0	0%	0	0%	1	1%
Js^b	0	0%	0	0%	0	0%	0	0%	1	8%	1	1%
Totals	22	100%	12	100%	5	100%	17	100%	12	100%	68	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
*FY2008: anti-C+K+Fy^b+S+N+V+Js^a+Go^a+warm autoantibody.
*FY2009: antibody combinations included E+Jkb, S+Jka+Jkb+K+Fya+Fyb+V+C+N+HTLA
**FY2005: 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.
**FY2009: Includes one report of an unidentified warm autoantibody and one report of Hyperhemolysis Syndrome[14].

Figure 3: Hemolytic Transfusion Reactions, FY2001 through FY2009



In FY2009, there were four reports of fatal hemolytic transfusion reactions due to ABO-incompatible blood transfusions:

- 1 case: recipient identification error at the time of transfusion (nursing error)
- 1 case: patient sample labels switched (phlebotomist error)
- 1 case: sample collected from incorrect patient (phlebotomist error)
- 1 case: patient sample mistyped (lab error)

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

D. Microbial Infection

In FY2009, there were 5 reported fatalities attributed to microbial infection – similar to the numbers reported in the previous four fiscal years. Three different bacteria were implicated in three fatalities, and *Staphylococcus aureus* was implicated in two (40%) of the fatalities. Although *Babesia* accounted for 36% (10/28) of reported cases over the previous four fiscal years, there were no reported cases in FY2009. *Babesia* now accounts for 30% (10/33) of deaths due to microbial infection over the 5-year reporting period, followed by *Staphylococcus aureus*, which accounted for 21% (7/33) (Table 4).

After seven years with no reported deaths due to transfusion-transmitted Babesiosis, CBER received reports of 10 transfusion-transmitted Babesiosis deaths during fiscal years 2006 through 2008. Recent articles provide additional information about this topic.[15,16]

There was one strict anaerobe, *Eubacterium limosum,* implicated in a fatal bacterial infection during the 5-year reporting period; this fatality occurred in FY2005. The remaining bacteria are facultative anaerobes.

In FY2009, there were no reports of fatal microbial infections associated with Red Blood Cells, compared to 5 reports in FY2008, which were all due to *Babesia* infections. There was a small increase in the number of reports of fatal microbial infections associated with apheresis platelets[17] in FY2009 (Figure 4). However, this finding is still consistent with an overall decrease in the number of bacterial infections associated with apheresis platelets since FY2001 (Figure 5).

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[15] Gubernot DM, Nakhasi HL, Mied PA, et al.Transfusion-transmitted babesiosis in the United States: summary of a workshop. Transfusion 2009;49:2759-2771.

[16] Tonetti L, Eder AE, Dy B, et al. Transfusion-transmitted *Babesia Microti* identified through hemovigilance. Transfusion 2009;49:2557-2563.

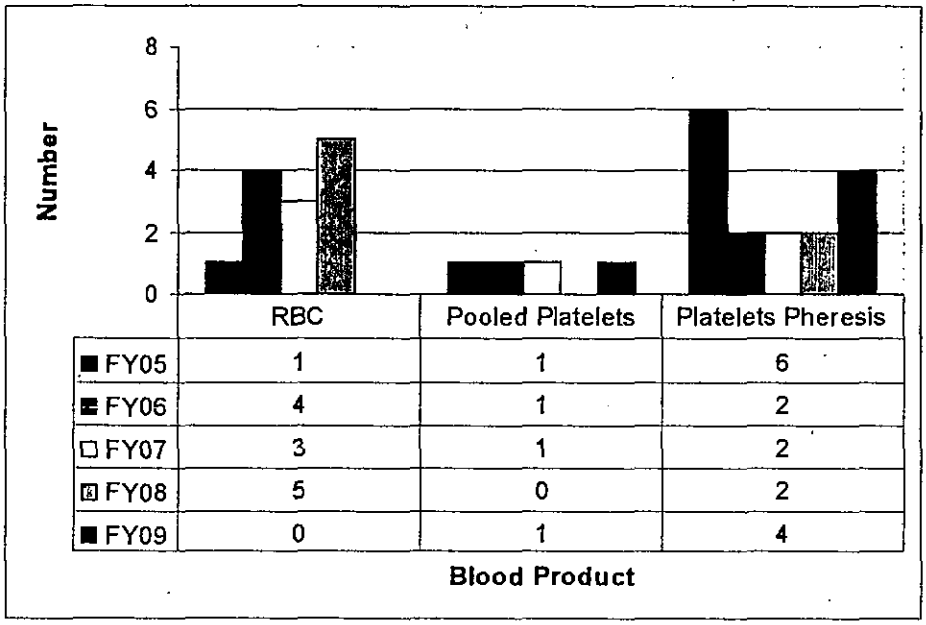
[17] Fuller AK, Uglik KM, et al. Bacterial culture reduces but does not eliminate the risk of septic transfusion reactions due to single-donor platelets. Transfusion 2009;49:2588-2593.

Table 4: Microbial Infection by Implicated Organism, FY2005 through FY2009

Organism	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	FY09	FY09	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
*Babesia**	0	0%	2	29%	3	50%	5	71%	0	0%	10	30%
Staphylococcus aureus	3	37%	0	0%	1	17%	1	14%	2	40%	7	21%
Escherichia coli	0	0%	3	43%	0	0%	0	0%	0	0%	3	9%
Serratia marcescens	2	24%	0	0%	0	0%	0	0%	0	0%	2	6%
Staphylococcus epidermidis	1	13%	0	0%	0	0%	1	14%	0	0%	2	6%
Staphylococcus lugdunensis	1	13%	0	0%	0	0%	0	0%	0	0%	1	3%
Eubacterium limosum	1	13%	0	0%	0	0%	0	0%	0	0%	1	3%
Morganella morganii	0	0%	1	14%	0	0%	0	0%	0	0%	1	3%
Yersinia enterocolitica	0	0%	1	14%	0	0%	0	0%	0	0%	1	3%
Streptococcus dysgalactiae (Group C)	0	0%	0	0%	1	17%	0	0%	0	0%	1	
Klebsiella oxytoca	0	0%	0	0%	1	17%	0	0%	0	0%	1	3%
Streptococcus viridans	0	0%	0	0%	0	0%	0	0%	1	20%	1	3%
Streptococcus pneumoniae	0	0%	0	0%	0	0%	0	0%	1	20%	1	3%
Staphylococcus warneri	0	0%	0	0%	0	0%	0	0%	1	20%	1	3%
Total	8	100%	7	100%	6	100%	7	100%	5	100%	33	100%

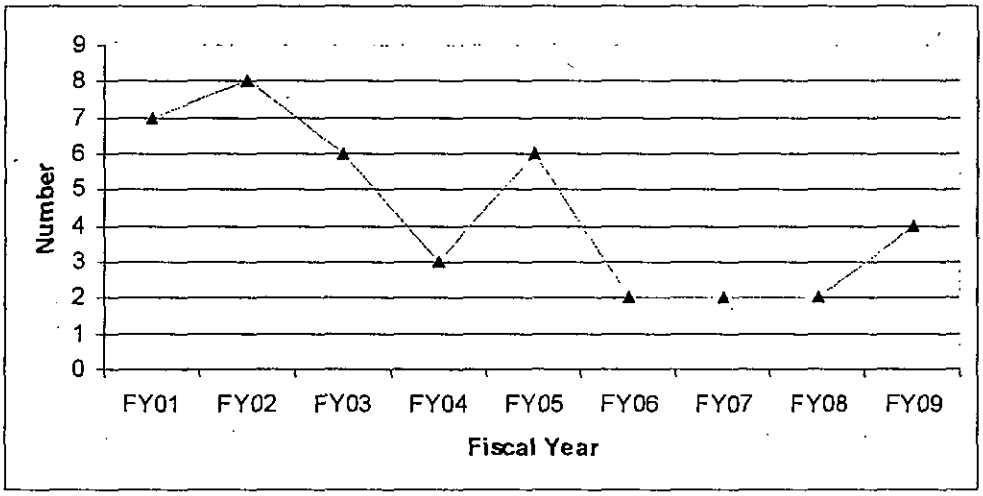
*Nine *Babesia microti* and one probable *Babesia MO-1* species

Figure 4: Microbial Infection by Implicated Blood Product, FY2005 through FY2009



Red Blood Cells microorganisms: *S. marcescens (1), E. coli (1), Y. enterocolitica (1), B. microti (9), B. MO1(1)*
Pooled Platelets microorganisms: *S. aureus (1), E. coli (1), S. dysgalactiae (1), S. pneumoniae (1)*
Platelets Pheresis microorganisms: *S. aureus (6), S. marcescens (1), S. lugdunensis (1), S. epidermidis (2), E. limosum (1), E. coli (1), M. morganii (1), K. oxytoca (1), S.viridans (1), S. warneri (1)*

Figure 5: Bacterial Infection by Apheresis Platelets, FY2001 through FY2009



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 total of 66 reported fatalities in FY2009, as compared to 54 in FY2008 and 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 FY2009

	FY05	FY06	FY07	FY08	FY09
Not Transfusion Related	21	8	13	18	8
Not Ruled Out	14	10	11	8	22
Totals	35	18	24	26	30

G. Post-Donation Fatalities

FY2009 showed a continued decrease since FY2007, in the number of reported fatalities following Source Plasma donation (Table 6). In all of these cases (FY2005 through FY2009), 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 donations and subsequent death of the donors.

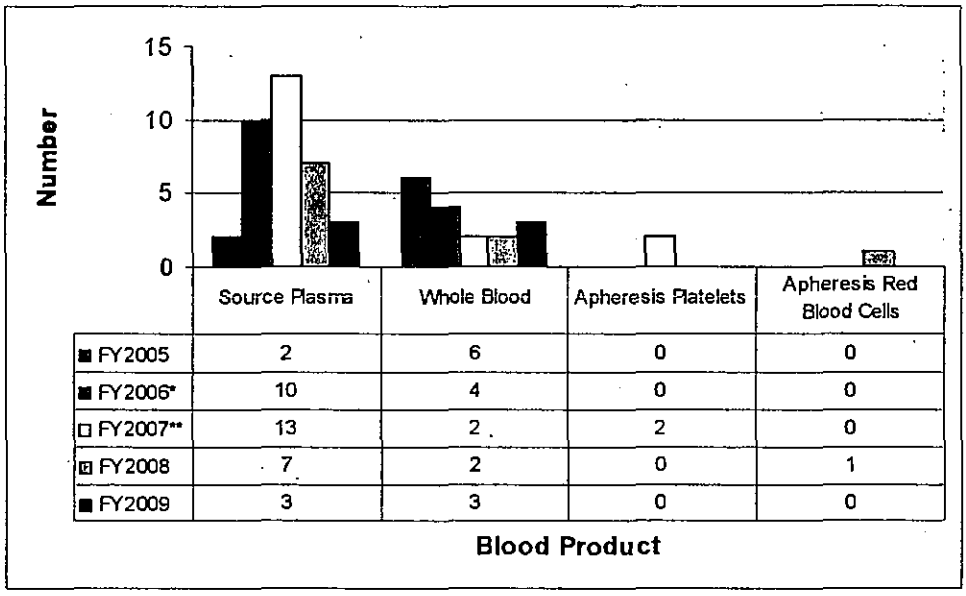
We received three FY2009 reports of fatalities following Whole Blood donation collected by manual methods. In two of these cases, our medical reviewers ruled out the donation as the cause of death due to evidence found in the donor's medical records. In the third case, although the donation could not be definitively ruled out as being implicated in the donor's death, our medical reviewers found no evidence to support a causal relationship between the donation and subsequent death of the donor.

Table 6: Post-Donation Fatality Reports by Donated Product, FY2005 through FY2009

Donated Product	FY05	FY06	FY07	FY08	FY09
Source Plasma	2	10	13	7	3
Whole Blood	6	4*	2**	2	3
Apheresis Platelets	0	0	2	0	0
Apheresis Red Blood Cells	0	0	0	1	0
Total	8	14	17	10	6

*Includes 2 autologous donations
**Autologous donations

Figure 6: Post-Donation Fatality Reports, FY2005 through FY2009



*Includes 2 autologous Whole Blood donations
**Both Whole Blood donations in FY07 were autologous