別紙様式第2－1

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年2月22日	該当なし	
一般的名称	別紙のとおり		研究報告の公表状況	CDC／Travelers' Health (Updated: February 18, 2010)	公表国 インドネシア タイ マレーシア	
販売名（企業名）	別紙のとおり					

研究報告の概要	使用上の注意記載状況・その他参考事項等
問題点：2009年から2010年初頭にかけてインドネシア、タイ、マレーシアにおいてチクングニヤウイルス熱のアウトブレイクが発生している。 2006年以降、アジア及びインド洋領域でチクングニヤ熱の活動が報告されているが、2009年にインドネシアでは12の県に渡って43,206例（死亡例は無し）が、タイではPhuketを含む南部を中心に49,069例超が、マレーシアではSarawak Kedah県北部を中心に4,430例超（死亡例は無し）の当該症例が報告された。また、インドネシアではSumatra島のlampung県南部において2009年12月後半から2010年1月初頭に6,700例のチクングニヤ感染例が、マレーシアでは2010年最初の5週間で325例のチクングニヤ熱症例が報告されている。	記載なし

報告企業の意見	今後の対応
別紙のとおり	今後とも関連情報の収集に努め、本剤の安全性の確保を図っていきたい。

MedDRA12.1

別紙

一般的名称	①人血清アルブミン、②人血清アルブミン、③人血清アルブミン*、④人免役グロブリン、⑤人免役グロブリン、⑥人免役グロブリン、⑦乾燥ペプシン処理人免疫グロブリン、⑧乾燥ペプシン処理人免疫グロブリン、⑨乾燥スルホ化人免疫グロブリン、⑩乾燥スルホ化人免疫グロブリン、⑪乾燥スルホ化人免疫グロブリン、⑫乾燥スルホ化人免疫グロブリン、⑬乾燥スルホ化人免疫グロブリン、⑭乾燥スルホ化人免疫グロブリン*、⑮乾燥濃縮人活性化プロテインC、⑯乾燥濃縮人血液凝固第Ⅷ因子、⑰乾燥濃縮人血液凝固第Ⅷ因子、⑱乾燥濃縮人血液凝固第Ⅷ因子、⑲乾燥濃縮人血液凝固第Ⅷ因子、⑳乾燥濃縮人血液凝固第Ⅸ因子、㉑乾燥濃縮人血液凝固第Ⅸ因子、㉒乾燥濃縮人血液凝固第Ⅸ因子、㉓乾燥濃縮人血液凝固第Ⅸ因子、㉔乾燥抗破傷風人免疫グロブリン、㉕乾燥抗破傷風人免疫グロブリン、㉖抗HBs人免疫グロブリン、㉗抗HBs人免疫グロブリン、㉘トロンビン、㉙フィブリノゲン加第ⅩⅢ因子、㉚フィブリノゲン加第ⅩⅢ因子、㉛乾燥濃縮人アンチトロンビンⅢ、㉜乾燥濃縮人アンチトロンビンⅢ、㉝ヒスタミン加人免疫グロブリン製剤、㉞タミン加人免疫グロブリン製剤、㉟人血清アルブミン*、㊱人血清アルブミン*、㊲乾燥ペプシン処理人免役グロブリン*、㊳乾燥濃縮人アンチトロンビンⅢ
販売名（企業名）	①献血アルブミン20“化血研”、②献血アルブミン25“化血研”、③人血清アルブミン“化血研”*、④“化血研”ガンマーグロブリン、⑤ガンマーグロブリン筋注450mg/3mL「化血研」、⑥ガンマーグロブリン筋注1500mg/10mL「化血研」、⑦献血静注グロブリン“化血研”、⑧献血グロブリン注射用2500mg「化血研」、⑨献血ベニロンーⅠ、⑩献血ベニロンーⅠ静注用500mg、⑪献血ベニロンーⅠ静注用1000mg、⑫献血ベニロンーⅠ静注用2500mg、⑬献血ベニロンーⅠ静注用5000mg、⑭ベニロン*、⑮注射用アナクトC2,500単位、⑯コンファクトF、⑰コンファクトF注射用250、⑱コンファクトF注射用500、⑲コンファクトF注射用1000、⑳ノバクトM、㉑ノバクトM注射用250、㉒ノバクトM注射用500、㉓ノバクトM注射用1000、㉔テタノセーラ、㉕テタノセーラ筋注用250単位、㉖ヘパトセーラ、㉗ヘパトセーラ筋注200単位/mL、㉘トロンビン“化血研”、㉙ボルヒール、㉚ボルヒール組織接着用、㉛アンスロビンP、㉜アンスロビンP500注射用、㉝ヒスタグロビン、㉞ヒスタグロビン皮下注用、㉟アルブミン20%化血研*、㊱アルブミン5%化血研*、㊲静注グロブリン*、㊳アンスロビンP1500注射用
報告企業の意見	チクングニヤウイルス（Chikungunya virus）は、トガウイルス科（Togaviridae）のアルファウイルス属（Alphavirus）に分類される1本鎖のRNAを核酸として持つ直径70nmのエンベロープを有する球状粒子であり、これまでに国内での発生、流行は報告されていないが、2010年12月までに海外からの輸入症例として15例の報告がある。チクングニヤウイルスは蚊によって媒介されるが、感染後ウイルス血症を起こすことから、血液を介してウイルス感染する可能性を完全に否定できないため本報告を行った。 上記製剤の製造工程には、冷エタノール分画工程、ウイルス除去膜ろ過工程あるいは加熱工程等の原理の異なるウイルス除去・不活化工程が存在しているので、仮にウイルスが原料血漿に混入していたとしても、ウイルスクリアランスが期待される。各製造工程のウイルス除去・不活化効果は、「血漿分画製剤のウイルスに対する安全性確保に関するガイドライン（医薬発第1047号、平成11年8月30日）」に従い、ウシウイルス性下痢ウイルス（BVDV）、仮性狂犬病ウイルス（PRV）、ブタパルボウイルス（PPV）、A型肝炎ウイルス（HAV）または脳心筋炎ウイルス（EMCV）をモデルウイルスとして、ウイルスプロセスバリデーションを実施し、評価を行っている。今回報告したチクングニヤウイルスはエンベロープの有無、核酸の種類等からモデルウイルスとしてはBVDVが該当すると考えられるが、上記バリデーションの結果から、BVDVの除去・不活化効果を有することを確認している。また、これまでに上記製剤によるチクングニヤウイルス感染の報告例は無い。 以上の点から、上記製剤はチクングニヤウイルスに対する安全性を確保していると考える。

*現在製造を行っていない

Centers for Disease Control and Prevention
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Outbreak Notice
Chikungunya Fever in Asia and the Indian Ocean

This information is current as of today, April 07, 2010 at 21:25 EDT

Updated: February 18, 2010

Situation Information

Since 2006, parts of Asia and the Indian Ocean region have reported chikungunya fever activity. Several countries have increased surveillance for this disease, and cases continue to be reported throughout this region.

Chikungunya fever is a disease caused by a virus that is spread to people through the bite of infected mosquitoes. Symptoms can include sudden fever, joint pain with or without swelling, chills, headache, nausea, vomiting, lower back pain, and a rash. Chikungunya mainly occurs in areas of Africa and Asia. In 2007, limited transmission of *chikungunya virus occurred in Italy.*

The following examples highlight some recent chikungunya activity in Asia and the Indian Ocean region:

Indonesia

A chikungunya outbreak has been reported in the southern province of Lampung on the island of Sumatra. From the second half of December 2009 through the beginning of January 2010, 6,700 chikungunya cases were reported. In 2009, no deaths due to chikungunya fever were reported, although a total of 43,206 cases were reported across the country from 12 provinces.

Thailand

In 2009, a large outbreak of chikungunya fever affected the country, particularly the southern region, including some tourist destinations, such as Phuket. According to the Ministry of Public Health in Thailand, over 49,069 cases were documented in more than 50 provinces. Reports from Thailand show that chikungunya virus continues to circulate throughout the country.

Malaysia

In 2009, the Ministry of Health in Malaysia reported over 4,430 cases of chikungunya fever. No deaths were reported. The most affected areas are the northern provinces of Sarawak Kedah, followed by Kelantan, Selangor, and Perak. Chikungunya activity has continued in 2010, with an additional 325 cases reported in the first 5 weeks. The cases occurred predominately in Serawak.

Advice for Clinicians

Clinicians should be aware of the ongoing global chikungunya activity. Chikungunya may present in a similar fashion to malaria and dengue, with fever, chills, and generalized myalgias. However, after the acute illness, patients with chikungunya may have a prolonged course of arthralgias or arthritis, which may lead health-care providers to consider and begin testing for rheumatic diseases. These signs and symptoms can persist for several months.

For more information, please see Chikungunya Fever section of *CDC Health information for International Travel 2010.*

Advice for Travelers

No medications or vaccines are available to prevent a person from getting sick with chikungunya fever. CDC recommends that people traveling to areas where chikungunya fever has been reported take the following steps to protect themselves from mosquito bites.

- When outdoors during the day and at night, use insect repellent on exposed skin.
  - 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 (%) of any of these active ingredients. However, concentrations above 50% do not offer a distinct increase in protection time. Products with less than 10% of an active ingredient may offer only limited protection, often only 1–2 hours.
  - The American Academy of Pediatrics approves the use of repellents with up to 30% DEET on children over 2 months of age.

If you get sick with a fever and think you may have chikungunya fever, you should seek medical care. Although there is no specific treatment for the disease, a doctor may be able to help treat your symptoms. Avoid getting any other mosquito bites, because if you are sick and a mosquito bites you, it can spread the disease to other people.

For more travel health information, see the destinations section and search for the country you are planning to visit.

More Information

The incubation period for chikungunya (time from infection to illness) is usually 3–7 days, but it can range from 2–12 days. Chikungunya fever typically lasts a few days to 2 weeks, but some

patients feel fatigue lasting several weeks. Most patients report severe joint pain or arthritis, which may last for weeks or months. The symptoms are similar to those of dengue fever, but, unlike some types of dengue, people who have chikungunya fever do not experience hemorrhage (bleeding) or go into shock. People with chikungunya fever generally get better on their own and rarely die from the disease.

Medical care for chikungunya fever is usually focused on treating the symptoms of the disease. Bed rest, fluids, and mild pain medications such as ibuprofen, naproxen, or acetaminophen (paracetamol) may relieve symptoms of fever and aching, provided there are no medical contraindications for using these medications. Most people are not sick enough to need to stay in the hospital. All people who become sick with chikungunya fever should be protected against additional mosquito bites to reduce the risk of further transmission of the virus.

For more information, see—

- Chikungunya (CDC Fact Sheet)
- Traveling with Children: Resources (CDC Travelers' Health website)

Other Mosquito-Related Diseases

In many of the areas where chikungunya is present, mosquito bites spread other diseases, such as dengue, malaria, Japanese encephalitis, and yellow fever. If you are traveling to any tropical and subtropical areas of the world, you should take steps to avoid mosquito bites.

- Page last reviewed: November 19, 2009
- Page last updated: February 18, 2010
- Page created: August 21, 2008
- Content source:
  Division of Global Migration and Quarantine
  National Center for Preparedness, Detection, and Control of Infectious Diseases

USA.gov Government Made Easy

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800-CDC-INFO (800-232-4636) TTY: (888) 232-6348 24 Hours/Every Day - cdcinfo@cdc.gov

別紙様式第2-1

No. 15

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
				2009. 11. 19	該当なし	
一般的名称	人血清アルブミン		研究報告の公表状況	Stramer S L, Linnen J M, Carrick J M, Krysztof D, McMilin K D, De Vera A, Hunsperger E A, Muñor J L, Dodd R Y. AABB Annual Meeting and TXPO; 2009 Oct. 24-27; New Orleans.	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) 赤十字アルブミン20%静注4g/20mL(日本赤十字社) 赤十字アルブミン20%静注10g/50mL(日本赤十字社) 赤十字アルブミン25%静注12.5g/50mL(日本赤十字社)					

研究報告の概要

○2007年のデング熱アウトブレイク時におけるプエルトリコからの供血のデング熱ウイルス血症

背景:デング熱ウイルスは世界で最も重要なアルボウイルスであり、流行範囲を拡大させている。WNV同様、デング熱は蚊によって自然感染するが、輸血によっても伝播する。デング熱流行地域であるプエルトリコの2005年流行期後半のウイルス血症発現率は1:1300を示した。2007年に非常に大規模なデング熱アウトブレイクが発現し、流行期間中の供血者検体が保管された。

方法:ウイルス血症検査のために検体を2セットに分類した(アメリカ本土/プエルトリコで輸血された血液)。研究用transcription mediated amplification assay (TMA)により個別に検体を検査した。初回陽性(IR)検体に再検査を行い、反復陽性(RR)検体は確定とみなされた。プエルトリコのCDCデング熱部門にて、血清型およびウイルス量を明らかにするためPCR、蚊細胞培養、IgM検査などを実施した。RR血液供給先の病院に連絡を取り、受血者の調査を行った。

結果:合計15,350検体を検査し、28がIR、25がRRとなった。有病率は1:614であった。陽性血液のうち12(1:533)が米国本土に輸出され、13がプエルトリコに残った。特異性は99.98%であった。1:16希釈で14/25(56%)のRR供血が検出された。CDCの追加検査では、プエルトリコで循環している血清型1、2、3が示され、11/25(44%)の検体は、RNA力価10^5-10^9copies/mLであり、11検体すべてが細胞培養で感染性があった。9/11(82%)のPCR陽性検体が1:16希釈で検出された。IgM検査を行った6/22(27%)検体のうち2検体のみウイルスの定量が可能(10^6、10^9)であり、うち1つは1:16の希釈で検出された。残り4つのIgM陽性検体では1つのみが1:16希釈で陽性であり、合計2つのIgM陽性検体が希釈時に陽性であった。米国本土とプエルトリコで受血者調査を実施中である。

結論:流行期間中のウイルス血症頻度が高いことが示された。RNA陽性血液の半数近くがIgM陰性で高力価ウイルス血症があり、細胞培養で感染性が確認された。デング熱流行時には供血者のスクリーニングを検討すべきである。

報告企業の意見	今後の対応
プエルトリコにおけるデング熱流行期間中の供血者のウイルス血症頻度が高いことが示され、RNA陽性血液の半数近くがIgM陰性で高力価ウイルス血症があり、細胞培養で感染性が確認されたとの報告である。 デングウイルスは脂質膜を持つ中型RNAウイルスである。これまで、本製剤によるデングウイルス感染の報告はない。本製剤の製造工程には、平成11年8月30日付医薬発第1047号に沿ったウイルス・プロセスバリデーションによって検証された2つの異なるウイルス除去・不活化工程が含まれていることから、本製剤の安全性は確保されていると考える。	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

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン20%静注4g/20mL
赤十字アルブミン20%静注10g/50mL
赤十字アルブミン25%静注12.5g/50mL

血液を原料とすることに由来する感染症伝播等

(13)

S64-030F

HOD RBCs Stored For 14 Days Are Significantly More Immunogenic Than Fresh HOD RBCs

J E Hendrickson[1] (jeanne.hendrickson@choa.org), E A Hod[2], S L Spitalnik[2], C D Hillyer[3], J C Zimring[3]. *[1]Department of Pediatrics, Emory University, AFLAC Cancer Center and Blood Disorders Service, Atlanta, GA, USA; [2]Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY, USA; [3]Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA*

Background: Within FDA limits, red blood cells (RBCs) are generally transfused without regard to length of in vitro storage. However, recent studies have raised concerns that transfusion of older stored (i.e. aged) RBCs may lead to adverse events in certain patients. We hypothesized that aged RBC transfusions would lead to higher rates of RBC alloimmunization, and developed a murine model to test this hypothesis. **Materials and Methods:** RBCs from HOD donors (expressing transgenic RBC specific hen egg lysozyme (HEL) fused to human Fyb) were collected in 12.3% CPDA, leukoreduced (LR) with a Pall neonatal LR filter, volume reduced to a Hct of 75%, and stored at 4° C for 14 days. C57BL/6 recipients were transfused intravenously with 500 µL of a 20% solution of fresh or aged (stored 14 days) LR or non-LR RBCs. Flow cytometric testing of HEL and Fyb expression on pre and post-transfusion RBCs was done, with 24 hour post-transfusion survival determined by extrapolation to time 0. Blood cultures were performed on representative samples prior to transfusion. Alloimmunization was tested 2 weeks post-transfusion by anti-HEL IgG ELISA using titrated sera. **Results:** In 5 of 6 independent experiments (n = 62 mice), transfused aged RBCs were 10-100 fold more immunogenic than fresh RBCs as determined by HEL specific ELISA ($p < 0.05$ by 2 way ANOVA with Bonferroni posttest). This increase in immunogenicity was also seen with LR RBCs; in 3 of 4 experiments (n = 42 mice), aged LR RBCs were more immunogenic than fresh LR RBCs ($p < 0.001$). In 2 of 2 experiments (n = 20 mice), aged RBCs washed 3 times in saline led to similar levels of alloimmunization as did unwashed aged RBCs. Gram's stain and culture of 7 of 9 representative units was negative. The calculated 24 hour post-transfusion survival for fresh, aged, and aged LR blood was 100%, 38.7% (95% CI 31.8-45.6), and 43.9% (95% CI 35.9-51.9). In 4 of 5 experiments, HEL and Fyb expression on aged RBCs was identical to that of fresh RBCs. **Conclusions:** Transfusion of LR and non-LR transgenic HOD RBCs, stored for 14 days in conditions similar to those used in human blood banking, induce higher levels of alloimmunization than freshly collected and transfused RBCs. This cannot be explained solely by the presence of contaminating WBCs or bacteria. In addition, because washed RBCs are as immunogenic as unwashed RBCs, the RBCs themselves may be responsible for the increased immunogenicity. Although the 24 hour post-transfusion survival is below the average for human RBCs, this study is a proof of principle testing of the effect of aging on RBC alloimmunization. The reproducibility of these findings in other RBC antigen systems, as well as the potential translational applicability, remains to be determined.

Disclosure of Commercial Conflict of Interest

J. E. Hendrickson: Nothing to disclose; C. D. Hillyer: Nothing to disclose; E. A. Hod: Nothing to disclose; S. L. Spitalnik: Nothing to disclose; J. C. Zimring: Nothing to disclose

Disclosure of Grants Conflict of Interest

J. E. Hendrickson: Nothing to disclose; C. D. Hillyer: Nothing to disclose; E. A. Hod: Nothing to disclose; S. L. Spitalnik: Nothing to disclose; J. C. Zimring: Immucor Inc., Grants or Research Support

S65-030F

Crossmatch Incompatible RBCs Have an Intrinsic Range of Susceptibility to Hemolysis

J S Liepkalns[1] (jsliepk@emory.edu), J C Zimring[1]. *[1]Center for Transfusion and Cellular Therapies, Emory University School of Medicine, Atlanta, GA, USA*

Background: During crossmatch incompatible transfusions, clinically significant antibodies can lead to brisk hemolysis. However, for some blood group antigens, antibodies are hemolytic in certain patients but not in others. The reason for this variability is poorly understood. Using a mouse model of crossmatch incompatible transfusion involving human glycophorin A (hGPA) as an RBC antigen, we have previously observed that some hGPA RBCs clear but others continue to circulate despite being coated with IgG. We have also reported that the mechanism of resistance was neither antibody depletion nor saturation of the reticuloendothelial system. To further characterize hemolysis resistance, we tested whether resistance is an acquired or intrinsic property of the RBC. **Methods:** Incompatible hGPA RBCs and compatible wild-type RBCs were labeled with fluorescent dyes DiI and DiO, respectively. Mixtures of the labeled RBCs were transfused into wild-type recipients (transfusion 1) that had been passively immunized with a monoclonal antibody against hGPA (6A7). Two days post transfusion, RBCs were collected and were mixed with freshly isolated hGPA RBCs labeled in a third color (DiD). This mixture was then transfused into naive mice (transfusion 2), which were likewise passively immunized with 6A7. In all cases, RBC survival was determined through enumerating each population by flow cytometry. Clearance in transfusion 1 was determined by calculating survival of hGPA RBCs as a function of compatible wild-type RBCs. Hemolysis resistance was defined during transfusion 2 as decreased clearance of hGPA RBCs from transfusion 1 compared to clearance of fresh hGPA RBCs. Titrations of 6A7 were performed in transfusions 1 and 2. **Results:** In transfusion 1, hGPA RBCs showed initial rapid clearance proportional to the amount of 6A7 injected. In all cases, the surviving hGPA RBCs were 90-100% resistant to clearance in transfusion 2 when exposed to the same concentration of 6A7 as in transfusion 1. However, if an increased concentration of 6A7 was used in transfusion 2, then resistance to clearance was less (range 20-60%). **Conclusion:** The observation that hGPA RBCs are resistant to clearance by the same concentration of 6A7 in transfusion 2 as in transfusion 1, but are less resistant to increased amounts of 6A7 in transfusion 2, suggest that RBCs have a range of susceptibility to clearance as a function of antibody concentration. The mechanism of differential susceptibility to clearance is uncertain, but may include RBC age or antigen density.

Disclosure of Commercial Conflict of Interest

J. S. Liepkalns: Nothing to disclose; J. C. Zimring: Nothing to disclose

Disclosure of Grants Conflict of Interest

J. S. Liepkalns: Nothing to disclose; J. C. Zimring: Immucor Inc., Grants or Research Support

Transfusion-Transmitted Diseases: Arboviruses

S66-030G

Dengue Viremia in Donations from Puerto Rico During the 2007 Dengue Outbreak

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Background: Dengue virus is the most important arbovirus in the world; its range is expanding. Like WNV, dengue is transmitted naturally by the bite of an infected mosquito but also is transfusion transmitted. Data from 2005 in Puerto Rico (PR), a dengue-endemic area, demonstrated a rate of donor viremia of 1:1300 during the latter half of the 2005 epidemic season. In 2007, a much larger dengue outbreak occurred in PR from which samples from donors during the epidemic period were retained for testing to further confirm donor viremia rates and for recipient tracing of components from positive donations. **Methods:** Samples were retained in a repository and split into two sets for viremia studies: those units exported and transfused in the continental US and those transfused in PR. Samples were tested individually by a research transcription mediated amplification assay (TMA, Gen-Probe). Initially reactive (IR) samples were retested by the original TMA and an alternate TMA (alt TMA used for the units transfused in PR only) without dilution and at a 1:16 dilution to model pooling. All TMA-repeat reactive (RR) samples were considered confirmed. Additional virologic/infectivity and serologic testing was performed at the CDC dengue branch in PR including PCR to define the dengue serotype and viral load, mosquito cell culture and IgM testing. Hospitals receiving components from RR donations were contacted to initiate recipient tracing including a detailed questionnaire about symptoms and risk factors. The study was IRB approved. **Results:** A total of 15,350 samples were tested with 28 IR and 25 RR samples considered confirmed positive (pos) for a prevalence of 1:614 consisting of 12 dengue-pos donations exported from PR into the continental US (1:533) and 13 pos donations that remained in PR (1:689). Specificity was 99.98%. A 1:16 dilution detected 14/25 (56%) RR donations. Further supplemental testing (CDC) demonstrated dengue virus serotypes 1, 2 and 3 (corresponding to those circulating in PR); 11/25 (44%) samples had RNA titers of 10^5-10^9 copies/mL of which all 11 also infected C636 mosquito cell cultures. 9/11 (82%) PCR-pos samples were detected at a 1:16 dilution. 6/22 (27%) samples tested for IgM were pos, only 2 of which had quantifiable virus (10^6 and 10^8) with 1 detected at a 1:16 dilution. Of the 4 remaining IgM pos samples, only 1 was pos at a 1:16 dilution (low level pos) for a total of 2 IgM-pos samples detected when diluted. Recipient tracing in the continental US and PR is underway. **Conclusions:** Like the prior study identifying dengue viremic donations in PR, this study demonstrates a high frequency of viremia during dengue-epidemic periods with nearly half of the RNA-pos donations lacking IgM, having high-titer viremia and infectious in cell culture. Screening of donors should be considered during dengue-epidemic periods.

Disclosure of Commercial Conflict of Interest

J. M. Carrick: Gen-Probe Incorporated, Ownership or Partnership; A. De Vera: Nothing to disclose; R. Y. Dodd: Nothing to disclose; E. A. Hunsperger: Nothing to disclose; D. Krysztof: Nothing to disclose; J. M. Linnen: Gen-Probe Incorporated, Stocks or Bonds; K. D. McMillin: Gen-Probe Incorporated, Other; J. L. Muñoz: Nothing to disclose; S. L. Stramer: Nothing to disclose

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S67-030G

Highly Sensitive and Equivalent Detection of Dengue Virus Serotypes 1, 2, 3, and 4 with an Enhanced Transcription-Mediated Amplification Assay

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Background: Based on WHO estimates, the incidence of dengue has grown dramatically around the world in recent decades and is now considered to be a major international public health concern. To investigate the risk of dengue virus (DENV) transfusion transmission, we developed a prototype nucleic acid test (NAT) based on Transcription-Mediated Amplification (TMA) that was used to show the feasibility of detecting DENV RNA in asymptomatic blood donors from Honduras, Brazil, and Puerto Rico and in clinically ill patients from Puerto Rico. Our previous results demonstrated the importance of detecting all 4 DENV serotypes at low copy levels with equivalent sensitivity. Recently, we developed an improved TMA Assay with increased sensitivity for each of the 4 serotypes. **Methods:** The enhanced TMA assay uses the same technology as other PROCLEIX® assays, consisting of lysis and target capture of viral RNA followed by TMA and chemiluminescent detection by Hybridization Protection Assay (HPA). Analytical sensitivity for serotypes 1, 2, 3, and 4 were determined by probit analysis of results from testing serially diluted live DENV and DENV RNA transcripts. Live DENV was obtained from the Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, CO. Assay specificity was determined by testing 988 US blood donor specimens and 8,680 donor specimens from Puerto Rico that were screened previously with the earlier version of the TMA assay. Previous screening of these specimens yielded 14 positive results. Samples were tested on the fully automated PROCLEIX® TIGRIS® System. **Results:** The enhanced dengue assay showed 95% detection at 14.9, 18.3, 13.0, and 16.4 copies/mL of DENV 1, DENV 2, DENV 3, and DENV 4, respectively. Analytical sensitivities for each of the four serotypes were determined to be not statistically different. There were no reactive samples among the US donations. The improved assay was able to detect all 14 positive donations identified by the original assay in the Puerto Rican donations; an additional 7 reactive samples were identified with the improved assay, of which 4 were repeat reactive. The overall assay specificity from testing the US and Puerto Rican donations was 99.97% (95% CI: 99.91-99.99). **Conclusions:** Using the improved dengue TMA assay we demonstrated reliable detection of all 4 serotypes of DENV below 20 copies/mL while maintaing high clinical specificity. The analytical and clinical sensitivity results from this study indicate that the improved dengue assay has the potential to identify a larger number of low viral load DENV infections in both blood screening and diagnostic applications.

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S68-030G

Correlation between Yield of WNV NAT Screening of North Dakota Donors Over 6 Epidemic Seasons with WNV Seroprevalence at the End of 2008

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Background: MP-NAT for WNV was implemented in 2003, with progressive enhancement in screening sensitivity over the next 6 years by using targeted ID-NAT in epidemic areas with increasingly stringent trigger criteria. In our system, North Dakota (ND) has had the highest overall rate of WNV+ donations. Seasonal yield has fluctuated, but remained below the 2003 peak yield. This lower yield may be partly attributable to prior WNV infections in the population, leading to population immunity. This cross-sectional study determined WNV antibody seroprevalence after the 2008 transmission season, and correlated this seroprevalence with annual NAT yield rates in the state. **Methods:** 5000 samples from ND blood donations were archived from late Oct-Dec 2008, >1 month after the last NAT yield donation and last WNV case report in ND. Samples from donors resident in ND were selected and tested for WNV IgG. IgG-positive donations were further tested for WNV IgM to identify recent infections (Focus Diagnostics). NAT yield cases (confirmed by replicate NAT/serology on index donation and/or follow-up samples) from ND donors were compiled by year, and further sorted into those detectable by MP-NAT (based on MP-NAT detection, or reactivity at 1:16 dilution if detected by ID-NAT) vs those detectable only by ID-NAT. Annual incidence was projected based on annual MP-NAT yield and a 6.9-day MP-NAT yield window period (Busch et al, EID, 2005). **Results:** Of 3594 donations by ND donors from Oct-Dec 2008 tested for IgG, 296 (8.2%; 95%CI 7.3-9.1) were positive for WNV IgG; of these 26 (8.8%) confirmed positive for WNV IgM. The yield of WNV MP-detectable (MP-NAT+) and ID-only detectable (ID-NAT+) donations, and the projected WNV incidence/year, are shown in the table. **Conclusions:** The proportion of ND residents previously exposed to WNV, based on donor IgG seropositivity in late 2008, is currently 8.2%. Thus the general decline in WNV NAT yield in the past 6 years is not attributable to human population immunity, but rather likely due to ecological factors influencing WNV transmission to humans. The 8.8% rate of IgM detection among IgG+ donations is consistent with the proportionate yield of infections in 2008 (7/124, 5.6%), with some contribution of persistent IgM from 2007 infections. Cumulative annual incidence projected from annual MP-NAT yield cases correlated reasonably well with observed IgG seroprevalence, suggesting that cumulative MP-NAT yield data from other areas can be used to project WNV infection rates throughout the US.

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Year	Donations	Total NAT+	MP-NAT+	ID-NAT+	Incidence
2003	66,109	62	42	20	3.3%
2004	67,117	1	1	0	0.1%
2005	68,150	10	5	5	0.4%
2006	68,652	16	6	10	0.5%
2007	73,640	28	12	16	0.9%
2008	78,306	7	5	2	0.4%

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No. 16

医薬品 研究報告 調査報告書

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研究報告の概要

○バベシア症拡大を示す研究を受け、米国赤十字は7州での供血検査の実施を提案

Transfusion誌で近く発表される最近の3つの研究で、供血血液におけるバベシア症の原因となる寄生虫の陽性率増加および輸血伝播バベシア症(TTB)の増加が認められた。1つはコネチカット州とマサチューセッツ州において供血血液のどの程度の範囲に拡大しているかを示した。2つ目の研究ではロードアイランド州において、輸血を介した伝播範囲を確認した。3つ目では、米国赤十字のヘモビジランス・プログラムを通して報告された症例を用いて、感染した供血者と受血者の特徴を調べている。これらの研究から、バベシア症とTTBの危険が増大しているという懸念が明らかになった。

これらのデータに基づき、米国赤十字は疾患が流行する北東部および中西部北部の7州で供血血液のIFA検査を開始する2つの計画を作成した。

バベシア症は、Ixodes属のマダニによって伝播し、米国ではほとんどが*Babesia microti*(マラリアと類似した赤血球を汚染する寄生虫)に起因する。大部分の感染者は無症候か軽症であるが、特定の健康要因を有する人では、重症、致命的となる場合もある。無症候感染は何ヶ月も続く可能性がある。現在、米国食品医薬品局(FDA)が認可したバベシア症の検査はなく、血液センターは供血者にバベシア症の既往を尋ねるのみである。しかし、大半の罹患者は自分の感染を知らないため、問診の効果には疑問がある。寄生虫保有者が供血した場合、受血者に輸血を介して感染させる可能性がある。これまでに赤血球と血小板で輸血による伝播が報告されている。合併症と死亡者数の急増により、TTBに対する懸念が浮上した。1997～2004年にFDAに報告されたTTB関連死亡例は1例のみだったが、2005年11月～2008年9月では9例以上となった。FDAは2008年9月にワークショップを開催し、AABBは70以上の症例の報告を受けて2009年8月に公報を発行した。

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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」
新鮮凍結血漿-LR「日赤」成分採血

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
米国東部と中西部におけるバベシア症拡大を示す研究を受け、米国赤十字が7州での供血検査の実施を提案したとの報告である。	今後も引き続き情報の収集に努める。

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Red Cross Lobbying (continued from page 3)

In 2008, Congress appropriated $100 million in emergency funding to the American Red Cross to replenish its disaster relief reserves, which were depleted when the charity provided shelter, food and other services during a string of hurricanes earlier in the year. The Red Cross appropriation was set out in two sections 10502-03 of the Homeland Security bill, HR 2638 (Consolidated Security, Disaster Assistance, and Continuing Appropriations Act, 2009) and is explicitly for disaster relief purposes.

So far this year, the organization reports spending $154,890 on lobbying. Lobbyists for 2009 are listed as Cherae Bishop, Marc Decourcey, Neal Denton, Davn Latham and Marin Reynes. (Sources: Senate Lobbying Disclosure Database; Implu Corp., an online business intelligence database) ◆

With Studies Showing Spread of Babesiosis, ARC Proposing to Test Donated Blood in Seven States

Three recent studies have discovered increases in the incidence of the parasite that causes babesiosis in donated blood and of transfusion-transmitted babesiosis (TTB). On the strength of that data, the American Red Cross (ARC) has developed two proposals to begin testing donated blood in states in the Northeast and the upper Midwest where the disease is endemic.

The picture emerging from the studies – each of which is forthcoming in *Transfusion* – shows babesiosis to be a growing threat. Each focuses on a different aspect of the problem. One study shows how widespread it is among blood donations in Connecticut and Massachusetts, another identifies the extent of its transmission through transfusions in Rhode Island, and the third determines the characteristics of infected donors and recipients, using cases reported through ARC's Hemovigilance Program.

Individually and collectively, the studies emphasize that concerns over the dangers of babesiosis and TTB are increasing. The ARC proposals involve setting up testing in affected areas, starting with Connecticut and potentially expanding to seven states – 16 percent of the nation's population.

Babesiosis is carried by *Ixodes* ticks; in the US, it is mostly caused by *Babesia microti*, a parasite that is similar to malaria and that infects red blood cells. Most people infected with it do not experience any symptoms or experience only mild symptoms that can be mistaken for the flu; however, the disease can be severe and even fatal, particularly for people with certain complicating health factors. Asymptomatic infection may last for months. Currently, there is no Food and Drug Administration-approved test for the disease, and blood centers merely ask potential donors whether they have a history of babesiosis. But the fact that most people with the disease do not know they have it casts doubt on the effectiveness of the question.

If a person who carries the parasites donates blood, the disease can be transmitted through transfusion to a susceptible recipient. To date, transmission has been reported only with red blood cells (both fresh and frozen) and platelets.

Concerns about TTB have risen as the number of complications and deaths related to it has jumped. The Food and Drug Administration received only one report of a TTB-related death from 1997 to 2004; however, from November 2005 to September 2008, it received at least nine (see *ABC Newsletter*, 12/5/08). In September 2008, FDA held a workshop on TTB in the US. In August 2009, AABB issued a bulletin on it, prompted by reports of more than 70 cases of it (see *ABC Newsletter*, 8/14/09).

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Babesiosis (continued from page 4)

The three forthcoming studies aim at shedding light on the epidemiology of the babesiosis. In one study, led by Stephanie T. Johnson, MT (ASCP), MPH, who is with the ARC branch in Farmington, Conn., scientists tested blood donated at selected drives in Connecticut and Massachusetts from 2000 to 2007 for the presence of immunoglobulin (Ig)G antibodies to *Babesia microti*. Using an immunofluorescence assay (IFA), they found the antibodies in blood donated in all eight counties in Connecticut and three counties in Massachusetts. They also found it in blood donated not just during the season peak for the tick that causes the virus – from July through September – but also during the rest of the year.

Although the results of this study helped them identify particular areas and times of the year when the likelihood of *Babesia microti* in blood is highest, they also made clear that the threat extended beyond certain areas and months, which led the scientists to conclude that year-round, regional testing may be necessary to fully safeguard the blood supply from the transmission of the disease.

Scientists in Rhode Island reached a similar conclusion when they carried out a retrospective study in which they analyzed babesiosis cases that were reported to the Department of Health in that state from 1999 to 2007. Led by Leonard Mennel, DO, an infectious disease specialist and the director of infection control for the Rhode Island Hospital, this team identified 21 cases of TTB in the nine years they studied.

Their analysis of information about where donors lived and when they donated reinforced the finding in Johnson's study that some people with babesiosis lived in areas without high tick populations and had merely traveled to an area where babesiosis is more common. Drawing also on other studies that show that the virus can survive for extended periods in blood bank conditions, including refrigeration up to 35 days, these researchers conclude that TTB is possible any time of year and in any location. Their study also revealed a troubling rise in cases of TTB: from 1999 to 2007, 326,081 units of red blood cells were transfused, according to the Rhode Island Blood Center. The 21 cases of TTB during that period give an incidence rate for TTB of just more than 1 in 15,000 transfusions. However, by the last three years studied, that rate had risen to 1 in 9,000 units transfused.

To determine the characteristics of infected donors and recipients, the third team of researchers – led by Laura Tonnetti, PhD, a scientist with the ARC's Transmissible Diseases Department, Jerome H. Holland Laboratory, in Rockville, Md. – analyzed cases of suspected TTB that were reported to ARC's Hemovigilance Program from 2005 to 2007.

They carried out follow-up testing of previously collected blood donations, by IFA, Western blot, and/or real-time polymerase chain reaction (PCR) analysis. They found 18 definite or probable *Babesia microti* infections among transfusion recipients. Five of those recipients died. Of the 18 cases, two recipients had sickle cell disease and four were asplenic; 13 were between the ages of 61 and 84 and two were 2 years old or younger. The researchers concluded that TTB "can be a significant cause of transfusion-related morbidity and mortality," particularly when transfusion recipients were elderly, very young, or asplenic. Like the researchers in Rhode Island, these scientists also found that TTB stemmed both from donors who lived in areas where the disease is endemic as well as those who had merely traveled to those areas. They also found that IFA testing was more effective than PCR analysis: the formed identified all 18 donors, while the latter identified only one.

What Should Be Done? The conclusions of these studies – that babesiosis can occur anywhere at any time, that the number of TTB cases is rising, and that TTB can lead to serious complications from transfusions, including death – gave new data to support ARC proposals for testing donated blood for evidence of infection, which Dr. Tonnetti discussed in a presentation at the recent AABB Meeting.

(continued on page 6)

Babesiosis (continued from page 5)

The first proposal is to establish testing donated blood in Connecticut by IFA. ARC's recommendations include year-round IFA testing under investigational new drug regulations. Only whole-blood donations would be tested. Donors associated with positive results would be deferred, and their donations would be discarded. Testing could be done throughout the state or only in highly endemic areas. The latter approach would be less expensive, but it may only identify one-third of at-risk donors, so ARC favors testing across the state.

Depending on the results of that project, said Dr. Tonnetti, ARC would like to expand the area to include Rhode Island, Massachusetts, New York, New Jersey, Minnesota, and Wisconsin. Connecticut was chosen as the starting point, she explained in a phone call, because earlier studies had found a number of endemic areas in the state. But she emphasized that expanding the testing to other states would be important, given that babesiosis and TTB can spread so easily. No timeline has been set for testing under either proposal.

Citations. Asad S, *et al.* Transfusion-transmitted babesiosis in Rhode Island. Transfusion. 2009 Sep 16 [epub ahead of print]; Johnson ST, *et al.* Seroprevalence of *Babesia microti* in blood donors from *Babesia*-endemic areas of the northeastern United States: 2000 through 2007. Transfusion 2009 Oct. 10 [epub ahead of print]; Tonnetti L, *et al.* Transfusion-transmitted *Babesia microti* identified through hemovigilance. Transfusion. 2009 Jul 16 [epub ahead of print] ♦

FDA Finalizes Guidance on Testing Donated Blood for West Nile Virus

The Food and Drug Administration has finalized its guidance for blood centers on how they should test donations of whole blood and blood products for West Nile Virus (WNV). This guidance replaces the draft guidance dated April 28, 2008, and it takes into account a number of the comments FDA received from America's Blood Centers (ABC) and other sources.

While the draft guidance included recommendations for screening cells, tissues, and cellular-based products, the final guidance covers only donations of whole blood and blood products. Key recommendations are that blood centers should test whole blood and blood products for WNV year-round; that they may use minipool tests when there is not high WNV activity in their area; that each center may establish its own criteria for high WNV activity; that centers switch to individual testing as soon as possible, but not later than 48 hours, after high WNV activity is found in their area; and that if a minipool tests as reactive for WNV, each unit in that minipool should be tested with an individual test. It also recommended that, for individual units that test positive, additional testing "may be of value in donor counseling."

Background. It has been known since 2002 that donors who were infected with WNV could be viremic but not have any symptoms; it has also been known that the virus could be transmitted through blood transfusions and organ transplantation. FDA began studies the following year aimed at evaluating nucleic acid tests (NAT) for detecting WNV, and it has approved biologics license applications for two NAT since 2005. Both tests are used for individual donor samples, and for minipools of samples taken from either 6 or 16 donations.

Studies have found that the individual test (ID-NAT) has greater sensitivity than the minipool test (MP-NAT), and that, in fact, up to 25 percent of viremic units were not detected by the MP-NAT. However, it is not feasible or practical to test every unit individually, because of limited availability of the tests and personnel and logistical issues. This guidance, then, is meant to clarify when blood centers should use ID-NAT and when they may use MP-NAT.

(continued on page 7)