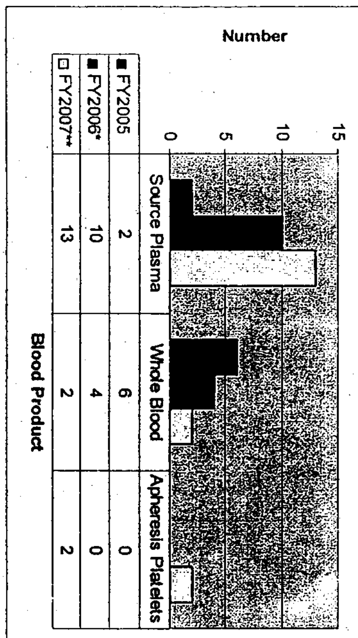
Table 6: Post-Donation Fatality Reports by Donated Product, FY2005 through FY2007

Donated Product	FY05	FY06	FY07
Source Plasma	2	10	13
Whole Blood	6	4*	2**
Apheresis Platelets	0	0	2
Total	8	14	17

*Includes 2 autologous donations
**Autologous donations

Figure 6: Post-Donation Fatality Reports, FY2005 through FY2007



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

別紙様式第2-1

No. 6

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2008. 11. 20	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況	Gubernot D, Lucey C, Lee K, Conley G, Holness L, Wise R. AABB Annual Meeting and TXPO 2008; 2008 Oct 4-7; Montreal.	公表国 米国	
販売名（企業名）	新鮮凍結血漿「日赤」（日本赤十字社） 新鮮凍結血漿-LR「日赤」（日本赤十字社）					

研究報告の概要

○輸血を介したバベシア症の伝播：FDAに届けられた最近の死亡報告

背景：バベシア症は輸血を介した伝播リスクが知られているが、認可されたスクリーニング法は存在しない。本試験は、FDAに報告されたバベシア関連輸血事象の重症度と特徴について、最近の輸血関連バベシア症死亡報告と生物学的製品逸脱報告サマリー（BPDRs）に焦点を当て検討した。

方法：過去10年間にFDAに報告された3つのFDA調査システム（採血および輸血死亡報告、MedWatchプログラム、BPDRs）のデータを収集した。

結果：輸血感染バベシア症死亡報告は1998年の1例以降しばらく無かったが、2006年1月～10月にはFDAに5例が報告された。受血者は関連血液製剤の輸血から4～7週間後に発症し、全員が*Babesia microti*に感染していた。過去10年間のバベシア症関連のBPDRsは68件であり、近年この報告が増加傾向にあることは、当該寄生虫による輸血関連リスクが増加していることを示している。

結論：最近の死亡報告は、増加中のBPDRsと合わせて、稀な輸血後合併症であるバベシア症のリスク増大を明らかにした。発熱を呈した受血者にはバベシア症の可能性があることを医師が認識することにより、効果的治療のための迅速な診断を容易にし、また、残存する血液製剤を差止める検査の実施が促進されると考える。バベシア症供血者および輸血関連事象の報告は、FDAによるリスク範囲の評価、公衆衛生上の感染制御対策の一助となる。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
FDAに報告されたバベシア関連輸血事象の重症度と特徴について、最近の輸血関連バベシア症死亡報告と生物学的製品逸脱報告サマリーに焦点を当て検討した結果、近年、当該寄生虫による輸血関連リスクが増加していることを示しているとの報告である。	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。

(36)

SP246

Quantitative Real-time PCR Assay for *Trypanosoma cruzi*

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Background: *Trypanosoma cruzi* infects about 18 million people, and results in 50,000 deaths from Chagas disease annually, primarily in Latin America. Latin American blood donors in the US may harbor chronic *T. cruzi* infection and be potential reservoir of *T. cruzi* transmission by blood transfusion. US blood centers began donor screening for *T. cruzi* antibody (Ab) in early 2007 and have identified hundreds of seropos blood donors. Our objective was to develop a sensitive assay for *T. cruzi* parasite detection and quantitation in whole blood (WB) samples from seropos donors. The assay is also needed for studies of *T. cruzi* transfusion-transmission and disease pathogenesis. **Methods:** Trypomastigotes of *T. cruzi*, grown in culture, were harvested, counted, and spiked into fresh WB to create samples containing 8, 4, 2, and 1 parasite/20 mL WB. Lysis of parasites was performed by adding 20 mL of Guanidium-EDTA lysis buffer (6M Guanidine HCl with 0.2M EDTA, pH8.0) to 20 mL WB and vortexing. The lysed WB was heated at 100C for 15 mins to disentangle minicircle kinetoplast DNA present at ~10,000 copies/parasite. Total DNA was prepared from 0.4 mL of the lysate by precipitating hemoglobin and inhibitors. Parasitic DNA was captured by *T. cruzi* specific oligonucleotide probes bound to magnetic beads. After being eluted from the beads, parasite DNA was amplified by real-time (RT)-PCR with SyBr green dye & an optimized buffer system using a *T. cruzi* kinetoplast DNA specific primer pair (Tc-121/Tc-S36). **Results:** Table summarizes RT-PCR results for 5 replicate amplifications of the spiked dilution series. A single parasite in 20 mL WB gave strong signal (~10 cycles below 45-cycle cutoff) & good precision quantitation of up to 8 parasites. We tested 27 coded specimens from *T. cruzi* Ab-reactive donors: 2/7 RIPA(+) and 0/20 RIPA(–) donors tested PCR(+); the 2 pos donors had ~1 parasite/20 mL WB. **Conclusion:** We can detect single *T. cruzi* parasites in 20 mL WB with this sensitive quantitative RT-PCR assay. Additional *T. cruzi* seropos donor blood samples from the US, Argentina, Honduras & Brazil are being collected for analysis.

	# of *T. cruzi* Spiked Into 20 mL Whole Blood				
n = 5	8	4	2	1	0
Mean Cp (±STD)	31.4 (±0.5)	32.64 (±0.1)	33.48 (±.01)	15.18 (±~0.0)	>45

A one unit change in Cp in a real-time PCR assay is expected to equate to an ~ doubling of parasite load. Our assay performs as expected in the range of 1-8 parasites.

Disclosure of Conflict of Interest

Tzong-Hae Lee, Ester Sabino, Lani Montalvo, Li Wen, Daniel Chafets, Brian Custer, Michael P. Busch, for the Retrovirus Epidemiology Donor Studies-II (REDS-II): Nothing to Disclose

SP247

Screening for *Trypanosoma cruzi* in the Blood Donor Setting

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Background: Our blood donor center recently began testing for antibodies to the agent that causes Chagas' Disease (*Trypanosoma cruzi*). We reviewed incidence among our current blood donor population and all look-back cases to determine if there were any reports of transfusion-transmitted *Trypanosoma cruzi*. **Methods:** At our center all allogeneic and autologous donations were tested for antibodies to *T. cruzi* using a US Food and Drug Administration licensed enzyme immunoassay (EIA) methodology. Those donations that were repeat reactive (RR) on EIA were sent for an unlicensed confirmatory radioimmunoprecipitation assay (RIPA). In accordance with AABB Association Bulletin 06-08 donors RR on EIA were indefinitely deferred and notified of results. Look-back was performed on those donors who tested RIPA positive and included all electronic donor records available. **Results:** From 7/30/07-3/15/08 222,059 donations (212,505 whole blood, 7,520 autologous, 2,034 directed and of which 51,298 were first-time donors) were tested by EIA for anti-*T. cruzi*. 16/222,059 (0.007%) donations were EIA RR donations. Confirmatory RIPA results were as follows: 7/16 (43.75%) or 7/222,059 (0.003%) were positive and 9/16 (56.25%) were negative. 2/7 (28.6%) or 2/51,298 (0.004%) RIPA positive results were from first-time donors. Look-back was performed on the 5 RIPA positive repeat donors and involved 75 transfusable blood components (70 were transfused, 2 discarded and 3 no information was provided). There were no reports of recipients of the 70 transfused blood components testing reactive for antibodies to *T. cruzi*. **Conclusions:** At our blood center, the introduction of testing for *T. cruzi* prevented transfusion of a small number of units that confirmed positive for the presence of antibodies. Look-back revealed no reports of transfusion-transmission of *T. cruzi* from previously donated untested units.

Disclosure of Conflict of Interest

Richard Gammon, Michael Pratt: Nothing to Disclose

TTID 2: Tickborne Disease, CJD

SP248

A Fatal Case of Transfusion-Transmitted Babesiosis in the State of Delaware

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Background: Babesiosis is an emerging zoonotic disease caused by intraerythrocytic protozoa. Although the disease is usually transmitted by tick bite, there has been an increase in the number of transfusion-transmitted cases reported. This report describes a fatal case of transfusion-transmitted babesiosis in Delaware. **Case Report:** The patient was a 43-year-old Caucasian woman with history of transfusion-dependent Diamond-Blackfan Syndrome, hepatitis C, pulmonary hypertension and splenectomy. She had been receiving two units of RBCs every 2 weeks. She presented on 1/9/08 with fever, chills, cough and fatigue, and was treated with antibiotics initially for presumptive pneumonia. Examination of the peripheral blood smears revealed numerous intraerythrocytic ring forms, consistent with Babesia. The diagnosis of babesiosis was confirmed by positive polymerase chain reaction (PCR) for B. microti DNA and high titer of antibody to B. microti (1:2048). Despite aggressive therapy including Clindamycin and Quinine, the patient's condition rapidly deteriorated with multi-system organ failure and she expired 3 days after admission. The patient resided in Delaware and had no history of tick bites or recent travel history outside Delaware. Thirteen implicated donors were subsequently tested for B. microti. All tested donors were negative by PCR for B. microti. However, one of them had a significantly elevated B. microti antibody titer (1:1024). This donor resides in New Jersey and had recently traveled to Rhode Island. The donor has no known history of tick bites or flu-like symptoms within the past 2 years. The donor has not been diagnosed with Babesiosis, Lyme's disease or Ehrlichiosis, and has never received a blood transfusion. The implicated unit was donated on 8/8/07, frozen, and transfused as a deglycerolized unit on 11/27/07, 6 weeks prior to development of the patient's symptoms. **Conclusion:** This case emphasizes the need to review peripheral blood smears in febrile, immunocompromised patients who have been recently transfused. Prompt recognition and treatment are important, as Babesia infections can be severe or fatal in splenectomized and/or immunocompromised patients. It also illustrates the need for better strategies, including more sensitive, specific and rapid screening tests, to prevent transfusion-transmitted babesiosis.

Disclosure of Conflict of Interest

Yong Zhao, Ken Love, Scott Hall, Frank Beardell: Nothing to Disclose

SP249

Babesiosis Transmission through Blood Transfusion: Recent Fatality Reports Received by FDA

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Background: Babesiosis is a known transfusion-transmitted disease risk, with no licensed donor screening assay. There are estimates that 70 transfusion-transmitted cases have occurred from 1979 through 2007. This research evaluated the magnitude and characteristics of Babesia-related transfusion events reported to the Food and Drug Administration (FDA) with focus on the recent transfusion-related babesiosis fatality reports and a summary of Biological Product Deviation Reports (BPDRs) submitted to the FDA. **Methods:** Data were collected by querying three FDA surveillance systems for reports received within the past decade: Blood Collection and Transfusion Fatality Reporting, the MedWatch Program, and BPDRs. **Results:** Between January and October 2006, the FDA received five transfusion-related babesiosis fatality reports after only one prior report in 1998. Recipients presented with symptoms 4 to 7 weeks after transfusion of implicated blood units, and all were infected with Babesia microti. No MedWatch report was received; however 68 Babesia-related BPDRs over the past decade, with increasing numbers in more recent years, suggest a rising risk for transfusion-transmission from this parasite. **Conclusions:** The recent fatality reports, along with growing numbers of BPDRs, underscore babesiosis as a rare post-transfusion complication whose risk may be increasing. Enhanced clinician awareness of the possibility of babesiosis in febrile transfusion recipients may facilitate prompt diagnosis with more effective treatment and timely investigations to interdict extant infected units. Reporting of babesiosis donor and transfusion-related events assists the FDA in assessing the scope of the risk and developing appropriate public health control measures. Disclaimer: 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.

Disclosure of Conflict of Interest

Diane Gubernot, Charles Lucey, Karen Lee, Gilliam Conley, Leslie Holness, Robert Wise: Nothing to Disclose

SP250

Evaluation of Candidate Reentry Proposals for *Babesia microti* Infection

R Cable[1] (leibyd@usa.redcross.org), S Johnson[2], L Tonnetti[3], D Leiby[3]. [1]*American Red Cross Blood Services, New England Div, Farmington, CT;[2]American Red Cross, Farmington, CT;[3]American Red Cross, Rockville, MD.*

Background: B. microti (Bm) is a tick-borne rbc parasite which can be transmitted by transfusion from chronically infected donors. Implication in transfusion babesiosis (TB) or clinical babesiosis (CB) requires permanent donor deferral. As part of a multi-year longitudinal research study in New England, Bm seropositive blood donors are deferred despite apparent clearance of infection in many cases. We evaluated several candidate donor reentry proposals (Schemes) that also may be applicable to donors with CB or implicated in TB. **Methods:** Consenting blood donors were screened by IFA for Bm (positive ≥1:64) using retention tubes (index sample). Consenting positive donors agreed to provide subsequent samples at 1-2 month intervals which were screened by IFA and nested- or RT-PCR. 18 donors were released from study before 1 year after 3 consecutive negative bleeds. 45 donors dropped out and could not be evaluated. Study data were used to evaluate 4 potential reentry Schemes based on the initial PCR result (<12 week after the initial IFA) and on the first IFA and PCR result ≥11 months following the index sample (Table 1). Reentry failure was defined as a PCR positive samples following successful reentry. **Results:** 76/139 donors completed 1 year or more of follow-up and were eligible for assessment using the four candidate reentry Schemes (Table 2). All 43 eligible donors with IFA titers ≤1:128 after the index sample could be reentered. Only 21/33 (64%) donors with 1 or more IFA titers >1:128 after the index sample could be reentered. Requiring all IFA titers to be ≤1:128 would eliminate only 1/3 Scheme failures, but would require multiple donor samples. Requiring 2 rather than 1 year wait after the seropositive screen would eliminate the observed Scheme failures in all cases. However, this could not be fully assessed because of limited follow-up. **Conclusion:** Reentry for Bm is feasible using approaches similar to other TTD markers. Evaluated Schemes could reenter a significant portion of donors; however, there was a small, but unacceptable failure rate. In addition, 18 donors released from the study before a year could also be considered for reentry, but there was no follow-up to assess this approach. Sampling beyond 1 year may be required to develop an acceptable reentry Scheme. Such a Scheme could be useful for donor management if Bm screening is implemented, and could allow reentry of donors implicated in TB or recovered CB.

TABLE 1. Reentry schemes

#	Initial IFA	Initial PCR	IFA 1 Year	PCR 1 Year	Other PCR
1a	≥1:64	Neg	≤1:128	Neg	All Neg
1b	≥1:64	Neg	≤1:128	Neg	Any
2a	≥1:64	Pos or NA	≤1:128	Neg	All Neg
2b	≥1:64	Pos or NA	≤1:128	Neg	Any

TABLE 2. Evaluation of reentry schemes

Reentry scheme	1a	1b	2a	2b
Eligible initially	116	116	139	139
Followed 1 year	55	55	76	76
Reentered	42	47	55	64
% reentered	76%	85%	72%	84%
Scheme failures*	2	3	2	3

* PCR positive samples following successful reentry

Disclosure of Conflict of Interest

Ritchard Cable, Stephanie Johnson, Laura Tonnetti: Nothing to Disclose
David Leiby: Not Specified

SP251

Seasonal and Geographic Distribution of *Babesia microti* Seroprevalence in Connecticut Blood Donors: 2006 and 2007

S Johnson[1] (tonnettil@usa.redcross.org), R Cable[2], D Leiby[3], E V Tassell[4], L Tonnetti[3]. [1]*American Red Cross, Farmington, CT;[2]American Red Cross Blood Services, New England Div, Farmington, CT;[3]American Red Cross, Rockville, MD;[4]Farmington.*

Background: *Babesia microti* is an intraerythrocytic parasite, transmitted by *Ixodes* ticks, that is found throughout the northeastern United States. *B. microti* is also transmitted by blood transfusion, with over 70 cases reported to date. Individuals exposed to the parasite may develop babesiosis, a potentially life threatening illness. Those at greatest risk for developing serious disease include asplenic, elderly and immunocompromised individuals. Our blood center has been studying the presence of antibodies to *B. microti* in Connecticut blood donors since 1999. The purpose of this analysis is to provide data, and highlight the need, for the development of methods for screening the blood supply to improve blood safety. **Methods:** Consenting blood donors are tested at select blood drives. A donor is considered seropositive when they test positive for *B. microti* antibodies by IFA (≥1:64). Beginning in 2006 testing was conducted year round and included blood drives in all eight counties of Connecticut. **Results:** Seropositive individuals were identified in every county (Table 1), although the two southeastern counties (Middlesex and New London) each had significantly higher seroprevalence rates when compared to the remaining six counties ($p < 0.05$ for both). Seropositive individuals were identified in every month and seroprevalence varied month to month but there was no apparent seasonal pattern. **Conclusions:** Seroprevalence of *B. microti* in Connecticut varies significantly by county, but every county had substantial seroprevalence, 0.4% or greater seropositive rate (40/10,000 donors). Seropositive donors were identified in every month of the year. Based on these results, using seasonal or geographic exclusion criteria to interdict *Babesia* from the blood supply would be an ineffective approach. These data support the need for developing efficient methods for screening the blood supply for *Babesia*, and thereby improving blood safety.

TABLE 1. 2006 & 2007

County	# Tested	# Positive	Seroprevalence per 10,000 Donors
Fairfield	1631	10	61
Hartford	2609	17	65
Litchfield	375	2	53
Middlesex	654	10	153
New Haven	1521	10	66
New London	1062	19	179
Tolland	418	3	72
Windham	252	1	40

Disclosure of Conflict of Interest

Stephania Johnson, Ritchard Cable, Eric Van Tassell, Laura Tonnetti: Nothing to Disclose
David Leiby: Not Specified

SP252

Transfusion Transmitted Babesiosis in an ITP Patient: A Case Report

Juan Merayo-Rodriguez[1] (Ramon.kranwinkel@danhosp.org), R Duran[2], R Birusingh[1], J Stratidis[1], P Nee[1], R Kranwinkel[3]. [1]*Danbury Hospital, Danbury, CT;[2]University of Pennsylvania, Philadelphia, PA;[3]Danbury.*

Our case is a 79 years old male who presented to Danbury Hospital Emergency Department (ED) complaining of fever and chills that started a few hours earlier. The patient was discharged 2 weeks prior following a Clostridium difficile (C. difficile) infection. On physical examination the patient

別紙様式第2-1

No. 3

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2008. 12. 16	該当なし	
一般的名称	新鮮凍結人血漿		研究報告の公表状況	Benjamin RJ, Kline L, Dy BA, Kennedy J, Pisciotto P, Sapatnekar S, Mercado R, Eder AF. Transfusion. 2008 Nov;48(11):2348-55. Epub 2008 Jul 22.	公表国	
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社)				米国	

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
○全血由来血小板の細菌汚染：米国赤十字(ARC)の初流血除去および保存前プール培養検査の導入 背景：全血由来血小板(WBP)輸血後の細菌性敗血症は、現在も患者にとって大きなリスクであり、これは細菌汚染の抑制あるいは検出するための実用的、効果的な方法がないことが主な原因である。我々は、WBPと初流血除去後のプール全血由来血小板(PSP)の敗血症性反応リスクおよび細菌培養結果について報告する。 試験デザインおよび方法：Acrodose PLシステム(Pall Medical)で調べた製品適合および品質管理(QC)について、4つの地域血液センターにて評価を行った。細菌汚染リスクは、報告されたWBPによる敗血症性輸血反応の調査および自動化細菌検出システム培養(BacT/ALERT 3D, bioMérieux)を用いた白血球除去PSPの好気QC培養により評価した。 結果：PSP実施前(2003年1月～2006年12月)には2,535,043単位のWBPが供給され、死亡2例を含む敗血症性反応20例の報告があった(敗血症性反応：100万あたり7.9[1:126,752]、死亡：100万あたり0.79[1:1,267,522])。2006年10月にPSPが導入され製品適合率は99.6%となり、1プールあたりのPLT数は平均4.0×10^{11}であった。実施トライアル中に初流血除去技術を用いた全血採血セットが導入され、PSP細菌培養の確定陽性率は100万あたり2,111(1:474)から965(1:1036)に減少した(オッズ比0.46;95%信頼区間0.22～0.95)。供給されたPSP 25,936単位による敗血症性反応は報告されなかった。 結論：初流血除去および細菌培養は、WBP輸血の細菌リスクを低減させる有効な方法である。PSPの細菌汚染率は、同等の培養プロトコールを用いたARCの現在のアフェレーシスPLTの5.8倍であると評価された。	新鮮凍結血漿「日赤」 新鮮凍結血漿-LR「日赤」 血液を介するウイルス、細菌、原虫等の感染 vCJD等の伝播のリスク

報告企業の意見	今後の対応
全血由来血小板の細菌汚染リスクを低減させるためには、初流血除去および細菌培養によるスクリーニングが有効な方法であるとの報告である。	日本赤十字社では、輸血による細菌感染予防対策として、すべての輸血用血液製剤を対象に保存前白血球除去及び初流血除去を導入している。さらに、輸血情報リーフレット等により細菌感染やウイルス感染について医療機関へ情報提供し注意を喚起しているほか、細菌感染が疑われる場合の対応を周知している。今後も細菌やウイルスの検出や不活化する方策について情報の収集に努める。

(37)

Bacterial contamination of whole blood–derived platelets: the introduction of sample diversion and prestorage pooling with culture testing in the American Red Cross

Richard J. Benjamin, Linda Kline, Beth A. Dy, Jean Kennedy, Patricia Pisciotto, Suneeti Sapatnekar, Rachel Mercado, and Anne F. Eder

BACKGROUND: Bacterial sepsis following whole blood–derived platelet (WBP) transfusion has remained a substantial patient risk, primarily due to a lack of practical and effective means to limit or detect bacterial contamination. We describe the risk of reported septic reactions to WBPs and the introduction of prestorage-pooled whole blood–derived platelets (PSPs) collected using initial sample diversion and cultured for bacterial contamination.

STUDY DESIGN AND METHODS: Product qualification and quality control (QC) testing with the Acrodose PL system (Pall Medical) were evaluated in four regional blood centers. Bacterial contamination risk was assessed by review of reported septic transfusion reactions to WBPs and by aerobic QC culture of leukoreduced PSPs utilizing automated microbial detection system cultures (BacT/ALERT 3D, bioMérieux).

RESULTS: Before implementing PSPs (January 2003-December 2006), we distributed 2,535,043 WBP units and received 20 reports of septic reactions including 2 fatalities (7.9 per million [1:126,752] reactions and 0.79 per million [1:1,267,522] fatalities). In October 2006, PSPs were effectively implemented with a product qualification success rate of 99.6 percent and a mean yield of 4.0×10^{11} platelets (PLTs) per pool. Whole blood collection sets with sample diversion technology were introduced during the operational trial and decreased the rate of confirmed-positive bacterial culture of PSPs from 2111 (1:474) to 965 (1:1036) per million (odds ratio, 0.46; 95% confidence interval, 0.22-0.95). No septic reactions to PSPs were reported (25,936 PSP units distributed).

CONCLUSION: Sample diversion and bacterial culture are effective methods to reduce bacterial risk with WBP transfusion. Bacterial contamination of PSPs was assessed at 5.8-fold our current rate for apheresis PLTs utilizing comparable culture protocols.

The introduction of the Food and Drug Administration (FDA)-approved Acrodose PL system (Pall Medical, East Hills, NY) for producing prestorage-pooled, leukoreduced whole blood–derived platelets (PSPs) now offers the possibility of quality control (QC) bacterial culture testing of whole blood–derived platelets (WBP) at the blood center, utilizing either the eBDS (Pall Medical) or the BacT/ALERT 3D (bioMérieux, Durham, NC) culture systems.[1,2] In addition to providing a means to screen WBPs, the Acrodose PL system offers the potential advantages of eliminating the time and labor needed for point-of-issue pooling at the hospital transfusion service and reducing outdate rates, because PSPs do not evoke a 4-hour outdate after pooling. PSPs, however, carry a disadvantage that confirmed-positive and indeterminate culture results lead to the discard of not only the final pooled product, but also to the retrieval and discard of all the associated red blood cell (RBC) and plasma products from the original whole blood

ABBREVIATIONS: PSP(s) = prestorage-pooled whole blood–derived platelet(s); WBP(s) = whole blood–derived platelet(s).

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RJB is a consultant to Immucor, Inc., and Cerus Corp. The authors attest that they have no conflicts of interest with respect to this study.

Received for publication April 25, 2008; revision received May 24, 2008; and accepted May 26, 2008.
doi: 10.1111/j.1537-2995.2008.01853.x
TRANSFUSION 2008;48:2348-2355.

collections, because the single implicated WBP component in the pool is generally not identified. Limiting the initial bacterial contamination of each WBP component in the pool therefore is critical and expected to occur with optimized skin preparation techniques and initial whole blood diversion at collection.[3,4]

In this report we describe the baseline risk of sepsis associated with transfusion of WBPs, as measured by the rate of septic transfusion reactions reported to the American Red Cross Hemovigilance Program in 2003 through 2006.[5] After successful implementation of PSPs at four American Red Cross regional blood centers, we assess the impact of sample diversion on the risk of contamination during collection and document the ability of culture testing to identify contaminated products and prevent their release into inventory.

MATERIALS AND METHODS

Whole blood was collected into collection sets with or without a sample diversion system (Leukotrap-RCPL, Pall Medical) from routine blood donors in four American Red Cross Blood Services Regions (A-D). The time frame for the introduction of PSPs and whole blood collection utilizing sample diversion strategies overlapped, such that the first 5211 PSPs were manufactured with WBP that lacked sample diversion. The phlebotomy site was prepared by our standard, FDA-recommended, skin disinfection protocol utilizing povidone-iodine scrubs (or chlorhexidine gluconate in 70% isopropyl alcohol scrubs for donors allergic to iodine)[4] throughout the study. Leukoreduced WBP concentrates were prepared and stored at 20 to 24°C. After a minimum of 24 hours, five ABO-identical WBP concentrates were pooled into a 1.5-L CLX storage bag (Acrodose PL System, Pall Medical) by means of multiple sterile connections (TSCD or SCD sterile tube welders, Terumo Medical Corp., Elkton, MD). Pools were labeled D+ if there was one or more D+ WBP unit in the pool.

An 8-mL sample for bacterial testing was removed from the storage bag using a platelet (PLT) sampling device (SampLok sampling kit, ITL, Reston, VA; or accessory sampling assembly, Gambro BCT, Lakewood, CO). An additional 1.5 to 2 mL was used for product qualification testing (PLT count, pH). PLT yield was calculated from the PLT concentration and the volume of the PSPs.

At the start of the evaluation of the Acrodose PL system, process control testing was performed. PLT yield, concentration and product volume, sterility by bacterial culture, and pH were determined and success was defined by our standard process control procedures. This entailed testing the first 60 pools with no failures or 91 pools with one allowable failure. pH testing was performed for 60 pools by determining the pH of 40 PSPs at issue, 10 PSPs on Day 5, and 10 PSPs at outdate; for 90 pools: by determining pH of 61 PSPs at issue, 15 PSPs on Day 5 and 15 PSPs at outdate. After successfully completing process control, monthly QC testing of 1 percent of PSPs was initiated.

Detection of bacterial contamination

An automated microbial detection system (BacT/ALERT 3D, bioMérieux) was used for aerobic cultures, with bottle inoculation performed in a laminar-flow hood, as previously described.[6-8] PSPs were released into inventory for distribution after at least 12 hours with negative culture results, and cultures were monitored until product outdate on Day 5. All components associated with positive initial culture results were quarantined or retrieved if already distributed to transfusion services. A second 8-mL sample was taken from the initially positive PSPs and/or cocomponents and inoculated into a new aerobic bottle for confirmatory culture. The initial and subsequent positive culture bottles were sent to independent microbiology laboratories for bacterial isolation and identification. Bacterial culture test results were classified according to AABB Bulletin 04-07[9] with further subcategorization as follows: A confirmed-positive result is a true-positive result with the growth of the *same organism* in the initial and confirmatory sample; a false-positive result is a positive bottle signal but a negative result on subsequent culture. False-positive results were further characterized as either possible sampling contamination, if bacteria were detected in the initial bottle but not the confirmatory culture, or instrument error, if the initial culture bottle was found to be sterile.[6] If PLT components were not available for confirmatory culture because they were transfused or destroyed during the manufacturing process, the initial-positive signal could not be resolved and the results were classified as "indeterminate." Occasions where an initial-positive culture was detected but the subsequent confirmatory culture revealed a different bacterial isolate were labeled "discrepant." In the AABB classification, these cases would be included in the "true-positive" category.

Septic transfusion reactions

All septic transfusion reactions reported to the 35 regional American Red Cross blood centers were investigated and compiled in a centralized database through the American Red Cross Hemovigilance Program, as previously described.[5] Clinical criteria for a possible septic transfusion reaction to apheresis PLTs were any of the following symptoms within 4 hours of transfusion: fever of 39°C or greater or a change of 2°C or more from pretransfusion value, rigors, tachycardia greater than 120 bpm or a change of 40 bpm or more from pretransfusion value, or a change of more than 30 mm Hg in systolic or diastolic blood pressure.[10] A definite septic transfusion reaction

fulfilled the clinical criteria and yielded the same bacterial species from the residual PSP component and the patient. A probable septic transfusion reaction fulfilled the clinical criteria but was associated with a positive culture on the residual component without a matching positive blood culture result in the recipient. Transfusion reactions that did not meet the criteria of probable or definite septic reactions were excluded.

Statistical analysis

Odds ratios (ORs) and 95 percent confidence intervals (CIs) were computed to compare the odds of contamination before and after the implementation of sample diversion strategies.[11] Differences between groups were significant at p value of less than 0.05. The American Red Cross Institutional Review Board determined that the operational trial was exempt under 45CFR46, 21CFR50.

RESULTS

Baseline risk of bacterial sepsis from WBPs before implementation of PSPs

We assessed the baseline risk of bacterial sepsis with WBPs as reported to the American Red Cross Hemovigilance Program, before the introduction of PSPs and sample diversion. Between January 1, 2003, and December 31, 2006, the 35 American Red Cross blood regions distributed 2,535,043 WBP units and 20 septic reactions were reported, including 2 fatalities, for an overall rate of 7.9 per million (1:126,752) reactions and 0.79 per million (1:1,267,522) fatalities per distributed component (Table 1). Products involved in septic reactions were pooled at the transfusion service in a median pool size of 5 components (mean, 4.75; range, 2-8 components). The median calculated risk per transfused product, assuming that 5 products were pooled, was therefore 39.4 per million (1:25,350) for sepsis and 3.94 per million (1:253,504) for fatality.

Eight of the reported reactions fulfilled the criteria for definite septic reactions and 12 were probable septic reactions, because the incriminated organism was not cultured from the patient, either due to lack of blood culture testing (5 cases) or due to negative culture results for patients on antibiotic therapy (7 cases). The most common bacterial contaminants were likely commensal skin organisms (16 cases; 80%); 4 (20%) were likely enteric organisms (Table 1). The components that comprised each pool of WBPs were of uniform storage age, and 15 reactions occurred on Day 5 (75%), 3 on Day 4 (15%), 1 on Day 3 (5%), and 1 on Day 2 (5%) after collection. The two fatalities implicated *Staphylococcus aureus* and *Escherichia coli* and were transfused on Day 5 of storage.

TABLE 1. Bacteria implicated in septic transfusion reactions to WBPs distributed between January 1, 2003, and December 31, 2006

Bacterial isolate	Number of septic reactions
Coagulase-negative *Staphylococcus*	11
*S. aureus**	2
Staphylococcus spp. (mixed culture)†	1
Bacillus spp.	1
Corynebacterium spp.	1
Likely skin contaminants (subtotal)	16
S. bovis	1
*E. coli**	2
Multiple (*Klebsiella pneumonia*, *E. coli*)	1
Likely enteric organisms (subtotal)	4
Total reactions	20
Number of WBP units distributed	2,535,043
Septic reactions, rate per 10^6	7.9
Fatalities, rate per 10^6	0.79

* Associated with a fatality.
† Coagulase-negative and coagulase-positive *Staphylococcus*.

Operational trial and implementation of PSPs

Because of the potential safety benefit of QC bacterial detection and other operational advantages, we implemented the Acrodose PL PSP system. In an initial operational trial, four regions of the American Red Cross manufactured 7628 PSP units, of which 5211 were produced before and 2417 after the implementation of whole blood collection sets with initial sample diversion. A pool size of 5 units was necessary to produce a consistent component containing more than 3×10^{11} PLTs, as losses due to pooling and sampling for QC tests and bacterial culture amounted, on average, to 16.1 percent (range, 8.3%-31.5%) of the PLT yield. The pooling and sampling procedure was accomplished on average in 17.5 minutes (range, 13.5-21.3 min) once staff were fully trained and familiar with the technique.

All four regions successfully completed the phase of process control testing. Two regions had no failures in their first 60 pools and two regions had one failure in their first 91 pools (see *Guidance for Industry and FDA Review Staff Collection of Platelets by Automated Methods*, December 2007 for current criteria[12]). One failure was due to a high PLT concentration greater than 2300×10^3 per μL, and the other, to PLT yield less than 2.2×10^{11} per pool. Once process control was established, monthly QC testing was then initiated, involving pH testing between Day 2 and outdate, of at least 1 percent of PSPs or 4 PSP units per month if fewer than 400 pools were prepared. A total of 131 pools (all four regions) were tested over 2 to 6 months and 100 percent had pH values of 6.2 or greater within a range of 6.58 to 7.70.

The vast majority of PSPs had PLT yields equivalent to the minimum yield for plateletpheresis (i.e., $\geq 3.0 \times 10^{11}$; Table 2). The Acrodose PL system incorporates acceptance product qualification criteria that are determined by

TABLE 2. Product qualification data (±1 standard deviation) during the operation trial for the Acrodose PL system for PLTs pooled in four regions of the American Red Cross

Total pools: 7628	Region A	Region B	Region C	Region D	Mean	Requirement
Number of pools	2224	4313	604	487		
Volume (mL)	253 ± 8	266 ± 10	232 ± 9	250 ± 6	258 ± 13	180-420
PLTs ($\times10^3/\mu L$)	1547 ± 206	1530 ± 224	1647 ± 240	1548 ± 193	1546 ± 220	≤2300
Yield ($\times10^{11}$)	3.9 ± 0.5	4.1 ± 0.6	3.8 ± 0.6	3.9 ± 0.5	4.0 ± 0.6	2.2-5.8
Pools ≥ 3.0×10^{11} (%)	97.10	98.10	94.50	98.80	97.60	
pH ≥ 6.2* (%)	100	100	100	100	100	100
PLT qualification success (%)	99.96	99.56	98.68	100	99.60	

* Includes process control and monthly QC.

TABLE 3. Bacterial detection in PSPs before and after the implementation of sample diversion (SD)

Variable	Before SD Number	Before SD Rate per 10^6	After SD Number	After SD Rate per 10^6	After SD vs. before SD OR (95% CI)
Pools	5,211		20,725		
Confirmed-positive	11	2111	20	965	0.46 (0.22-0.95)
False-positive (machine error)	3	576	8	386	0.67 (0.18-2.53)
False-positive (contamination)	5	960	6	290	0.30 (0.09-0.99)
Indeterminate	2	384	4	193	0.50 (0.09-2.75)
Discordant	0	0	2	97	ND
Total	21	4030	40	1930	0.48 (0.28-0.81)

ND = not determined.

the manufacturer for PLT yield ($2.2 \times 10^{11} - 5.8 \times 10^{11}$ per pool), pool volume (180-240 mL), PLT concentration ($<2.3 \times 10^6/\mu L$), pH at the time of issue (≥6.2), and sterility (bacterial culture-negative). The product qualification success rate was 99.6 percent for pools manufactured during the operational trial (Table 2). Twenty-eight of 7628 pools failed, due to a concentration of greater than 2.3×10^6 per mL (11 cases), a yield of less than 2.2×10^{11} per pool (8 cases), or a yield of more than 5.8×10^{11} per pool (14 cases; 5 pools failed on multiple criteria).

Sample diversion during collection of WBPs

The first 5211 PSP units were manufactured from collection sets lacking sample diversion and 21 products yielded an initial-positive result (4030 per million [1:248]; Table 3). In each case, the PSPs and all cocomponents (RBCs and plasma) were retrieved and destroyed if they had not yet been transfused. After the introduction of sample diversion, 20,725 pools were manufactured and tested by culture (during the operational trial and subsequent routine production until December 31, 2007). Only 40 of the 20,725 PSPs yielded an initial-positive culture result (1930 per million [1:518]) indicating a significant 52 percent reduction in the rate of bacterial contamination (OR, 0.48; 95% CI, 0.28-0.81). This reduction reflected a significant decrease associated with sample diversion in the rates of both confirmed-positive culture rates (2111 vs. 965 per million; OR, 0.46; 95% CI, 0.22-0.95) and false-positive (contamination) rates (960 vs. 290 per million; OR, 0.30; 95% CI, 0.09-0.99), but not in the rates of indeterminate or false-positive samples due to machine error (Table 3). Most of the bacterial isolates in confirmed-positive cultures were likely skin flora (Table 4), and the rate of detection was significantly decreased after implementation of sample diversion (1727 vs. 724 per million; OR, 0.42; 95% CI, 0.18-0.96). The rate of detection for likely enteric organisms, however, did not change with sample diversion (384 vs. 241 per million; OR, 0.63; 95% CI, 0.12-3.24). All organisms detected as false-positive samples due to contamination were likely skin commensal organisms (Table 4).

PSPs with confirmed-positive or false-positive cultures were all successfully removed from inventory and not distributed for transfusion. Four pools with indeterminate culture results were transfused on Day 3 or Day 4 of storage, before the initial-positive culture was detected, but no adverse reactions to these components were reported.

DISCUSSION

Retrospective passive surveillance studies performed before the advent of screening cultures, initial sample diversion, and standardized skin preparations, revealed that the risk of a septic reaction with transfusion of WBPs ranged from 1:14,000 to 1:95,000.[10,13,14] The data presented herein from the American Red Cross Hemovigilance

TABLE 4. Bacteria detection and time to initial culture-positive in PSPs before and after the introduction of sample diversion (SD)

Bacterial isolate	Confirmed-positive: Before SD* (5,211 pools) Number (rate per 10^6)	Confirmed-positive: Before SD* (5,211 pools) Mean time to positive (hr)	Confirmed-positive: After SD (20,725 pools) Number (rate per 10^6)	Confirmed-positive: After SD (20,725 pools) Mean time to positive (hr)	False-positive (contamination): Before SD (5,211 pools) Number (rate per 10^6)	False-positive (contamination): Before SD (5,211 pools) Mean time to positive (hr)	False-positive (contamination): After SD (20,725 pools) n (rate per 10^6)	False-positive (contamination): After SD (20,725 pools) Mean time to positive (hr)
Coagulase-negative *Staphylococcus*	8	17.5	13	17.5	3	22.7†	4	30.6
S. aureus	1	10.5	1	10.5				
Streptococcus spp. (β-hemolytic)			1	7.0				
Bacillus spp.								
Corynebacterium spp.					2	44.1	2	28.6
Likely skin contaminants	9 (1727)		15 (724)		5 (960)		6 (290)	
S. bovis			2	9.3				
E. coli			1	7.7				
Serratia marcescens	2	7.5						
Proteus mirabilis			1	14.5				
Enterococcus faecalis			1	4.9				
Likely enteric organisms	2 (384)		5 (241)		0		0	
All isolates	11 (2111)		20 (965)		5 (960)		6 (290)	

* SD = initial sample diversion.
† Mean time to a positive culture for all (before SD and after SD) coagulase-negative *Staphylococcus* confirmed-positive cultures was 17.5 hours and for all false-positive cultures was 27.2 hours.

Program provide an estimate derived from 2,535,043 distributed WBP units between January 1, 2003, and December 31, 2006, with 20 reports of sepsis after transfusion, including 2 fatalities. Assuming a mean pool size of 5 WBP components, we calculated a rate per distributed product of 39.4 per million (1:25,350) for sepsis and 3.94 per million (1:253,504) for septic fatality. A limitation of this approach is that the actual number of transfused PLT doses is not known with certainty. The 2005 National Blood Collection and Distribution Survey records that a mean of 18.1 percent of WBPs were discarded before use, further suggesting that the actual septic transfusion rate per transfusion was higher than documented here.[15] Furthermore, several small studies and a large single-institution active surveillance study performed over 15 years have established that active surveillance may detect considerably more contaminated products and septic reactions than passive surveillance, supporting a higher actual contamination rate, currently estimated at 1:1000 to 1:3000 transfused products.[16,17] For comparison, our published estimates of the risk of plateletpheresis samples tested by bacterial culture and distributed by the American Red Cross during the same period (2004-2006) was 1:74,807 for septic reactions and 1:498,711 for fatalities, suggesting that WBPs may have been associated with a greater bacterial risk than apheresis PLTs for each transfused dose.[5] Similarly, the organisms involved in these reactions were mostly skin organisms; fatalities occurred predominantly on Day 5 of storage and frequently involved major pathogens.[16]

In an effort to improve the safety profile of WBPs, we successfully implemented and validated PSPs with the Acrodose PL system and sample diversion and demonstrated reduced contamination at the time of collection. Our preliminary experience suggested that the Acrodose PL system requires a significant investment in staff training and hands-on experience to optimize yields and to minimize QC loses (data not shown). We therefore performed an operational trial in four regions that routinely distribute WBPs. After successful production and distribution of 7628 PSPs over a 5-month period, we implemented PSPs for routine manufacture. We demonstrated the ability to consistently meet all of the manufacturers' quality variables for PSPs; indeed, 97.6 percent contained more than 3×10^{11} PLTs and only 0.4 percent (28 of 7628 pools) of pools failed QC testing, either on yield or on PLT concentration variables.

For bacterial culture, we selected the bioMérieux BacT/ALERT 3D system rather than the Pall eBDS system, because the former approach allows greater culture sensitivity by testing 8-mL rather than 3- to 4-mL samples, allows product release into inventory at 12 hours rather than 24 to 36 hours after culture inoculation, and is consistent with our laboratory approach with apheresis PLTs.

Bacterial culture of 5211 PSPs before and 20,725 PSPs after the introduction of sample diversion at the time of collection revealed a significant reduction in the overall rate of initial positive samples, which was accounted for by a significant decrease in the rate of confirmed-positive and false-positive (contamination) cultures. In contrast, the rate of indeterminate cultures and false-positive cultures due to machine error were unchanged. Similar decreases in confirmed-positive cultures with sample diversion have been previously documented in WBPs.[18,19] In our hands, sample diversion reduced the confirmed positive rates by 54 percent, from 2111 per million to 965 per million pools (OR, 0.46; 95% CI, 0.22-0.95) and the false-positive (contamination) rate by 70 percent from 960 per million to 290 per million pools (OR, 0.30; 95% CI, 0.09-0.99; Table 3).

Sample diversion technology likely reduces bacterial contamination by skin commensal bacteria mobilized during phlebotomy.[3,20] Our finding (Table 4) that confirmed-positive cultures derived from skin commensal bacteria decreased from 1727 to 724 per million after the implementation of sample diversion (OR, 0.42; 95% CI, 0.18-0.96), while the rates of enteric contaminants were unchanged (384 vs. 241 per million: OR, 0.63; 95% CI, 0.12-3.24), supports this concept. The finding that false-positive cultures (contamination) were also significantly reduced supports our previously published hypothesis that some false-positive samples are likely due to components contaminated by low levels of bacteria that do not proliferate on PLT storage.[21] In this view, a truly contaminated product that gives rise to an initial-positive culture is labeled a false-positive culture due to inadequate sampling during reculture of the product, such that the sample is sterile. Further evidence to support the hypothesis is provided by analyzing the time between culture inoculation and the initial positive test result. The most frequent species involved in false-positive (contamination) cultures is *Staphylococcus* (coagulase-negative), which took significantly longer to grow in false-positive than confirmed-positive cultures (mean, 27.2 hr vs. 17.5 hr; p = 0.02, t test; Table 4). This delay in growth may be ascribed to lower initial concentrations, prolonged lag phase of growth, or longer doubling times in culture, although the latter is less likely for a given species of bacteria.

PSP implementation required appropriate management of cocomponents associated with initial-positive cultures, directed by the culture results. After implementation of sample diversion, there were 40 initial-positive cultures of 20,725 pools tested (1930 per million [1:518]), and these products and their cocomponents were placed into hold quarantine; 14 of the initial-positive samples were shown to be false-positive samples and their cocomponents were released into inventory. The other positive culture results were associated with 130 RBCs and 130 plasma cocomponents that were retrieved and discarded if they had not been transfused. Because only a single WBP component likely contaminated the pool but could not be isolated in retrospect as the source by the current procedure, approximately 80 percent of the destroyed cocomponents were likely sterile and acceptable for transfusion. The direct and indirect cost of these component losses represent a disadvantage of the Acrodose PL system and should be accounted for in the cost analysis of PSP manufacturing. Of the 20 confirmed-positive cultures after implementation of sample diversion, 15 (75%) were still skin commensal organisms, raising the possibility that further improvements in skin preparation may be effective at lowering contamination and mitigating the loss of cocomponents with PSP production. Two of the four enteric organism contaminants were *Streptococcus bovis*, a species that has been linked to colonic carcinoma, and the donors of these products were counseled to seek further medical investigation.[22]

The confirmed-positive rate of 965 per million (1:1036) bacterial cultures of PSPs after the implementation of sample diversion is 5.2-fold greater than our published rate for apheresis PLTs of 185 per million (1:5399) collected between 2004 and 2006. In that report, the BacT/ALERT cultures were inoculated with 4-mL samples and only a proportion (~39%) of the products were collected with inlet line sample diversion strategies.[5] We recently implemented universal inlet line sample diversion for plateletpheresis, doubled the BacT/ALERT sample volume to 8 mL, and report a confirmed-positive culture rate of 167 per million (1:5,922) after testing 431,490 collections (Table 5 and A.F. Eder et al., submitted for publication).

These data suggest that when utilizing a standardized protocol of skin preparation, sample diversion, and culture, a unit-per-unit comparison of PSPs and plateletpheresis reveals a 5.8-fold (OR, 5.8; 95% CI, 3.5-9.5) greater risk of confirmed-positive contamination for PSPs, suggesting that individual WBP and plateletpheresis collections carry a similar risk of contamination (given the pooling of 5 WBP products in PSPs). These data raise the possibility that PSPs may pose a greater risk of sepsis to transfusion recipients due to false-negative bacterial culture results, after pooling five components. Despite this theoretical risk, PSPs offer to supplement the available PLT inventory at relatively low cost and may mitigate the risk of some transfusion reactions (e.g., transfusion-related acute lung injury, immune hemolysis), due to lower plasma volume derived from individual donors. The counterargument that there may be greater risk from increased donor exposure will need careful evaluation.

Direct comparison of absolute PLT contamination rates assessed by different institutions is not possible, due to variations in sampling time, volume of sample, and conditions of culture (e.g., aerobic/anaerobic conditions). Nevertheless, in those institutions where WBP and

TABLE 5. Comparison of confirmed-positive bacterial contamination rates of apheresis and WBP-derived samples utilizing the PLT-rich plasma (PRP) or buffy coat (BC) methods[7,18,23,24]

Study	PLT pool size	PLT preparation	WBPs: Products tested	WBPs: Rate per million (95% CI)	Apheresis PLTs: Products tested	Apheresis PLTs: Rate per million (95% CI)	OR (95% CI)
This report	5	PRP	20,725	965 (542-1,388)	431,490	167 (128-205)	5.8 (3.5-9.5)
Kleinman et al.[7]	1	PRP	13,579	74 (0-218)	21,914	46 (0-135)	NS
Yomtovian et al.[17]	5	PRP	12,961	2,392 (1,550-3,234)	15,493	452 (117-787)	5.3 (2.3-12.0)
Schrezenmeier et al.[23]	5	BC	22,044	726 (370-1,081)	15,198	855 (390-1,320)	NS
Murphy et al.[24]	5	BC	30,407	329 (125-533)	12,823	312 (6-618)	NS
de Korte et al.[18]	5	BC	6,749	1,322 (397-2,519)	4,963	2,418 (1050-3,786)	NS

NS = not significant, p ≥ 0.05.

plateletpheresis collections were assessed utilizing a standard protocol, the relative contamination rates are informative. Our finding that individual WBPs are likely contaminated at similar rates as plateletpheresis collections is substantiated by the report of Kleinman and colleagues,[7] who tested individual WBP and plateletpheresis products using the BacT/ALERT system and by Yomtovian and coworkers who tested pooled WBP and plateletpheresis products at issue using plate cultures[17] (Table 5). In all three cases, the WBPs were manufactured using the PLT-rich plasma method. These results are in contrast to those reported from Europe, where WBPs are produced using the buffy coat technique: In these reports, prestorage-pooled buffy coat PLTs have the same confirmed-positive contamination rate as similarly tested plateletpheresis (Table 5).[18,23,24] This difference has been ascribed to the overnight hold process in the manufacture of buffy coat PLTs, which may allow some bacteria to be inactivated by white cells before leukoreduction.[24]

We remain aware of the continued, residual risk of sepsis from bacterially contaminated WBP units. In 2007, the American Red Cross distributed 381,884, single WBP components and received one report of a severe septic reaction to a single WBP unit transfused to an infant, in which coagulase-negative *Staphylococcus* was implicated after pulsed-field gel electrophoresis demonstrated identical isolates from both the patient and residual product. We received no reports of septic reactions to PSPs in 2006 or 2007, although a false-negative QC culture result in 1 of 543 PSPs tested was detected by a transfusion service using a culture-based point-of-issue test. In this case, the PSP unit was transfused on Day 4 without reaction, but a 1- to 2-mL sample of the PSPs collected at the time of issue grew coagulase-negative *Staphylococcus* on plate culture at a titer of 2×10^4 colony-forming units per mL (M. Jacobs and R. Yomtovian, personal communication, 2008).[16]

In summary, the successful implementation of Acrodose PL PLTs by the American Red Cross now provides an alternative source of QC-cultured PLTs for transfusion. PSPs undoubtedly present lower bacterial risk to patients than WBPs that are pooled at the point of issue and tested with non–FDA-approved surrogate tests, such as pH or glucose content. Ongoing hemovigilance for septic transfusion reactions, however, will be required to document the relative safety of PSPs considering their approximately 5.8-fold higher rate in detectable contamination compared to that of plateletpheresis.

ACKNOWLEDGMENTS

We would like to thank T. Donato, American Red Cross, Penn-Jersey Region; M. Gaughan, American Red Cross, North Central Region; G. Kotnik, American Red Cross, Northern Ohio Region; and P. Sundara, American Red Cross, Connecticut Region, for their hard work in ensuring the success of the Acrodose PL operational trial.

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番号 7

医薬品
医薬部外品　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2009年2月13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	①乾燥抗 HBs 人免疫グロブリン ②ポリエチレングリコール処理抗 HBs 人免疫グロブリン		研究報告の公表状況	CDC/MMWR 2009; 58(5): 105-109	公表国 アメリカ	
販売名 (企業名)	①ヘブスブリン（ベネシス） ②静注用ヘブスブリン－IH（ベネシス）					

研究報告の概要

カリフォルニア州において Confidential Morbidity Reports (CMR) のデータの入手が常に可能になった 1995 年以降に収集された、2000-2007 年の間のコクシジオイデス症の報告症例数および入院数の増加、ならびに最も高い罹患率について報告する。
コクシジオイデス症は、土壌中の真菌である Coccidioides immitis または Coccidioides posadasii の浮遊胞子を吸い込むことによって感染する。1995-2000 年の間、カリフォルニア州でのコクシジオイデス症の報告症例数は、人口 100,000 人当たりで毎年平均 2.5 であった。しかし、2000-2006 年の報告数は 3 倍を超え、人口 100,000 人当たり 2.4 から 8.0 に増加した。この増加を特徴付けるため、カリフォルニア州公衆衛生局は 2000-2007 年の症例および入院データ、ならびに 2008 年の予備的症例報告データを分析した。その結果の示すところによれば、2000-2006 年の間、カリフォルニア州におけるコクシジオイデス症の報告症例数および入院数は毎年増加しており、2007 年に減少した。2000-2007 年の間の年間症例数は Kern 郡が最も高く（人口 100,000 人当たり 150.0）、入院率は非ヒスパニックの黒人が最も高く、人口 100,000 人当たりで 3.0 から 7.5 に増加した。
カリフォルニア州のコクシジオイデス症の増加は隣のアリゾナ州および米国全体に観察された増加と類似している。アリゾナ州は毎年米国のコクシジオイデス症例全体の約 60% を報告しており、1999 年の 1,812 症例（人口 100,000 人当たり 37）から 2006 年の 5,535 症例（人口 100,000 人当たり 91）と実質的な増加を報告した。米国全体では、コクシジオイデス症報告症例数は 1996 年の 1,697 症例（人口 100,000 人当たり 0.64）から 2006 年の 8,917 症例（人口 100,000 人当たり 6.79）に増加した。コクシジオイデス症報告数が最近増加している理由については、十分に解明されていない。

使用上の注意記載状況・その他参考事項等

代表として静注用ヘブスブリン－IH 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、かつALT（GPT）値でスクリーニングを実施している。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抗HBs抗体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HBs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。

報告企業の意見	今後の対応
コクシジオイデス症はカルフォルニア州で最近 3 倍以上に大幅増加し、米国全体においても同じ傾向にあることについての報告である。 コクシジオイデス・イミチスは、コクシジオイデス症の原因となる真菌であり、宿主の体内で観察される最も小さな単位は2〜5 μmの内生胞子である。万一、原料血漿にコクシジオイデス・イミチスが混入したとしても、除菌ろ過等の製造工程にて十分に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と考えるので、特段の措置はとらない。

38

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MMWR

Weekly
February 13, 2009 / 58(05);105-109

Increase in Coccidioidomycosis --- California, 2000--2007

Coccidioidomycosis is an infection resulting from inhalation of airborne spores of Coccidioides immitis or Coccidioides posadasii, soil-dwelling fungi endemic to California's San Joaquin Valley; southern regions of Arizona, Utah, Nevada, and New Mexico; western Texas; and regions of Mexico and Central and South America (1). Of an estimated 150,000 new infections annually in the United States (2), approximately 60% are asymptomatic (1). Patients with symptoms usually experience a self-limited influenza-like illness (ILI), although some develop severe pneumonia. Fewer than 1% of patients develop disseminated disease. Infection usually produces immunity to reinfection. During 1995--2000, the number of reported coccidioidomycosis cases in California averaged 2.5 per 100,000 population annually. However, from 2000 to 2006, the incidence rate more than tripled, increasing from 2.4 to 8.0 per 100,000 population. To characterize this increase, the California Department of Public Health (CDPH) analyzed case and hospitalization data for the period 2000--2007 and preliminary case report data for 2008. The results indicated that, during 2000--2006, the number of reported cases and hospitalizations for coccidioidomycosis in California increased each year, before decreasing in 2007. Annual incidence during 2000--2007 was highest in Kern County (150.0 cases per 100,000 population), and the hospitalization rate was highest among non-Hispanic blacks, increasing from 3.0 to 7.5 per 100,000 population. Health-care providers should maintain heightened suspicion for coccidioidomycosis in patients who live or have traveled in areas where the disease is endemic and who have signs of ILI, pneumonia, or disseminated infection.

Coccidioidomycosis is a reportable disease in California, although laboratories are not required to report. During 1991--1995, California experienced a large epidemic of coccidioidomycosis in the San Joaquin Valley; since 1995, cases of coccidioidomycosis have been reported consistently to local health departments in California using Confidential Morbidity Reports (CMRs). For the analysis summarized in this report, CDPH reviewed case and hospitalization data for the period 2000--2007 using CMRs and California Patient Discharge Data Set (CPDDS) data. Preliminary CMR case data for 2008 also were analyzed. CMRs include data on the patient's county of residence, sex, and dates of birth, illness onset, diagnosis, and case report. CPDDS data include inpatient discharge diagnoses from all California nonfederal hospitals. Cases with codes for coccidioidomycosis (114--114.5 and 114.9) from the *International Classification of Diseases, Ninth Edition* were selected. Duplicate records were removed so that the CMR data set retained only the first report of a case and the CPDDS retained only the first report of a patient's hospitalization. For the 3% of reported CMR cases with no date of illness onset or diagnosis, year of illness onset was presumed to be year of case report. CMR data were used to calculate incidence rates of reported cases overall and by age, sex, region, and county. Because 34% of reported CMR cases had missing data on race, incidence rates by race were not calculated. CPDDS data were used to calculate rates of first hospitalization overall and by age, sex, race/ethnicity, region, and county. California Department of Finance population projections were used for denominators (*3*). Negative binomial regression was used to test for statistical significance of change in rates of reported cases and hospitalizations during 2000--2006, the period of annual increase in reported cases and hospitalizations. Fatality rates among hospitalized patients were calculated by using CPDDS data for 2000--2007.

After remaining stable since 1995, reported coccidioidomycosis cases in California increased from 816 in 2000 (incidence rate: 2.4 per 100,000 population) to 2,981 in 2006 (8.0 per 100,000 population) ($p<0.001$) (Figure 1), before decreasing in 2007 to 2,791 cases (7.4 per 100,000 population). Preliminary 2008 CMR data indicated that 1,718 cases were reported in California during January 1--December 6, 2008, compared with 2,210 and 2,426 cases reported during the same period in 2006 and 2007, respectively.

During 2000--2007, estimated average annual incidence was highest among adults aged 40--49 years (3,518 cases [8.0 per 100,000 population]) versus other age groups (Table). A total of 10,909 (65%) cases were reported in male patients, for an average annual rate of 7.6 per 100,000 population, compared with 5,848 cases in females (4.0 per 100,000 population) (Table). The greatest incidence occurred in the San Joaquin Valley region, where coccidioidomycosis is endemic. A total of 12,855 (76%) of California's 16,970 cases were reported from the San Joaquin Valley during 2000--2007. Reported cases from this region increased from 490 (14.7 per 100,000 population) in 2000 to 2,135 (53.9 per 100,000 population) in 2007. Within the region, Kern County reported the highest incidence every year. Rates of reported cases in Kern County averaged 150.0 per 100,000 population during 2000--2007 (Figure 2), peaking in 2004 at 195.3 per 100,000 population.

In California, coccidioidomycosis cases requiring hospitalization increased from 611 in 2000 (1.8 per 100,000 population) to 1,587 in 2006 (4.3 per 100,000 population) ($p<0.001$), before decreasing to 1,368 (3.6 per 100,000 population) in 2007 (Figure 1). Hospitalizations for coccidioidomycosis were highest among persons aged 60--79 years, averaging 5.8 per 100,000 population during 2000--2007 (Table). By race/ethnicity, hospitalizations were highest among non-Hispanic blacks, compared with non-Hispanic whites, Hispanics, and Asians/Pacific Islanders. From 2000 to 2007, hospitalizations among non-Hispanic blacks increased from 66 (3.0 per 100,000 population) to 169 (7.5 per 100,000 population). Hospitalizations among non-Hispanic whites increased from 297 (1.9 per 100,000 population) in 2000 to 570 (3.5 per 100,000 population) in 2007; hospitalizations among Hispanics increased from 182 (1.6 per 100,000 population) to 485 (3.6 per 100,000 population), and hospitalizations among Asians/Pacific Islanders increased from 36 (0.9 per 100,000 population) to 86 (1.9 per 100,000 population).

By geographic region, hospitalizations for coccidioidomycosis in the San Joaquin Valley increased from 230 (6.9 per 100,000 population) in 2000 to 701 (17.7 per 100,000 population) in 2007. Within the region, Kern County reported the highest hospitalization rates, increasing from 121 (18.2 per 100,000 population) in 2000 to 285 (34.9 per 100,000 population) in 2007, and peaking in 2005 at 353 hospitalizations (45.8 per 100,000 population). Overall in California, during 2000--2007, a total of 752 (8.7%) of the 8,657 persons hospitalized for coccidioidomycosis died.

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Editorial Note:

This report describes increases in reported coccidioidomycosis cases and hospitalizations during 2000--2007 and the highest incidence rate in California since 1995, the first year that CMR data were available consistently. The number of reported cases and hospitalizations decreased in 2007, and preliminary data indicate those decreases might have continued in 2008. However, rates of coccidioidomycosis in California remain substantially higher than during 1995--2000. These increased rates likely are real, rather than surveillance artifact, because no major changes in diagnosis or reporting of coccidioidomycosis in California occurred before or during the period studied.

Increases in coccidioidomycosis in California are similar to those observed in neighboring Arizona and in the United States overall. Arizona, which annually reports approximately 60% of all coccidioidomycosis cases in the United States, reported a substantial increase in coccidioidomycosis from 1,812 cases (37 per 100,000 population) in 1999 to 5,535 cases (91 per 100,000 population) in 2006 (*4*). In the United States overall, the number of reported coccidioidomycosis cases increased from 1,697 (0.64 per 100,000 population) in 1996 to 8,917 (6.79 per 100,000 population in 2006) (*5*). Reasons for these recent increases in reported coccidioidomycosis are not fully understood. Some previous increases have been associated with local environmental and climatic variations (*6*). Other hypothesized causes include aerosolization of spores caused by soil disturbance during periods of increased construction activity (*4*), growing numbers of persons who are immunocompromised or have other risk factors for severe disease (*7*), and immigration of previously unexposed persons from areas where coccidioidomycosis is not endemic (*2*). Recent increases in coccidioidomycosis in California are partially attributable to several hundred cases reported from two San Joaquin Valley prisons (*8*) with inmates from areas where the disease is not endemic. Multiple clusters also have been reported at California military bases, where personnel often have intensive dust exposure (*9*). Such exposure is hypothesized to increase the risk for infection; local outbreaks of coccidioidomycosis have been noted after dust storms (*1*).

Coccidioidomycosis hospitalization rates in California were highest among persons aged 60--79 years, which is consistent with previous reports that older age might be a risk factor for severe coccidioidomycosis (*7*).

Hospitalization rates also were substantially higher among non-Hispanic blacks, compared with non-Hispanic whites, Hispanics, and Asians/Pacific Islanders. Black race has been associated previously with increased risk for coccidioidomycosis hospitalization (*7*). In addition, blacks and persons of Filipino ancestry have been found to have increased risk for disseminated coccidioidomycosis, possibly because of underlying differences in susceptible host genetics (*1,10*). Immunocompromised persons and women in their second and third trimesters of pregnancy also have increased risk for disseminated disease (*1*).

The findings in this report are subject to at least three limitations. First, because not all persons with coccidioidomycosis seek medical care and not all diagnosed cases are reported to local health departments, this report likely underestimates the actual rate of coccidioidomycosis in California. Second, for cases in which patients were hospitalized, medical chart review was not performed to confirm laboratory diagnosis or cause of death from coccidioidomycosis, resulting in possible overestimation of hospitalizations and deaths in persons with coccidioidomycosis diagnosed. Finally, Kern County's public health laboratory performs much of the coccidioidomycosis testing for patients in that county and might be more likely to report cases routinely than laboratories in most other counties in the San Joaquin Valley region where this is not the practice. In 2009, California plans to make coccidioidomycosis a laboratory-reportable disease to improve completeness and timeliness of case reporting and delivery of targeted public health recommendations during periods of increased disease.

Given the recent increases in coccidioidomycosis in California and Arizona, heightened consideration of this disease is warranted in the differential diagnosis of any patient with ILI, pneumonia, or signs of disseminated infection who has lived or traveled in areas where coccidioidomycosis is endemic. Because intensive dust exposure appears to increase the risk for infection, CDC recommends that persons living or traveling in regions where coccidioidomycosis is endemic who are at risk for severe or disseminated disease (e.g., older persons, pregnant women, immunocompromised persons, and persons of black race or Filipino ancestry) should avoid exposure to outdoor dust as much as possible.* When such exposure is unavoidable, measures to reduce inhalation of outdoor dust, such as wetting soil and using respiratory protection when engaging in soil-disturbing activities, might be effective. However, options for environmental control of coccidioidomycosis are limited, and no safe, effective vaccine for the disease exists currently. Developing such a vaccine appears to be the best option for preventing disease in those persons at risk for coccidioidomycosis (*9*).

Acknowledgments

The findings in this report are based, in part, on contributions by SR Bissell, MS, California Department of Health; and EC Weiss, MD, Office of Workforce and Career Development, CDC.

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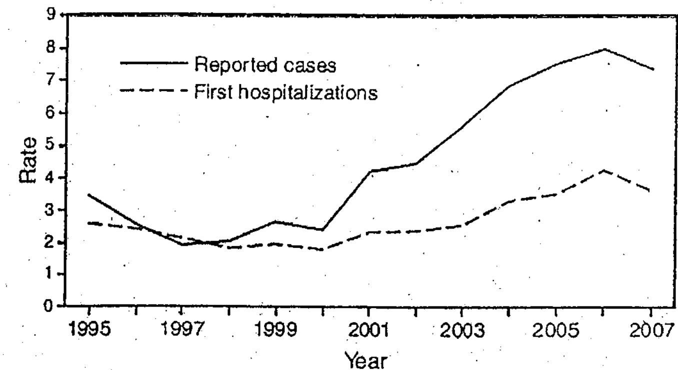
* Additional information available at http://wwwn.cdc.gov/travel/yellowbookch4-coccidioidomycosis.aspx.

Figure 1

FIGURE 1. Rates* of reported cases of coccidioidomycosis and first hospitalizations among persons with coccidioidomycosis diagnosed — California, 1995–2007†

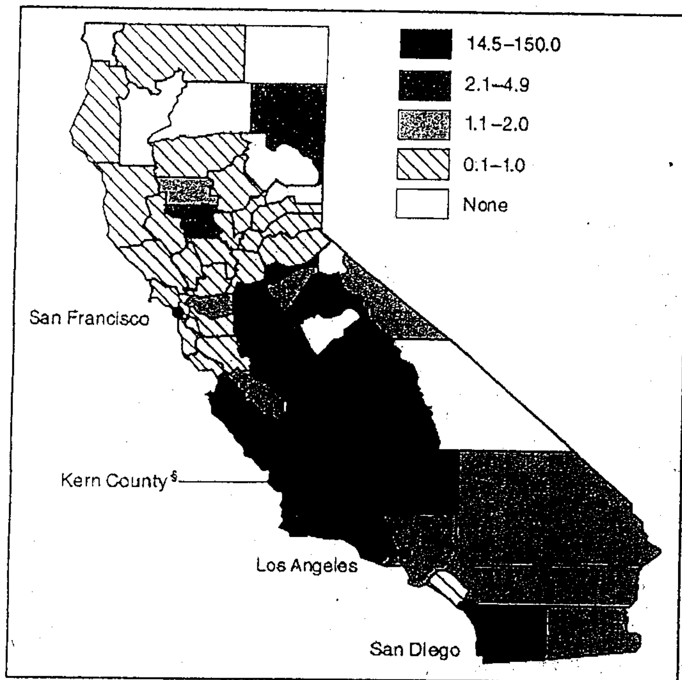


* Per 100,000 population.
† Data on reported cases of coccidioidomycosis are from California Department of Public Health Confidential Morbidity Reports. Data on first hospitalizations of persons with coccidioidomycosis diagnosed are from the California Patient Discharge Data Set. Population data are from California Department of Finance population projections.

Return to top.

Figure 2

FIGURE 2. Average annual rate* of reported cases of coccidioidomycosis, by county — California, 2000–2007†



* Per 100,000 population.

† Data on reported cases are from California Department of Public Health Confidential Morbidity Reports. County population data are from California Department of Finance population projections.

§ Kern County, located in the San Joaquin Valley region, where coccidioidomycosis is endemic, had the highest rate among counties (150.0 cases per 100,000 population).

Return to top.

Table

TABLE. Total numbers and average annual rates* of reported cases of coccidioidomycosis and first hospitalizations and deaths among persons with coccidioidomycosis diagnosed, by selected characteristics — California, 1995–1999 and 2000–2007†

Characteristic	1995–1999 No. of cases	1995–1999 Rate	2000–2007 No. of cases	2000–2007 Rate
Reported cases				
Age group (yrs)				
0–9	182	0.7	532	1.3
10–19	393	1.7	1,695	3.9
20–29	677	2.7	2,793	7.0
30–39	921	3.4	3,379	7.7
40–49	761	3.3	3,518	8.0
50–59	528	3.6	2,180	7.5
60–69	350	3.5	1,307	6.7
70–79	220	2.8	755	5.5
≥80	95	2.3	365	4.2
Sex				
Male	2,572	3.2	10,909	7.6
Female	1,529	1.9	5,848	4.0
Region				
California, overall	4,126	2.5	16,970	5.9
San Joaquin Valley§	2,829	17.9	12,855	44.1
Kern County	2,003	63.1	8,847	150.0
First hospitalizations				
Age group (yrs)				
0–9	47	0.2	151	0.4
10–19	148	0.6	361	0.8
20–29	348	1.4	853	2.1
30–39	574	2.1	1,409	3.2
40–49	709	3.1	1,851	4.2
50–59	609	4.1	1,690	5.1
60–69	509	5.0	1,130	5.8
70–79	439	5.6	785	5.8
≥80	170	4.2	427	5.0
Sex				
Male	2,237	2.8	5,960	4.1
Female	1,316	1.6	2,696	1.9
Region				
California, overall	3,553	2.2	8,657	3.0
San Joaquin Valley§	1,418	9.0	4,360	15.0
Kern County	704	22.2	2,206	37.4
Race/Ethnicity¶				
Black, non-Hispanic	349	—	1,005	5.3
White, non-Hispanic	1,947	—	3,800	3.0
Hispanic	881	—	2,869	2.9
Asian/Pacific Islander	212	—	552	1.7
American Indian/ Alaska Native	13	—	28	1.4
Multiracial/Other	60	—	192	3.4
Deaths	307	0.19	752	0.26

* Per 100,000 population.

† Data on reported cases are from California Department of Public Health Confidential Morbidity Reports. Data on first hospitalizations of persons with coccidioidomycosis diagnosed are from the California Patient Discharge Data Set. Denominator data are from California Department of Finance population projections.

§ Includes the following California counties: Fresno, Kern, Kings, Madera, Merced, San Joaquin, Stanislaus, and Tulare.

¶ Hospitalization rates by racial/ethnic population could not be calculated for 1995–1999 because population estimates for this period included inconsistent race/ethnicity categories.

Return to top.

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Date last reviewed: 2/12/2009

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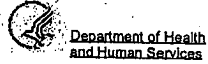

Department of Health and Human Services

B　個別症例報告概要

○　総括一覧表

○　報告リスト

個別症例報告のまとめ方について

個別症例報告が添付されているもののうち、個別症例報告の重複を除いたものを一覧表の後に添付した（国内症例については、資料3において集積報告を行っているため、添付していない）。