薬事・食品衛生審議会
平成２１年度　第３回　血液事業部会運営委員会

議 事 次 第

日時：平成２１年１２月１０日（木）
１３：００～１６：００
場所：九段会館　桐の間
東京都千代田区九段南１－６－５（４Ｆ）

議題：

1. 議事要旨の確認
2. 感染症定期報告について
3. 血液製剤に関する報告事項について
4. 日本赤十字社からの報告事項について
5. その他

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資料３－１　供血者からの遡及調査の進捗状況について
資料３－２　血液製剤に関する報告事項について
資料３－３　献血件数及びＨＩＶ抗体・核酸増幅検査陽性件数
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資料１

平成21年度第2回血液事業部会運営委員会議事要旨

日時： 平成21年7月28日（火） 15:00～17:00
場所： 九段会館 桐の間
出席者：高橋委員長、大平、岡田、佐川、花井、山口各委員
（事務局）
亀井血液対策課長、光岡血液対策企画官、秋野課長補佐、秋山需給専門官
（採血事業者）
日本赤十字社血液事業本部 田所経営会議委員、俵総括副本部長、日野副本部長、菅原供給管理課長

議 題： 1. 議事要旨の確認
2. 感染症定期報告について
3. 血液製剤に関する報告事項について
4. 日本赤十字社からの報告事項について
5. その他

（審議概要）

議題1について

議事要旨に関する意見等については、事務局まで連絡することとされた。

議題2について

感染症定期報告について、事務局から説明後、質疑応答がなされた。

議題3について

事務局及び日赤から、供血者からの遡及調査の進捗状況、血液製剤に関する報告事項、献血件数及びHIV抗体・核酸増幅検査陽性件数について説明後、下記のような意見が出された。

○ 近畿では保健所の検査体制を整備すると献血でのHIV抗体陽性件数が減少し、東京では保健所の検査体制があるものの、献血での陽性件数が増加していることが示されている。国はもちろん全国の血液センターにおいても各自治体に働きかけるなどして保健所での検査をアピールしてほしい。

議題4について

日赤から、血液事業本部のこの一年（平成20年度）の取組について報告がなされた。

議題5について

事務局、日赤、岡田委員及び山口委員から、新型インフルエンザ（A／H1N1）の国内発生に係る対応、新型インフルエンザの蔓延時等における献血量の確保及びCJD関連各種論文等について報告後、以下のような意見が出された。

（英国渡航歴による献血制限の緩和について）

○ 以前、献血制限を議論した際は需給にひっ迫のないようにという中で、最悪のケースを想定して議論された。もし、献血制限緩和するのであれば、新型インフルエンザを大きな理由に緩和するのか、今までの科学的知見が得られたため緩和するのかについて整理する必要がある。
○ 患者に対して、新型インフルエンザによる緊急時だから少しくらいのリスクは仕方ないと説明するのは合理的でないので、補足説明をして、医療者と、特に受血者である患者が理解できるような考え方を示すべき。
○ 以前献血制限を議論した際は情報がなかったが、今回、見直してみて、異常プリオン低減技術が向上していること、リスクが理論上課題評価されていたかもしれないことから緩和を検討するということだと思う。
○ 需給がひっ迫して変更するという議論もあるが、平成17年から4年間たっており、4年間の情報の蓄積がある。日本国内で発生したvCJD症例については、英国滞在歴が 24 日と短かったが、その情報はあった上で、どこの国もそれに基づいた献血制限は行っていない。
○ 献血制限を変更するとなると、システムの変更等いろいろと準備もかかるので、実務的な準備をしていただいて、準備状況を整理したところで、この委員会でご報告をお願いしたい。
○ 安全性の問題として情報をさらにしっかりと集めていただいて、何かあった場合には緊急的な対応を図れるようにしていくことも一つの条件だと思う。
○ 今までの対応でも、当面の間ということで、施策は進められているので、万が一の場合は切り替えることになるので、システムの変更の際はその点も考えてやってほしい。

（新型インフルエンザ対応方針等について）

○ 日赤の職員の健康をしっかり確保して、職員が足りなくて献血がスムーズにいかないことのないように、マニュアルにある程度入れて欲しい。
○ オーストラリアでは（7 月 28 日時点の情報では）、新型インフルエンザが日本の 10 倍異常蔓延していると思うが、年間の予想・予定採血量の3%減ではあるが、前年

と比較して採血量は多くなっており、ほとんど影響はないと聞いている。社会がパニック状況になっていないことが要因ではないかとのこと。

○ 国の中での施策の立て方が血液の確保に相当大きな影響を与えるので、日赤と緊密に連絡を取り合って対応してほしい。日赤についても、実際に献血に御協力いただく人に対するアナウンスメント等のいろいろな準備をしてほしい。

事務局から、アルブミン製剤の資料量について報告後、下記のような意見が出された。

○ アルブミンの国内自給率の低下は、遺伝子組換え製剤の問題、DPCの問題があると聞いているが、DPCに関連して薬価差の問題で自給率が低下しているのであれば、国内献血由来製品のインセンティブを高めるなどの検討とともに自給についての意識を高める啓発を行ってほしい。

○ どのアルブミン製剤を採用するかについては、病院の中の薬事委員会等で議論されるが、その委員が国内・海外献血由来等の情報に詳しくないことも多く、製剤がどこの血液由来か議論されず、経済的な判断により決定されることが多いので、病院におけるアルブミン製剤の選択にまで介入していくべきである。

○ 平成17年度には一番使用量が多かったが、平成20年度の調査で使用量の減少が最も大きかった愛媛県の例もあるように、県、血液センター、合同輸血療法委員会等様々な部署で連携すると改善されるという非常に良い例だと思う。

また、事務局から、フィブリノゲン製剤及び血液凝固因子製剤に関する公表等について報告がなされた。

以上

資料2

感染症定期報告に関する今後の対応について

平成１６年度第５回
運営委員会確認事項
（平成１６年９月１７日）

1. 基本的な方針

運営委員会に報告する資料においては、

(1) 文献報告は、同一報告に由来するものの重複を廃した一覧表を作成すること。

(2) 8月の運営委員会において、国内の輸血及び血漿分画製剤の使用した個別症例の感染症発生報告は、定期的にまとめた「感染症報告事例のまとめ」を運営委員会に提出する取り扱いとされた。これにより、感染症定期報告に添付される過去の感染症発生症例報告よりも、直近の「感染症報告事例のまとめ」を主として利用することとすること。

2 具体的な方法

(1) 感染症定期報告の内容は、原則、すべて運営委員会委員に送付することとするが、次の資料概要を作成し、委員の資料の確認を効率的かつ効果的に行うことができるようにする。

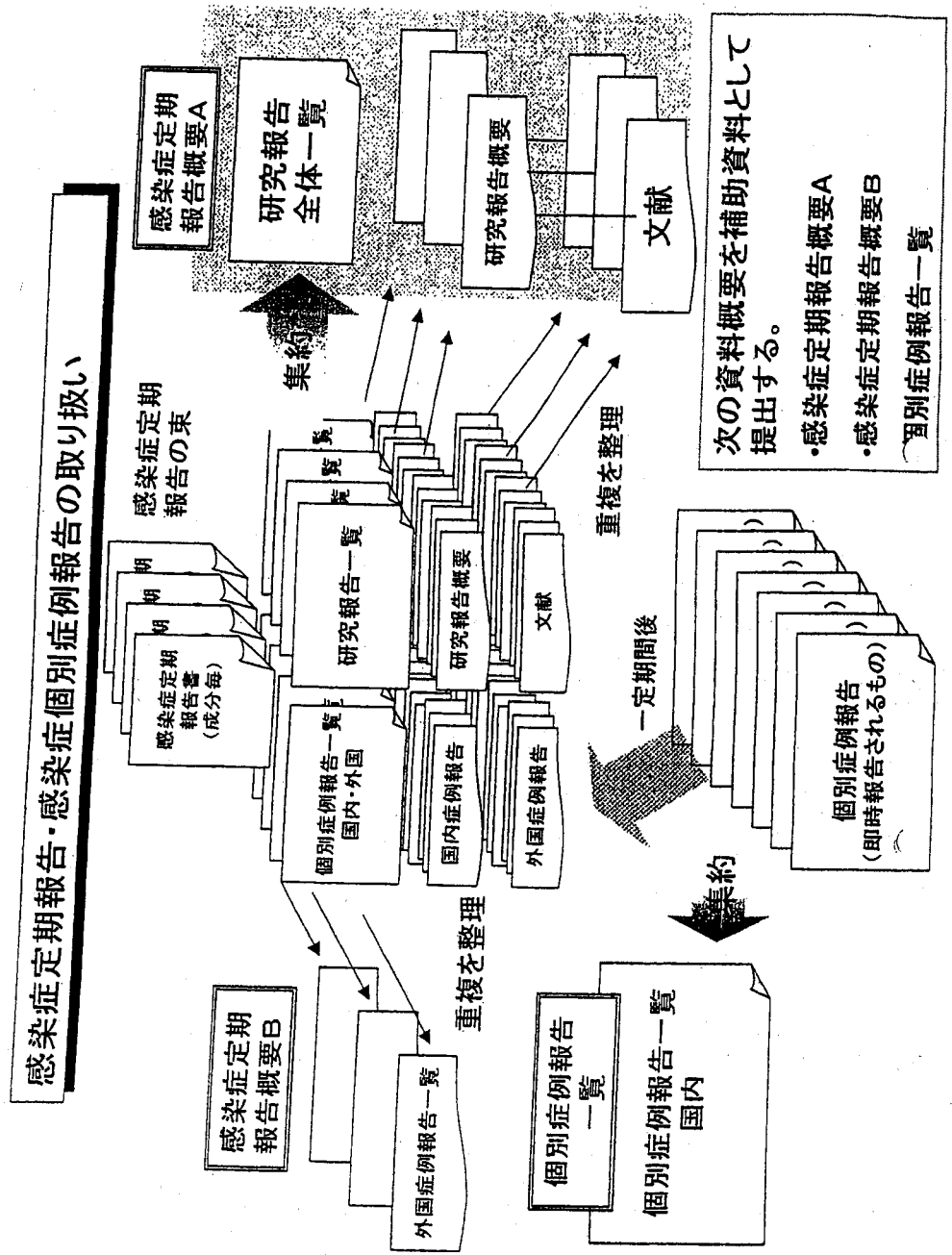
① 研究報告は、同一文献による重複を廃した別紙のような形式の一覧表を作成し、当該一覧表に代表的なものの報告様式（別紙様式第2）及び該当文献を添付した「**資料概要A**」を事務局が作成し、送付する。

② 感染症発生症例報告のうち、発現国が「外国」の血漿分画製剤の使用による症例は、同一製品毎に報告期間を代表する感染症発生症例一覧（別紙様式第4）をまとめた「**資料概要B**」を事務局が作成し、送付する。

③ 感染症発生症例報告のうち、発現国が「国内」の輸血による症例及び血漿分画製剤の使用による感染症症例については、「感染症報告事例のまとめ」を提出することから、当該症例にかかる「資料概要」は作成しないこととする。ただし、運営委員会委員から特段の議論が必要との指摘がなされたものについては、別途事務局が資料を作成する。

(2) 発現国が「外国」の感染症発生症例報告については、国内で使用しているロットと関係がないもの、使用時期が相当程度古いもの、因果関係についての詳細情報の入手が困難であるものが多く、必ずしも緊急性が高くないと考えられるものも少なくない。また、国内症例に比べて個別症例を分析・評価することが難しいものが多いため、緊急性があると考えられるものを除き、その安全対策への利用については、引き続き、検討を行う。

(3) 資料概要A及びBについては、平成16年9月の運営委員会から試験的に作成し、以後「感染症的報告について（目次）」資料は廃止することとする。



感染症定期報告概要

（平成２１年１２月１０日）

平成２１年６月１日受理分以降

Ａ　研究報告概要
Ｂ　個別症例報告概要

Ａ　研究報告概要

○　一覧表（感染症種類毎）
○　感染症毎の主要研究報告概要
○　研究報告写

研究報告のまとめ方について

１　平成２１年６月１日以降に報告された感染症定期報告に含まれる研究報告（論文等）について、重複している分を除いた報告概要一覧表を作成した。

２　一覧表においては、前回の運営委員会において報告したもの以降の研究報告について、一覧表の後に当該感染症の主要研究報告の内容を添付した。

感染症定期報告の報告状況(2009/6/1～2009/8/31)

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
90156	2009/6/2	90236	A型肝炎	Vox Sanguinis 2009; 96: 14-19	加熱及び高静水圧の物理的不活化処理法で4株のA型肝炎ウイルスの不活化を行ったところ、それぞれの処理はHAV感染性を3～5log10の範囲で低下させた。また、血液製剤のウイルス汚染に対する安全性を評価するのにもっとも適した株は、耐熱性のKRM238であった。	
90156	2009/6/2	90236	B型肝炎	J Med Virol 2008; 80: 1880-1884	1971～2005年の35年間に虎ノ門病院に来院した急性HBV感染患者153名および慢性HBV感染患者4277名について5年間毎のHBVジェノタイプ/サブジェノタイプを調べた。急性感染患者数は35年間中増加し続けた。慢性感染患者は1986～1990年が最大であった。ジェノタイプは急性感染患者と慢性感染患者で大きく異なった(A、B、C型:28.6%、10.3%、59.5% vs 3.0%、12.3%、84.5%)。最近では外国のサブジェノタイプB2/Bsが増加する傾向がある。	
90173	2009/7/29	90337	B型肝炎	Transfusion Med. 2008; 18: 379-381	日本における、不顕性HBV感染者(HBsAg陰性)からの輸血によるB型肝炎感染に関する報告。	
90156	2009/6/2	90236	B型肝炎	Vox Sanguinis 2008; 95: 174-180	HBV DNA陽性かつ表面抗原(HBsAg)陰性オカルトHBV感染の検出感度を上げるために、HBV DNAとHBsAgを同時に濃縮する新規方法を開発した。二価金属存在下でpoly-L-lysineでコートした磁気ビーズを使用し、ウイルス凝集反応を増強させ、ウイルスを濃縮する方法により、HBV DNAとHBsAg量は、最高4～7倍に濃縮された。本方法により、EIAとHBV NATの感度が上昇し、HBsAg EIAを用いてオカルトHBV感染者40名のうち27名を検出することができた。	
90156	2009/6/2	90236	B型肝炎	日本肝臓学会第37回東部会 O-85	日本の首都圏において、HBVの中でも慢性化率の高いgenotypeAは急速に増加しており、新規日本人キャリアからの二次感染が疑われることが急性B型肝炎症例の検討から明らかになった。	1
90156	2009/6/2	90236	B型肝炎	日本小児感染症学会第40回総会・学術集会 E-20	母親がHBsAg陰性かつ家族内に患者以外のHBVキャリアが存在する成人及び小児HBVキャリアである7家族を対象とし、HBV全遺伝子解析に基づく分子系統樹を用いて感染源を検索したところ、3家族で父親以外の感染源の可能性があり、祖母からの感染は分子疫学的に感染経路を証明できた。	
90156	2009/6/2	90236	C型肝炎	第70回 日本血液学会総会 2008年10月10-12日	再生不良性貧血の54歳女性で、初回輸血前検査はHCV抗体陰性、HCVコア蛋白陰性であったが、複数回輸血後、HCVコア蛋白が陽性化したため、遡及調査を開始した。保管検体の個別NATにより、1検体からHCV-RNAを検出した。患者と献血者のHCV Core-E1-E2領域の塩基配列が一致した。日本で20プールNAT導入後、初めて確認された輸血によるHCV感染症例である。	
90156	2009/6/2	90236	C型肝炎	日本血液事業学会第32回総会	1999年7月～2008年3月までにNATで検出された111本のHCV-RNA陽性検体のGenotype解析の結果、Genotype 2aが最も多く、1bと2bがほぼ同数であった。	
90156	2009/6/2	90236	E型肝炎	AABB Annual Meeting and TXPO 2008	2005～2007年に北海道で実施したプールNATによるHEV-RNAスクリーニングの結果、献血者の約1/8,300はHEV-RNA陽性であった。ほとんどの献血者は動物内臓を摂取しており、無症候性であったが、ウイルス血症は数ヶ月間持続した。	

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
90156	2009/6/2	90236	E型肝炎	Clin Infect Dis 2009; 48: 373-374	急性白血病の33歳の男性がE型肝炎を発症し、HEV遺伝子検査の結果、重複する時期に同じ病棟に入院していた別のE型肝炎患者から感染していたことが示唆された。	
90156	2009/6/2	90236	E型肝炎	Transfusion 2008; 48: 2568-2576	日本全国でALT高値のため献血不適となった献血者の血液検体に、HEVマーカー(HEV-RNA及び抗HEV抗体)が認められ、いずれのマーカーとも東日本の法が西より高かった。	
90156	2009/6/2	90236	HHV-8感染	Transfusion 2008; 48: Supplement 105A	米国の供血者のヘルペスウイルス8(HHV8)ゲノム陽性率について、高感度定量RT-PCR法(検出限界8コピー)より684名の検体を分析したがHHV8ゲノムは検出されず、健康な供血者におけるHHV8陽性率は非常に低かった。	
90156	2009/6/2	90236	HIV	Eurosurveillance 2008; 13(50): 19066	ヨーロッパにおいて報告された人口100万人当たりの新規HIV感染率は、2000年以降ほぼ2倍となった。2007年は、当該地域53カ国中49カ国から合計48,892例のHIV感染が報告され、エストニア、ウクライナ、ポルトガルとモルドバ共和国で感染率が最も高かった。	
90156	2009/6/2	90236	アメリカ・トリパノソーマ症	AABB Annual Meeting and TXPO 2008-3	米国で2007年から開始された供血者に対するT. cruziスクリーニング検査の結果、2007年1月29日～2008年1月28日の陽性率は1/30,000であったが、受血者には明白な感染症例はなかった。最も陽性率が高い地域はフロリダ南部であった。	
90158	2009/6/18	90251	アメリカ・トリパノソーマ症	CBER (http://www.fda.gov/cber/gdlns/chagas.htm)	CBERから、輸血用全血、血液成分製剤、ヒト細胞・組織及びヒト細胞・組織由来製剤のTrypanosoma cruziが伝播する危険性を低減するための血清学的検査実施についてのガイダンス案を公表。	2
90158	2009/6/18	90251	アメリカ・トリパノソーマ症	Emerg Infect Dis 2009; 15:653-655	ブラジルで2006年1～11月に発生したアメリカ・トリパノソーマ症のアウトブレイク(178症例)について、調査の結果、アサイー果実を潰す際に、原虫を媒介するサシガメの排泄物が混入した可能性が考えられた。	3
90158	2009/6/18	90251	アメリカ・トリパノソーマ症	ProMED-mail20090406.1328	ベネズエラでグアヴァジュースの摂取によるアメリカ・トリパノソーマ症のアウトブレイクが発生し、同学校に通う児童47名と教師3名が感染。児童3名が死亡。	4
90156	2009/6/2	90236	アメリカ・トリパノソーマ症	Transfusion 2008; 48: 1862-1868	スペイン、カタルーニャ血液銀行は、高リスク供血者におけるシャーガス病スクリーニング計画を実行し、供血者集団でTrypanosoma cruzi(T. cruzi)感染の血清学的陽性率を調査した。その結果、全体の陽性率は0.62%(1770名中11名)で、最も陽性率が高かったのはボリビア人であった(10.2%)。陽性者11名中1名は、シャーガス病流行地域に数年間滞在したことのあるスペイン人であった。非流行国の高リスク供血者にT. cruziスクリーニング検査を実施する必要性がある。	
90156	2009/6/2	90236	ウイルス感染	BusNews online 2008年10月13日	南アフリカ、ヨハネスブルグで3名の死者を出したウイルスは、暫定的に西アフリカのラッサウイルスに近い、齧歯類媒介性アレナウイルスであると特定された。国立感染症研究所と保健省は共同で、このウイルスが体液を介してヒトからヒトに感染するため、「患者の看護に特別な予防的措置が必要である」との声明を発表した。3名の死因を確定するには更なる検査が必要である。	

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
90191	2009/8/26	90395	ウイルス感染	CDC/Travelers' Health 2009年2月4日	日本国内の前立腺がん患者30例の血清のうち2例からGagに対する特異的抗体反応が認められ、そのうち1例からはXMRV (Xenotropic MuLV-related virus)核酸を検出した。また、献血者120例中5例でもGagに対する特異的抗体反応が認められた。日本国内の前立腺がん患者集団中にもXMRV感染が存在することが示唆された。	
90171	2009/7/28	90312	ウイルス感染	N Engl J Med 2009; 360: 2099-2107	New Yorkの62歳の男性は、シカダニウイルスに感染したシカダニの咬傷後に髄膜脳炎で死亡した。これまでシカダニウイルスのヒト感染は報告されていないが、この症例はシカダニウイルスが致命的脳炎の原因でありえることを示している。	5
90167	2009/7/10	90294	ウイルス感染	PLoS Pathogens 2009; 4: e1000455	2008年に南アで発生した致死性出血熱のアウトブレイクにおいて、30年ぶりに新規の旧世界アレナウイルスが分離された。発見された地名(Lusaka, Johannesburg)より、Lujo virusと命名された。	6
90168	2009/7/13	90295	ウイルス感染	ProMED-mail20090129.0400	ユンガンウイルスは、マウスにおいて胎児死亡や奇形を起こすことが知られているが、疫学的データから、ヒトにおいても子宮内胎児死亡に関連していることが示唆された。	7
90156	2009/6/2	90236	ウイルス感染	ProMED-mail20090218.0669	ナイジェリアでは、2008年1月から12月にかけて、229人のラッサ熱感染疑い患者が報告され、30人が死亡している。また、2008年12月～2009年1月に、感染疑い患者及び感染確定患者はそれぞれ60%及び80%増加している。	
90167	2009/7/10	90294	ウイルス性脳炎	CDC/MMWR 2009; 58: 4-7	米国ウエストバージニアで妊婦における初めてのラクロス脳炎ウイルス(LACV)感染が見つり、その後、分娩時の臍帯血からLACV抗体が検出され垂直感染が疑われたが、出生後6ヶ月までLACV感染兆候は見られていない。親が子の血清検体採取を拒否しており感染は確定できていない。	
90156	2009/6/2	90236	ウエストナイルウイルス	ABC Newsletter No.38 2008年10月17日	2008年9月に、イタリアで何年かぶりにヒトのウエストナイルウイルス(WNV)脳炎が2例報告された。1例目はFerrarsとBolognaの間に住む80歳代の女性、2例目はFerrarsに住む60代後半の男性であった。また、ウマ6頭とトリ13羽でWNV感染が確認された。WNV髄膜脳炎の積極的サーベイランスプログラムが開始され、当該地域で供血者スクリーニング用NATが導入された。また、当該地域に1日以上滞在したことのある供血者を28日間供血延期する措置がとられた。	
90158	2009/6/18	90251	ウエストナイルウイルス	CDC(http://www.cdc.gov/ncidod/dvbid/westnile/surv&controlCaseCount08_detailed.htm)	2008年、米国におけるウエストナイルウイルス感染症例は46州から1356例が報告され、うち687例では脳炎や髄膜炎を発症、死亡に至ったのは44例だった。	8
90190	2009/8/24	90392	エボラ出血	WHO (2009年2月3日)	2009年1月23日、フィリピンにおいてブタからの感染と考えられるエボラウイルス・レストン株抗体陽性者が確認され、1月30日、さらに4例の抗体陽性者が確認されている。現在まで抗体陽性者の健康状態は良好であり、過去12ヶ月以内に主だった症状を呈していない。	

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90157	2009/6/18	90249	コクシジオイデス症	CDC/MMWR 2009; 58: 105-109	カリフォルニア州におけるコクシジオイデス症の報告数及び入院数は2000～2006年の間毎年増加しており、1995～2000年の3倍以上(8/10万人)となった。米国のコクシジオイデス症全体の約60%を占めるアリゾナ州でも同様で、2006年には5,535例(91/10万人)と増加している。米国全体でも、1998年の1,697例から2006年には8,917例(6.97/10万人)に増加しており、流行地への訪問や居住歴のあるインフルエンザ様症状や肺炎、播種性感染症の患者では本症が鑑別されるべきである。	
90163	2009/6/25	90272	コレラ	CDC/Travelers' Health 2009年2月4日②	ジンバブエ保健当局からのコレラアウトブレイクの報告。2008年8月28日から2009年1月31日までに61,304例の感染疑い、3,181例の死亡。また、ボツワナ、モザンビーク、ケニヤ、マラウイ、ナミビア、ナイジェリア、ギニアビサウ及びトーゴといった周辺国からも発生が報告されている。	
90156	2009/6/2	90236	バベシア症	2009 Feb 23: New York City, Department of Health	2008年9月以降の6ヶ月間、ニューヨーク市において輸血関連バベシア症の報告急増。市衛生局は医療従事者に対し、3ヶ月以内に輸血又は臓器移植の既往歴があり、発熱/溶血性貧血を呈する患者の鑑別診断にバベシア症を考慮するよう勧告した。	9
90156	2009/6/2	90236	バベシア症	AABB Annual Meeting and TXPO 2008-2	輸血を介したバベシア症死亡例の報告。1998年の1例以降しばらく無かったが、2006年1～10月にはFDAに5例が報告された。生物学的製品逸脱報告サマリーでは、過去10年間にバベシア症関連報告が68件あり、近年この報告が増加傾向にあることは、バベシア症伝播に係る輸血関連リスクが増加していることを示している。	
90170	2009/7/17	90298	バベシア症	Clin Infect Dis 2009; 48: 25-30	バベシア感染に関して、FDAは供血者及び受血者の死亡報告を2005年に2例、2006年に3例、2007年に3例受けていた。受血者は輸血後2.5～7週で症状が進展し、輸血後2ヶ月以内に死亡した。	
90156	2009/6/2	90236	マラリア	AABB Annual Meeting and TXPO 2008-4	オーストラリア赤十字は2005年7月から、マラリア感染のリスクのある供血者に対し、従来の医療歴・渡航歴の収集から、リスクへの暴露を特定した時から最低4ヶ月間のマラリア抗体のスクリーニングを実施する代替戦略を導入した結果、既存の供血者に由来する輸血可能な製剤の製造効率は著しく向上し、輸血伝播マラリア症例の報告もなかった。	
90156	2009/6/2	90236	マラリア	Am J Trop Med Hyg 2009; 80: 215-217	1997年より韓国軍はヒドロキシクロロキン及びプリマキンを用いた予防的化学療法を実施し、マラリア患者の急増を防ぐことができたが、調査登録患者484名中2名にクロロキン耐性Plasmodium vivaxを確認した。	
90163	2009/6/25	90272	マラリア	CDC/MMWR 2009; 58: 229-2	近年、5番目のマラリア原虫として、サルマラリアであるPlasmodium knowlesiのヒトへの感染例がマレーシア及びその周辺において多数確認されており、人畜共通感染症の病原体として新興している可能性が示されている。	
90156	2009/6/2	90236	リケッチア症	CDC/MMWR 2008; 57: 1145-1148	米国ミネソタ州の68歳男性が、2007年10月12～21日に手術後の輸血を受け、敗血症および多臓器不全をきたした後、10月31日に発熱を伴う急性血小板減少症を発現し、11月3～5日の血液検体からPCR及び抗体検査でアナプラズマ症感染が確認された。血液ドナーの1人にA. phagocytophilum陽性がPCR及びIFA検査で確認され、血液ドナーに感染源が確認された初の事例となった。	

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90156	2009/6/2	90236	リケッチア症	JAMA 2008; 300: 2263-2270	中国安徽省でヒト顆粒球性アナプラズマ症(HGA)と症状が一致する患者は、2006年10月30日に発症し、11月5日に死亡した。確定診断はされなかったが、発症する12日前にダニに刺されていた。11月9-11日に、この患者の血液および呼吸器分泌物との直接接触によると疑われる症例9例が報告され、HGAと確定診断された。中国におけるHGA症例の初めての報告である。	
90171	2009/7/28	90312	リケッチア症	第83回日本感染症学会総会 2009年4月23～24日	平成20年8月、仙台市においてリケッチア症を疑う患者が発生した。生検材料を用いたPCRにより陽性であったが、シークエンス解析により、ロシアや中国の患者から報告されているR.heilomgiangensisに一致した。国内に、日本紅斑熱とは異なる紅斑熱ケッチア症が存在することが示された。	10
90163	2009/6/25	90272	リケッチア症	日本細菌学会第82回総会 P2-182	Anaplasma phagocytophilumによるアナプラズマ症の本邦初の症例。2002～2003年の高知県で日本紅斑熱が疑われた18例の血餅から、2例で、A. phagocytophilumに特異的なp44/msp2外膜蛋白遺伝子群のPCR産物が検出された。	
90163	2009/6/25	90272	レトロウイルス	CDC/Travelers' Health 2009年2月4日	日本国内の前立腺がん患者30例の血清のうち2例からGagに対する特異的抗体反応が認められ、そのうち1例からはXMRV (Xenotropic MuLV-related virus)核酸を検出した。また、献血者120例中5例でもGagに対する特異的抗体反応が認められた。日本国内の前立腺がん患者集団中にもXMRV感染が存在することが示唆された。	
90156	2009/6/2	90236	レンサ球菌感染	Transfusion 2008; 48: 2177-2183	米国。ルーチンの細菌培養スクリーニングを実施したプール血小板の輸血を受けた患者が、C群連鎖球菌感染症により死亡した。遡及調査の結果、無症候性の供血者が原因と考えられた。現在の検査法の限界を示す報告。	
90172	2009/7/28	90317	レンサ球菌感染	日本化学療法学会第57回総会 201	50代後半の男性が右母指のウオノメをカッターで自己切除したところ黒変し、その範囲は急速に拡大。右下肢の腫脹が起こり入院。右母指には悪臭と壊疽を伴う重度の蜂巣炎、X線所見で右大腿部にガス像を認めた。Streptococcus dysgalactiae subsp. dysgalactiaeによる初めてのヒト感染例と考えられる。	11
90167	2009/7/10	90294	黄熱	ProMED-mail20090402.1272	サンパウロ奥地において2009年2月より黄熱が流行しており、その中で母子感染が確認された。初の黄熱の母子感染報告である。	
90156	2009/6/2	90236	感染	BMJ 2008; 337: a2622	欧州における2006年の感染症の発生報告はクラミジアが最も多く、以下、ランブル鞭毛虫症、カンピロバクター症、サルモネラ症、結核、流行性耳下腺炎、淋病、C型肝炎、侵襲性肺炎球菌疾患、HIVの順であった。	
90156	2009/6/2	90236	感染	http://www.fda.gov/cber/blood/fatal07.pdf.	2007年度のCBERに報告された供血後及び輸血後の死亡例概要。受血者76件、供血者17件の死亡報告。受血者死亡の内訳は、52件が輸血関連もの、11件が輸血関連性否定できないもの、13件が輸血と関連しないものであった。	

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90156	2009/6/2	90236	感染	http://www.fda.gov/cber/blood/fatal08.pdf.	2005～2008年度のCBERに報告された供血後及び輸血後の死亡例概要。2008年度は、受血者72件、供血者10件の死亡報告。受血者死亡の内訳は、46件が輸血関連もの、8件が輸血関連性否定できないもの、18件が輸血と関連しないもの。微生物感染はパベシア症5件、Staphylococcus aureus、Staphylococcus epidermidisがそれぞれ1件。05～08年度の微生物感染28件中、10件をパベシア症が占めている。	12
90156	2009/6/2	90236	細菌感染	Am J Infect Control 2008; 36: 602	減量法として両耳の上部耳介軟骨に置き鍼治療(Stapling)を受けた16歳の女性が、2週間後に左耳の鍼周囲の紅斑および圧痛を呈した。腫瘍ドレナージ検体の培養および感受性試験の結果、両耳で著しい緑膿菌の生育が認められた。21日間の経口シプロフロキサシン投与により回復した。外耳軟骨は、血流に乏しく特に感染しやすい。耳鍼が危険な緑膿菌感染を起こす可能性があることを医師は認識するべきである。	
90156	2009/6/2	90236	細菌感染	Transfusion 2008; 48: 2348-2355	全血血小板の細菌汚染リスクを低減させるためには、初流血除去及び細菌培養によるスクリーニングが有効な方法であることを示す報告。	
90157	2009/6/18	90249	細菌感染	日本細菌学会第82回総会 P2-182	Anaplasma phagocytophilumによるアナプラズマ症の本邦初の症例。2002～2003年の高知県で日本紅斑熱が疑われた18例の血餅から、2例で、A. phagocytophilumに特異的なp44/msp2外膜蛋白遺伝子群のPCR産物が検出された。	
90158	2009/6/18	90251	BSE	OIE (http://www.oie.int/eng/info/en_esbmonde.htm.)	1989年から2008年までに、世界各国(英国を除く)から国際獣疫事務局(OIE)に報告されたBSEの報告数である。	13
90158	2009/6/18	90251	BSE	OIE (http://www.oie.int/eng/info/en_esbru.htm.)	1987年以前から2008年までに、英国から国際獣疫事務局(OIE)に報告されたBSEの報告である。	14
90156	2009/6/2	90236	クロイツフェルト・ヤコブ病	Emerg Infect Dis 2009; 15: 265-271	弧発性CJD(sCJD)と医学的処置との関連性を解明するために、日本における1999～2008年の期間にCJDサーベイランス委員会に登録された患者について分析した。その結果、sCJD発症前に施行された医学的処置によりプリオン病が感染した証拠はみつからなかった。	
90156	2009/6/2	90236	クロイツフェルト・ヤコブ病	J Neurol Neurosurg Psychiatry 2008; 79: 229-231	オーストリアの39歳男性が感覚異常などの神経症状で入院後、急速に悪化し、4ヶ月後に死亡した。組織学的検査で海綿状変化、神経細胞脱落及びグリオーシスが、免疫組織化学的検査でびまん性シナプティックな異常プリオンの沈着が見られ、CJDと診断された。また患者のPRNPは129Met-Metであった。患者は22年前まで死体由来のヒト成長ホルモン(hGH)製剤治療を受けており、医原性リスクが認められるため、孤発性若年性CJDの可能性も否定できないが、WHO基準により確定医原性CJDと分類された。	
90156	2009/6/2	90236	クロイツフェルト・ヤコブ病	Transfusion Epub 2009 Jan 5	米国。輸血のCJD伝播リスクについて。後にCJD発症した供血者36例と受血者436例を調査。受血者のうち生存91例、死亡329例、不明16例。受血後にCJDを発症した例は特定されず。	15

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
90170	2009/7/17	90298	クロイツフェルト・ヤコブ病	Transfusion; 49(5); 977-984	米国での調査研究の結果は、輸血によるCJD伝播については根拠に欠けるとしている。2004年以降、英国ではvCJDの輸血による伝播が報告され、変異型でないCJDもしくは古典的CJDの伝播のリスクについて懸念が高まってきた。1995年、米国赤十字社はCDCと共同で輸血によるCJD伝播の懸念を評価する詳細な疫学的データを得るために、供血後にCJDと診断された供血者(CJDドナー)の長期後ろ向き調査を開始し、CJDドナーの血液成分を投与された受血者を特定した。本結果からは、CJDの輸血による伝播を示す根拠は示されなかった。CJDドナーによる異常プリオンの輸血伝播のリスクは、vCJDドナーによる伝播のリスクと比べて顕著に低いことを後押しする結果となった。	16
90171	2009/7/28	90312	異型クロイツフェルト・ヤコブ病	Health Protection Agency 2009/05/22	2004年にHealth Protection Agencyは扁桃腺に蓄積されたvCJD関連プリオンタンパク質の大規模な調査により、無症候性vCJD保有率を検討するNational Anonymous Tissue Archive(NATA)を開始。既に63000例の扁桃腺組織の収集・解析を行っており、100000例まで収集する計画であるが、現在のところ陽性サンプルは一つもなかった。	17
90156	2009/6/2	90236	異型クロイツフェルト・ヤコブ病	HPA/News 2009年2月17日	vCJDと関連のない疾患で死亡し、生前にvCJD又は他の神経学的症状を示していなかった男性血友病患者の剖検時に、異常プリオンタンパクが確認された。この男性は、献血後にvCJDを発症したドナー血漿を含む原料から製造された第Ⅷ因子製剤を使用していた。	
90165	2009/6/26	90275	異型クロイツフェルト・ヤコブ病	HPAweb February 17, 2009	1996年に血漿を提供し、その6ヵ月後にvCJDを呈したドナーの血漿由来の第8因子製剤を使用した血友病患者について、この度、検死によりvCJD感染が報告された。血漿分画製剤によるTSE伝播の可能性を示唆する初の報告である。	
90157	2009/6/18	90249	異型クロイツフェルト・ヤコブ病	Lancet Neurology 2009; 8: 57-66	BSEプリオンに対するヒトの感受性についてSNPを解析した。PRNP遺伝子座はプリオン病のいくつかのマーカーと全てのカテゴリーを通じてリスクに強く関連していた。疾病リスクへの主な寄与はPRNP多型コドン129であったが、別の近傍のSNPによってvCJDのリスク増大がもたらされた。	
90156	2009/6/2	90236	異型クロイツフェルト・ヤコブ病	Nature 2009; 457: 1079	最近、非定型BSEが日本、カナダ、米国、複数のヨーロッパ諸国で発生している。非定型BSEの可能性があるプリオン遺伝子の突然変異は豪州や新西蘭でも発生する可能性があり、反芻動物の厳密な飼料管理等、将来のアウトブレイクの防止に必要な規制を緩和すべきではない。	18
90159	2009/6/18	90252	異型クロイツフェルト・ヤコブ病	OIE (http://www.oie.int/eng/info/en_esbmonde.htm.)	1989年から2008年までに、世界各国(英国を除く)から国際獣疫事務局(OIE)に報告されたBSEの報告数である。	
90159	2009/6/18	90252	異型クロイツフェルト・ヤコブ病	OIE (http://www.oie.int/eng/info/en_esbru.htm.)	1987年以前から2008年までに、英国から国際獣疫事務局(OIE)に報告されたBSEの報告である。	

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
90156	2009/6/2	90236	異型クロイツフェルト・ヤコブ病	PLoS ONE 2008; 3: e3017	非定型BSE(BASE)に感染した無症候のイタリアの乳牛の脳ホモジネートをカニクイザルに脳内接種した。BASE接種サルは生存期間が短く、古典的BSEまたはvCJD接種サルとは異なる臨床的展開、組織変化、PrPresパターンを示した。感染牛と同じ国の孤発性CJD患者でPrPが異常なウエスタンブロットを示す4例のうち3例のPrPresに同じ生化学的特徴を認めた。BASEの宿主域における高い病原性および見かけ上孤発性CJDである症例との関連の可能性が示唆された。	
90158	2009/6/18	90251	異型クロイツフェルト・ヤコブ病	ProMED-mail20090108.0076	英国CJDサーベイランスユニットの統計によると、2009年1月5日時点でvCJD死亡患者数総数には変化はなく167例のままであり、英国におけるvCJD流行は減少しつつあるとする見解に一致する。	19
90156	2009/6/2	90236	異型クロイツフェルト・ヤコブ病	Transfusion 2008; 48: Supplement 33A	米国での古典的CJDを発症した供血者計35名に由来する血液成分の受血者430名の追及調査の結果、孤発性CJDが輸血で伝播する証拠は無く、リスクはvCJDと比較して有意に低かった。	
90157	2009/6/18	90249	異型クロイツフェルト・ヤコブ病	Vox Sanguinis 2009; 96: 270	1995年から3回/週でIVIG治療を受けていた61歳女性は、1997年1月～1998年2月の期間に、後にvCJDを発症した供血者由来の製剤を使用していた。この女性の死亡後、剖検により脾臓、リンパ節、脳内のプリオン蛋白を検査したが、検出されなかった。	
90190	2009/8/24	90392	インフルエンザ	FDA/CBER 2009年5月7日	新型インフルエンザ(H1N1)の輸血を介した感染可能性について。輸血により季節性インフルエンザに感染した例はこれまで報告されたことが無く、新型インフルエンザについても報告されていない。現時点で、輸血のメリットは新型インフルエンザの理論的リスクをはるかに上回る。なお、血漿分画製剤については製造工程におけるクリアランスが十分であることが確認されている。	20
90157	2009/6/18	90249	インフルエンザ	MMWR 2009; 58: 1-3	2009/4/17米CDCはカリフォルニア南部の小児2例の熱性呼吸器疾患をブタインフルエンザA(H1N1)感染であると特定した。アマンダジン、リマンダジンに抵抗性があり、過去に報告されていない固有の遺伝子断片の組み合わせが含まれていた。ブタ接触歴は無く感染源は不明。	21
90158	2009/6/18	90251	インフルエンザ	Virus Res. 2009; 140: 85-90	中国のブタからヒト様H1N1インフルエンザウイルスが検出され、ブタがヒトにおけるパンデミックを引き起こす古典的なインフルエンザウイルス保有宿主である証拠が示された。	22
90190	2009/8/24	90392	新型インフルエンザ	WHO/EPR 2009年4月24日, 2009年4月27日 WHO/Media centre 2009年4月27日	・米国、メキシコにおけるインフルエンザ様疾患について:米国政府は米国内の7人の豚インフルエンザA/H1N1確定症例(5人がカルフォルニア、2人がテキサス)と9人の疑いがある症例を報告した。死亡症例は報告されていない。メキシコ政府は3つの別々の事例を報告しており、メキシコ連邦区ではインフルエンザ様疾患が挙がり始め、4月23日までに854人以上の肺炎が発生し、うち、59人は死亡している。 ・豚インフルエンザupdate3:豚インフルエンザA(H1N1)の発生状況は刻々と変化しており、2009年4月27日現在、米国では40症例(死亡例なし)、メキシコでは7症例の死亡を含む26症例で同ウイルスへの感染が確認された。 ・豚インフルエンザ:国際保健規則(2005年)の元設立された緊急委員会が2009年4月27日、2回目となる会合を開催した。	23

血対ID	受理日	番号	感染症(PT)	出典	概要	新出文献No.
90170	2009/7/17	90298	新型インフルエンザ(H1N1)	CBER 2009年4月30日	新型インフルエンザ(H1N1)の輸血を介した感染可能性について。輸血により季節性インフルエンザに感染した例はこれまで報告されたことが無く、新型インフルエンザについても報告されていない。現時点で、輸血のメリットは新型インフルエンザの理論的リスクをはるかに上回る。なお、血漿分画製剤については製造工程におけるクリアランスが十分であることが確認されている。	24
90185	2009/8/24	90387	新型インフルエンザ(H1N1)	CIDRAP News 2009/04/24	2009年4月24日、CDCはメキシコでの致死的な呼吸器疾患発症例から分離されたウイルスは米国の患者のブタインフルエンザA/H1N1株と一致したと発表した。米国での感染例は現在8例である。メキシコ政府の公式発表では、メキシコシティーにおいて854例以上の肺炎患者が発生し、そのうち59例が死亡している。	25
90171	2009/7/28	90312	新型インフルエンザ(H1N1)	MMRW 2009; 58: 521-524	05～06年、06～07年、07～08年の季節性インフルエンザワクチン接種コホートの保存ペア血清を用いて、新型インフルエンザウイルスの交差反応性を検討した。18-64歳ではワクチン接種前に6～9%、60歳以上では33%が交差反応を示した。ワクチン接種後には交差反応を示した例が18-64歳で2倍程度に増え、60歳以上では全く増えなかった。	26
90163	2009/6/25	90272	新型インフルエンザ(H1N1)	MMWR 2009; 58: 1-3	2009年4月、南カリフォルニア周辺郡の小児2人がブタインフルエンザA(H1N1)ウイルスに感染した。2症例から検出されたウイルスは、米国やそれ以外の国でも報告されたことがないブタ又はヒトインフルエンザウイルスの遺伝子片を併せ持っていた。いずれの小児もブタとの接触はなく、感染源は不明である。	27
90171	2009/7/28	90312	新型インフルエンザ(H1N1)	Sience 2009; 10.1126/SCIENCE.1176062	新型インフルエンザA(H1N1)ウイルスは世界中に急速に広まっている。パンデミックの可能性を判断するのはデータが限られているため難しいが、適切な保険対応を伝えるには必須である。メキシコでの大流行、国際的な広がりの早期情報およびウイルス遺伝的変異について分析することにより、感染力と重症度の早期評価を実施した。	28
90172	2009/7/28	90317	新型インフルエンザ(H1N1)	共同通信HP 2009年4月28日	WHOは新型インフルエンザのPandemic Alertをフェーズ4に引き上げた。	29
90172	2009/7/28	90317	新型インフルエンザ(H1N1)	WHO 2009年4月28日	WHOは新型インフルエンザのPandemic Alertをフェーズ4に引き上げた。	30
90168	2009/7/13	90295	新型インフルエンザ(H1N1)	厚生労働省 新型インフルエンザに関する報道発表資料 2009年5月16日	兵庫県神戸市における新型インフルエンザ(インフルエンザA／H1N1)が疑われる患者発生についての報告。国内最初の新型インフルエンザ患者が確認された。患者は10代後半の男性。本人に渡航歴はない。国立感染症研究所からの検査の結果、A型(＋)、ヒトH1(－)、ヒトH3(－)、新型H1(+)であったため、新型インフルエンザ(インフルエンザA/H1N1)が否定でず、新型インフルエンザが疑われる患者として神戸市に届出があった。患者は感染症法に基づき、神戸市内の感染症指定医療機関に入院した。	31

別紙様式第2-1

No. 31

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. 3. 18	該当なし	
一般的名称	解凍人赤血球濃厚液		研究報告の公表状況	山田典栄, 四柳宏, 小板橋俊, 長瀬良彦, 高橋秀明, 奥瀬千晃, 安田清美, 鈴木通博, 伊東文生, 飯田清美, 飯野四郎, 小池和彦. 第37回日本肝臓学会東部会; 2008 Dec 3-4; 東京.	公表国 日本	
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社)					

研究報告の概要

○首都圏におけるB型急性肝炎の最近の動向

目的:わが国のB型急性肝炎(AH-B)はいまだ減少傾向にない。近年は慢性化率の高いgenotype AによるAH-Bが増加している。今回、2006年以降のB型急性肝炎の実態を2005年以前と比較し、現行のHBワクチンの有効性について検討した。

方法:首都圏3施設において診療したAH-B146例(1994-2005年109例、2006-2008年37例)に対しgenotype、感染経路、臨床経過を検討した。また、ワクチンの予防効果を検討するため63例に対し、a determinant regionのアミノ酸配列を決定した。

結果:(1)genotypeは1994-2005年ではA38%、B10%、C51%、D1%であった。2006-2008年ではA70.3%、B13.5%、C13.5%、F2.7%であり、Aの割合が急増していた。2006-2008年のgenotypeAの感染経路は同性間性交渉54%、異性間性交渉25%、不明21%であり、性交渉の相手は不特定の場合が多かったが、日本人特定パートナーからの感染を2例認めた。genotypeA26例中、慢性化1例、慢性化阻止のため核酸アナログを使用した2例を認めた。HIV抗体検査を37例中14例で施行し、陽性の2例はHBVgenotypeAだった。(2)ワクチン株3株間でAA126、131、143のアミノ酸配列の不一致を認めた。a determinant regionのアミノ酸配列は、genotype間で最高11個異なり、genotypeAの1例でVaccine-Induced Escape Mutantである145番のアミノ酸変異、genotypeCの4例で131番の変異を認めた。

考察:首都圏においてHBVgenotypeAは急増しており、新規日本人キャリアからの二次感染が疑われる。genotype間でアミノ酸配列は大きく異なり、ワクチンによる感染予防のためには十分な抗体価を誘導する必要がある。Vaccine-Induced Escape Mutantの蔓延状況を調査する必要がある。

結論:genotypeAのB型肝炎は急速に広がりつつあり、現行のワクチンの感染防御に関する検討、ユニバーサルワクチンを含めた感染対策の検討が必要である。

使用上の注意記載状況・その他参考事項等

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

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
首都圏においてHBVgenotypeAは急速に増加しており、新規日本人キャリアからの二次感染が疑われることが急性B型肝炎症例の検討から明らかになったとの報告である。	日本赤十字社では、HBs抗原検査及びHBc抗体検査を実施することに加えて、HBVについて20プールでスクリーニングNATを行い、陽性血液を排除している。また、これまでの凝集法と比べて、より感度の高い化学発光酵素免疫測定法(CLEIA)及び精度を向上させた新NATシステムを導入した。HBV感染に関する新たな知見等について今後も情報の収集に努める。

O-85 首都圏における B 型急性肝炎の最近の動向

○山田典栄1, 四柳 宏1, 小板橋俊1, 長瀬良彦2, 高橋秀明1, 奥瀬千晃1, 安田清美1, 鈴木通博1, 伊東文生1, 飯野四郎1, 小池和彦3
聖マリアンナ医大消化器・肝臓内科1, 東京大感染症内科2, 川崎市立多摩病院消化器肝臓内科3, 清川病態肝臓病研究センター4

【目的】わが国における B 型急性肝炎 (AH-B) はいまだ減少傾向にない. さらに近年は慢性化率の高い genotype A による AH-B が増加している. 今回, 2006 年以降の B 型急性肝炎の実態について調査し 2005 年以前と比較を行った. また, 現行の HB ワクチンの有効性について検討した.

【方法】首都圏 3 施設において診療した AH-B 146 例 (1994-2005 年 109 例, 2006-2008 年 37 例) に対し genotype, 感染経路, 臨床経過に関する検討を行った. また, ワクチンの予防効果を検討するため 63 例に対し, a determinant region のアミノ酸配列を決定した.

【結果】(1) genotype は 1994 年から 2005 年では type A 38%, type B 10%, type C 51%, type D 1% であった. 2006 年から 2008 年では type A 70.3%, type B 13.5%, type C 13.5%, type F 2.7% であり, type A の割合が急増していた. 2006 年から 2008 年の type A の感染経路は同性間性交渉 54%, 異性間性交渉 25%, 不明 21% であった. 性交渉の相手は不特定の場合が多かったが日本人特定パートナーからの感染を 2 例認めた. Type A 26 例中, 慢性化 1 例, 慢性化阻止のため核酸アナログを使用した症例 2 例を認めた. HIV 抗体検査を 37 例中 14 例で施行し 2 例で HIV 陽性でありいずれも HBVtype A であった. (2) ワクチン株 3 株間で AA126, 131, 143 のアミノ酸配列の不一致を認めた. A determinant region のアミノ酸配列は, genotype 間で最高 11 個異なり, アミノ酸の最大性・最小性および 2 次構造も異なっていた. また Type A の 1 例で Vaccine-Induced Escape Mutant として知られる 145 番のアミノ酸変異, type C の 4 例で 131 番のアミノ酸変異を認めた.

【考察】首都圏において HBV type A は急速に増加しており, 新規日本人キャリアからの二次感染が生じていることが疑われる. Genotype 間でのアミノ酸配列は大きく異なっており, ワクチン接種による B 型肝炎の予防のためには十分な抗体価を誘導する必要がある. また, Vaccine-Induced Escape Mutant の蔓延状況を調査する必要がある.

【結論】Genotype A の B 型肝炎は急速に広がりつつあり, 現行の HB ワクチンの感染防御に関するさらなる検討, およびユニバーサルワクチンを含めた感染対策を検討する必要がある.

O-86 抗 HIV 療法後の免疫再構築により B 型慢性肝炎の急性増悪をきたしたと考えられた 1 例

○吉野有紀子, 本間史子, 勅江恭子, 坂本夏美, 齋藤広信, 阿部和道, 高橋敏史, 横川眞子, 入澤篤志, 大平弘正
福島県立医科大学内科学第 2 講座

【症例】72 歳男性

【主訴】発熱

【既往歴】60 歳時: B 型慢性肝炎で 2 か月間入院. 輸血歴なし.

【家族歴】肝疾患なし.

【生活歴】喫煙: なし. 飲酒: 機会飲酒.

【海外渡航歴】60 歳頃から頻回にタイ, ミャンマーへ旅行.

【現病歴】

平成 19 年 2 月より 39℃ の発熱が出現し 4 月 11 日近医に入院. 抗生剤で改善に乏しく抗 HIV 抗体陽性であったため, 4 月 25 日当院内科を紹介された. 血液検査でトランスアミナーゼ正常, WBC 4100/μl, Ly 6% (CD4 39/μl), HBs 抗原陽性, HBs 抗体陰性, HBc 抗体陽性, HBe 抗原陰性, HBe 抗体陰性, HBV-DNA (TMA) 8.7 LGE 以上, HBV genotype, Ba, precore 野生型, core promotor 変異型, HAV IgM 陰性, HCV 抗体陰性, CMV IgM 陰性, CMV IgG 陽性, HIV-1 RNA 120,000 copies/ml であった. 5 月 16 日よりエムトリシタビン・フマル酸テノホビルジソプロキシル (TDF/FTC), リトナビル, 経口アタザナビルによる抗 HIV 療法が開始. 6 月 20 日, AST 92 IU/l, ALT 95 IU/l, ALP 309 IU/l, TB 22 mg/dl と肝障害が出現. HBV-DNA (TMA) は 5.8 LGE と低下していた. 7 月 4 日 AST 503 IU/l, ALT 657 IU/l, ALP 473 IU/l, TB 38 mg/dl と肝障害の増悪を認め当科紹介され入院.

【入院後経過】

肝機能障害の進行は CD4 の増加, HBV-DNA 量の低下の時期と一致しており, 抗 HIV 療法後の免疫再構築による B 型慢性肝炎の急性増悪と考えられた. TDF/FTC を内服していたため SNMC 投与にて経過観察していたところ肝機能は徐々に改善し 7 月 12 日に退院となった.

【考察】

HIV/HBV 重複感染患者における抗 HIV 療法は, HBV にも抗ウイルス効果を示す TDF を含む多剤併用療法 (HAART) が考慮される. HAART の効果がみられた際に, 免疫再構築に関連した免疫応答の改善が起こり, 細胞傷害性キラー T 細胞などを介する HBV 排除のため肝機能の悪化をみる場合がある. 本症例も臨床経過から免疫再構築による肝機能障害と考えられた. HIV/HBV 重複感染患者の治療は, 薬剤耐性の問題や HAART の longterm 使用に伴う HBV 増殖の問題などがあり, 個々の症例の病態に応じた治療計画が必要である. 当科で経験した HIV/HBV 重複感染患者の経過と問題点について若干の文献的考察を加えて報告する.

別紙様式第2-1

No. 11

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. 4. 10	該当なし	
一般的名称	人赤血球濃厚液		研究報告の公表状況	FDA, CBER. Available from: http://www.fda.gov/cber/gdlns/chagas.htm	公表国 米国	
販売名(企業名)	赤血球濃厚液-LR「日赤」(日本赤十字社) 照射赤血球濃厚液-LR「日赤」(日本赤十字社)					

研究報告の概要

○業界向けガイダンス案－輸血用全血・血液製剤およびヒト細胞・組織およびヒト細胞・組織由来製剤(HCT/Ps)の*Trypanosoma cruzi*が伝播する危険性を低減するための血清学的検査の使用

FDAは、輸血用全血・血液成分製剤、ヒト細胞・組織及びヒト細胞・組織由来製剤(HCT/Ps)の*Trypanosoma cruzi* (*T. cruzi*)が伝播する危険性を低減するための血清学的検査実施を勧告する。

・全ての供血に対し、供血者血液を用いて認可された*T.cruzi*抗体のスクリーニングを行う。

・再検査にて*T.cruzi*抗体陽性となった供血者及びシャーガス病の既往がある供血者は供血無期延期とし、その旨を本人に通知する。

・認可された確認検査の手段が無いことから、再検査で陽性となった供血者についてのリエントリーは推奨しない。

・再検査で陽性となった供血者には、感染の可能性について通知し、専門医や地域の保健機関等を紹介し、医学的診断検査に基づいたカウンセリングを実施する。

・認可された試験法では、*T.cruzi*以外の病原体との交差反応が認められることがあるため、リーシュマニア症等の*T.cruzi*以外の病原体への曝露や、スクリーニング検査の偽陽性などについても検討することが望ましい。

・再検査にて陽性となった供血者の一連の供血については製剤を確保し、廃棄又は研究用に転用とする。

・過去の供血についてはルックバック(製剤の回収と受血者への通知)を実施する。

・認可された*T.cruzi*検査法を用いて血液検査を行うこと。認可された検査法以外であっても、*T.cruzi*抗体陰性となった場合は、ドナーの適格性決定に使用してよい。陽性となった場合はドナー不適格とする。

報告企業の意見	今後の対応
米国FDAより、輸血用全血・血液成分製剤、ヒト細胞・組織及びヒト細胞・組織由来製剤(HCT/Ps)の*Trypanosoma cruzi*が伝播する危険性を低減するための血清学的検査実施についてのガイダンス草案が策定されたとの報告である。	日本赤十字社は、輸血感染症対策として献血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、シャーガス病の既往がある場合には献血不適としている。日本在住の中南米出身献血者については、厚生労働科学研究「献血血の安全性確保と安定供給のための新興感染症等に対する検査スクリーニング法等の開発と献血制限に関する研究」班と共同して検討する予定である。今後も引き続き情報の収集に努める。

使用上の注意記載状況・その他参考事項等

赤血球濃厚液-LR「日赤」
照射赤血球濃厚液-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

(2)

Guidance for Industry

Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Whole Blood and Blood Components for Transfusion and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance are available from the Office of Communication, Outreach and Development (OCOD) (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
March 2009

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Guidance for Industry

Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Whole Blood and Blood Components for Transfusion and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, FDA, are notifying you, establishments that manufacture Whole Blood and blood components intended for use in transfusion, and establishments that make eligibility determinations for donors of HCT/Ps, about FDA approval of a Biologics License Application (BLA) for an enzyme-linked immunosorbent assay (ELISA) test system for the detection of antibodies to *Trypanosoma cruzi* (*T. cruzi*). This test is intended for use as a donor screening test to reduce the risk of transmission of *T. cruzi* infection by detecting antibodies to *T. cruzi* in plasma and serum samples from individual human donors, including donors of Whole Blood and blood components intended for use in transfusion, and HCT/P donors (living and cadaveric (non-heart beating)). This guidance document does not apply to the collection of Source Plasma.

In addition, we are providing you with recommendations for unit and donor management, labeling of Whole Blood and blood components, and procedures for reporting implementation of a licensed *T. cruzi* test at your facility or at your contract testing laboratory, as required for blood establishments under Title 21 Code of Federal Regulations 601.12 (21 CFR 601.12). For establishments that make donor eligibility determinations for HCT/P donors, we are notifying you that we have determined *T. cruzi* to be a relevant communicable disease agent under 21 CFR 1271.3(r)(2), and are providing you with recommendations for testing and screening donors for antibodies to *T. cruzi*.

The recommendations made in this guidance with respect to HCT/Ps are in addition to recommendations made in the document entitled "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)," dated August 2007 (Ref. 1).

We recommend that you implement the recommendations provided in this guidance within one year after a final guidance is issued.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Chagas disease is caused by the protozoan parasite, *T. cruzi*. The disease is found primarily in Mexico and Central and South America; the pathogenic agent has rarely been reported to cause human infection in the United States (U.S.) by natural vector transmission (Ref. 2). Natural infections are transmitted mainly when the feces of certain blood sucking insects (triatomine bugs, commonly referred to as kissing or chinch bugs) that harbor the infection are rubbed into a bug bite, other wound, or directly into the eyes or mucous membranes. Other primary forms of transmission include congenital (mother to unborn infant), organ transplantation, and blood transfusion. Current estimates are that at least 11 million persons in Mexico and Central and South America carry the parasite chronically and could present a potential source of infection should they become donors. The presence of the pathogenic agent in U.S. and Canadian donors is increasing due to immigration of infected individuals from endemic areas. Some experts estimate that there may be as many as 100,000 persons unknowingly infected with *T. cruzi*, who reside in the U.S. and Canada.

Vector-borne infections are mostly mild in the acute phase and then persist throughout life, usually without symptoms. Acute infection in patients with compromised immune systems, for example, from cancer therapy or organ transplantation, can be very serious and sometimes fatal. Treatment options are limited, but are most effective early in the infection. The lifetime risk of severe cardiac complications (cardiomegaly, heart failure and arrhythmias) or intestinal disorders (megacolon, megaesophagus) in infected individuals averages about 30% (range of 10 to 40% depending on a variety of factors) and may occur many years after the initial infection. During the acute phase of vector-borne Chagas disease, parasites are found in skin lesions at the site of transmission. The parasites are then spread through the bloodstream to various tissues, particularly skeletal muscle (Ref. 3). During the chronic stage of Chagas disease, most persons who harbor the parasite are asymptomatic and unaware of their infection. During this phase, parasites have been demonstrated in muscle (especially cardiac muscle), nerves, and digestive tract, but there has been very little investigation of tissue distribution during that phase (Refs. 3 through 10).

A. Donor Screening Tests for Chagas Disease in the United States

At the September 1989 Blood Products Advisory Committee (BPAC) meeting, the committee recommended testing donors of Whole Blood and blood components for Chagas disease when a suitable test became available. In a 1995 BPAC meeting, the committee considered whether the performance characteristics of the two FDA-approved tests then available for diagnosis of Chagas disease would be suitable for blood donor screening. The committee concluded that the tests discussed were not suitable for blood donor screening. Furthermore, the committee sought clarification of the criteria that FDA would use to license a Chagas test for donor screening. At the September 2002 meeting of BPAC, FDA presented its current considerations on the regulatory pathway and standards for licensing a donor screening test for Chagas disease and encouraged manufacturers to develop tests based on those considerations (Ref. 11).

In December 2006, FDA granted a license to one manufacturer of an ELISA test system for the detection of antibodies to *T. cruzi* in individual living blood and HCT/P donors. Since the end of January 2007, a number of blood centers representing a large proportion of U.S. blood collections have been testing donors using this licensed assay. In February 2009, FDA licensed this ELISA test system for the detection of antibodies to *T. cruzi* in cadaveric (non-heart beating) HCT/P donors.

Blood donor testing by an ELISA test system identifies donors that are repeatedly reactive for antibodies to *T. cruzi*. The presence of antibodies to *T. cruzi* is strong evidence that a donor is infected with this parasite. Most donors that are repeatedly reactive by an ELISA test system for antibodies to *T. cruzi* have chronic, asymptomatic infections acquired years earlier during residence in areas endemic for *T. cruzi*. Therefore, prior donations from a donor who is repeatedly reactive on an ELISA test system were likely to harbor *T. cruzi* parasites.

At the April 2007 BPAC meeting, FDA requested comments on scientific issues related to the implementation of blood donor testing for infection with *T. cruzi* (Ref. 12). Issues discussed by the committee included the need for additional data on the incidence and risk of transmission of *T. cruzi* by transfusion, the severity of Chagas disease, the performance of the antibody test, and, the lack of a licensed supplemental test for confirmatory testing.

The committee also commented on the design of research studies to validate a strategy for selective testing of repeat blood donors. The committee noted that a period of universal testing of all blood donors would generate critical data on the prevalence of *T. cruzi* infections in donors and that donor questions for selective donor screening needed validation.

B. Risk of *T. cruzi* Infection from Transfusion of Whole Blood and Blood Components

Blood donations from individuals from endemic areas are the primary source of risk for *T. cruzi* infection from transfusion. Studies in the mid-1990s (Ref. 1) estimated that the rate of seropositive blood donors in the U.S. ranged from 1 in 5400 to 1 in 25,000, depending on where the studies were conducted. However, more recent studies suggest that these rates have increased in the areas where donor testing has been performed over a period of time. For example, a rate of 1 in 2000 was found recently in the Los Angeles metropolitan area (Ref. 14). Transfusion transmission in endemic areas has been a major public health concern, and many countries considered endemic for *T. cruzi* infection screen blood donors for the presence of antibody. Therefore, in response to changes in donor demographics, we are now recommending blood donor testing in the U.S.

In the U.S. and Canada, only seven cases of transfusion-transmitted *T. cruzi* infections (Refs. 15 through 19) and five cases of infection from organ transplantation (Refs. 20 and 21) have been documented. However, transmission in immunocompetent patients is not likely to be apparent, and in many cases, even if symptoms appear, infection may not be recognized (Ref. 22).

Studies in blood centers which question donors about birth and/or residence in a *T. cruzi*-endemic country have shown such questions to be incompletely effective at identifying the seropositive donors. Studies also have looked at the rate of transfusion transmission from *T. cruzi* antibody-positive individuals. Published lookback studies in the U.S. and in Mexico of 22 transfusion recipients of seropositive donations, identified five of these recipients (22.7%) who later tested positive for antibodies suggesting transfusion transmission of *T. cruzi* (Refs. 18, 23 and 24). This transmission rate of 22.7% is consistent with the literature from Latin America on rates of blood-borne transmission from seropositive donors in Mexico and Central and South America (Ref. 25). However, we are aware that lookback studies conducted using the licensed ELISA test indicate that the risk of *T. cruzi* by transfusion of a seropositive unit in the U.S. may be much lower risk than previously thought. We note that these studies have confirmed the demographic characteristics of the typical seropositive donor as described in the first two paragraphs of section II. However, the data also suggest that there are seropositive individuals who acquired their infections within the U.S. (Ref. 26). Despite this new data, the rate of transfusion transmission of *T. cruzi* in the U.S. continues to be uncertain because of the limited number of studies conducted to date and the rate of transfusion transmission remains under investigation.

C. Risk of *T. cruzi* Infection to Recipients of Donated HCT/Ps

Based on the risk of transmission, severity of effect, and availability of appropriate screening measures and/or tests, we have determined *T. cruzi*, the agent for Chagas disease, to be a relevant communicable disease agent or disease under 21 CFR 1271.3(r)(2). This determination was based on the following information.

Contains Nonbinding Recommendations

Draft – Not for Implementation

1. Risk of Transmission

There is a risk of transmission of *T. cruzi* by HCT/Ps and there has been sufficient incidence and/or prevalence to affect the potential donor population.

Recognizing the risk of transmission from donated HCT/Ps, countries endemic for *T. cruzi* infection have instituted various practices to minimize transmission through transfusion or transplantation including screening donors for the presence of *T. cruzi* antibodies. Further, when human leukocyte antigen-matched bone marrow is obtained from an infected individual, the donor receives anti-parasitic treatment before the bone marrow is taken for transplantation. The World Health Organization recommends that:

- a heart from an infected donor not be transplanted;
- a liver from an infected donor only be transplanted to recipients already positive for Chagas disease, except in emergency cases; and
- when other organs are transplanted from a Chagas-positive donor, the recipient should receive prophylactic treatment for Chagas disease (Ref. 3).

Published data regarding the transmissibility of *T. cruzi* indicate that vertical transmission (congenitally from mother to infant), oral transmission (through breast milk or contaminated food) and conjunctival transmission (from contact with contaminated hands) have occurred (Ref. 3). In animal studies, *T. cruzi* has been shown to infect multiple tissues, including skeletal muscle, heart, bladder, peripheral nerve, liver, spleen, adrenal gland, brain, adipose tissue, ocular tissue, osteoblasts, chondroblasts, macrophages, and fibroblasts (Refs. 27 through 30). Human placental cells also have been experimentally infected with *T. cruzi* (Ref. 31). As noted previously in this section, *T. cruzi* has been transmitted via blood transfusions and organ transplantation (Refs. 20 through 22, and 32).

At the BPAC meeting of April 26, 2007, the committee noted that, though some HCT/Ps are processed in a manner that might inactivate *T. cruzi* in HCT/Ps from seropositive donors, current data are insufficient to identify specific effective processing methods that consistently render HCT/Ps free of *T. cruzi*. The committee concluded that, absent such data, it would be prudent to test HCT/P donors to decrease the risk of transmitting infection with *T. cruzi* (Ref. 12).

Information about prevalence of *T. cruzi* in the U.S. is provided in section II.B. of this document.

2. Severity of Effect

T. cruzi infections can be fatal or life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

3. Availability of Appropriate Screening and/or Testing Measures

Appropriate screening measures have been developed for *T. cruzi*, such as the medical history interview. (Screening measures for *T. cruzi* are discussed in section IV.A. of this document.)

A donor screening test for *T. cruzi* has been licensed and labeled for use in testing blood specimens from living and cadaveric donors of HCT/Ps (see section IV.B. of this document). You must use a donor screening test for *T. cruzi* that is specifically labeled for cadaveric specimens instead of a more generally labeled donor screening test when applicable and when available (21 CFR 1271.80(c)). Current FDA-licensed, cleared or approved donor screening tests for use in testing HCT/P donors are listed at http://www.fda.gov/cber/tissue/prod.htm.

III. RECOMMENDATIONS FOR DONORS OF WHOLE BLOOD AND BLOOD COMPONENTS INTENDED FOR USE IN TRANSFUSION

A. Blood Donor Testing and Management

1. Donor Testing

We recommend testing of all donations of allogeneic units of blood using a licensed test for antibodies to *T. cruzi*. You must follow the regulations under 21 CFR 610.40(d) for determining when autologous donations must be tested.

2. Donor Deferral

We recommend that all donors who are repeatedly reactive on a licensed test for *T. cruzi* antibody or who have a history of Chagas disease be indefinitely deferred and notified of their deferral.

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3. Confirmatory Testing and Donor Reentry

At this time, there is no FDA licensed supplemental test for antibodies to *T. cruzi* that can be used for confirmation of true positive screening test results. FDA is not recommending reentry criteria for blood donors deferred indefinitely on the basis of a repeatedly reactive screening test for antibodies to *T. cruzi* due to the absence of a licensed supplemental test for antibodies to *T. cruzi*.

4. Donor Counseling and Physician Referral

We recommend that donors who are repeatedly reactive using a licensed test for antibodies to *T. cruzi* be informed about the likelihood and medical significance of infection with *T. cruzi*. Additional medical diagnostic testing may provide information useful in donor counseling.

All repeatedly reactive donors should be referred to a physician specialist. It also may be useful to refer them to their state and local health departments or to other appropriate community resources.

5. Further Testing of Repeatedly Reactive Donors for Cross–Reacting Diseases

Because the licensed test has demonstrated some reactivity in donors infected with pathogens other than *T. cruzi*, we recommend that medical follow up be considered for donors who are repeatedly reactive by the licensed test for antibodies to *T. cruzi* but who have no apparent basis for exposure to *T. cruzi* or who have negative results on more specific medical diagnostic tests. For example, testing for leishmaniasis may be appropriate in persons with geographic risk for exposure to *Leishmania* parasites and who appear to have a falsely reactive screening test for antibodies to *T. cruzi*.

B. Product Management

1. Index Donations

We recommend that blood components from repeatedly reactive index donations be quarantined and destroyed or used for research. Components determined to be unsuitable for transfusion must be prominently labeled: "NOT FOR TRANSFUSION," and the label must state the reason the unit is considered unsuitable (e.g., the component is positive for *T. cruzi* (21 CFR 606.121(f)).

2. Lookback (Product Retrieval and Recipient Notification)

Within 3 calendar days after a donor tests repeatedly reactive by a licensed test for *T. cruzi* antibody, you should:

- identify all in-date blood and blood components previously donated by such a donor, going back either 10 years (or indefinitely where electronic records are available), or else 12 months prior to the most recent time that this donor tested negative with a licensed test for *T. cruzi* antibody, whichever is the lesser period (the lookback period);
- quarantine all previously collected in-date blood and blood components held at your establishment; and
- notify consignees of all previously collected in-date blood and blood components to quarantine and return the blood components to you or to destroy them.

In addition, when you identify a donor who is repeatedly reactive by a licensed test for *T. cruzi* antibodies and for whom there is additional information indicating risk of *T. cruzi* infection, such as geographical risk for exposure in an endemic area, or medical diagnostic testing of the donor, we recommend that you:

- notify consignees of all previously distributed blood and blood components collected during the lookback period; and
- if blood or blood components were transfused, encourage consignees to notify the recipient's physician of record of a possible increased risk of *T. cruzi* infection.

We recommend that when there is additional information indicating risk of *T. cruzi* infection you make such notifications within 12 weeks of obtaining the repeatedly reactive test result.

There currently is no licensed *T. cruzi* supplemental test. When such a test is available, a positive test result will provide additional information indicating risk of *T. cruzi* infection.

Retrospective Review of Records

If you are a blood establishment that implemented screening with a licensed test for antibodies to *T. cruzi* prior to the effective date of this guidance, you may wish to perform a retrospective review of records to identify donors:

- with repeatedly reactive test results by a licensed test for *T. cruzi* antibodies; and
- for whom there is additional information indicating risk of *T. cruzi* infection, such as geographical risk for exposure in an endemic area, or medical diagnostic testing of the donor. There currently is no licensed *T.*

Contains Nonbinding Recommendations

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If a donor is identified at risk of infection during the retrospective review, you may want to consider performing all the lookback actions described above.

3. Autologous Donations

Although autologous use of blood does not increase a patient's/donor's risk of illness from a pre-existing infection, FDA regulations under 21 CFR 610.40(d) and (e) require testing of autologous blood donors under certain circumstances to prevent inadvertent allogeneic exposures to unsuitable units.

a. We recommend that blood components from autologous donors that are repeatedly reactive by a licensed test for *T. cruzi* antibody be released for autologous use only with approval of the autologous donor's referring physician. Establishments should provide the results of additional testing for antibodies to *T. cruzi*, as available to the autologous donor's referring physician.

b. Each autologous donation must be labeled as required under 21 CFR 610.40(d)(4), as appropriate. Given the seriousness of *T. cruzi* infections, autologous donations that are repeatedly reactive by a licensed test for *T. cruzi* antibody must bear a biohazard label as required under 21 CFR 610.40(d)(4).

4. Circular of Information

Consistent with other donor screening tests, the instruction circular, also known as the "Circular of Information" must be updated to state that a licensed test for antibodies to *T. cruzi* was used to screen donors and that the results of testing were negative (21 CFR 606.122(h)).

5. Biological Product Deviation Report and Fatality Report

Under 21 CFR 606.171, licensed manufacturers, unlicensed registered blood establishments, and transfusion services must report any event and information associated with the manufacturing, if the event either represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of the product; or represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of the product, and it occurs in your facility or another facility under contract with you and involves distributed blood or blood components. For additional information regarding reporting, you may refer to

FDA guidance, "Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments," dated October 2006 (Ref. 33). Also, when a complication of blood collection or transfusion (e.g., involving *T. cruzi*) is confirmed to be fatal, you must notify FDA in accordance with 21 CFR 606.170(b).

C. Reporting the Test Implementation

1. If you are a licensed blood establishment and you begin using a licensed serological test for the detection of antibodies to *T. cruzi* according to the manufacturer's product insert at your facility, then you must notify us of the testing change in your Annual Report (AR), in accordance with 21 CFR 601.12(d). If you already have an approved supplement to your BLA to use a contract laboratory to perform infectious disease testing of blood products, and the contract laboratory will now perform a serological test for antibodies to *T. cruzi*, you must report this change in your AR (21 CFR 601.12(d)).

2. If you are a licensed blood establishment and you use a new contract laboratory to perform a serological test for antibodies to *T. cruzi* (and the laboratory already performs infectious disease testing for blood products), then you must report this change by submission of a "Changes Being Effected" supplement, in accordance with 21 CFR 601.12(c)(1) and (c)(5). If your contract laboratory has not previously performed infectious disease testing for blood products, then you must report this change as a major change in a prior approval supplement, in accordance with 21 CFR 601.12(b).

IV. RECOMMENDATIONS FOR DONORS OF HCT/Ps

A. Donor Screening—Risk Factors or Conditions

Under 21 CFR 1271.75(d), you must determine to be ineligible any potential donor who is identified as having a risk factor for or clinical evidence of relevant communicable disease agents or diseases. Ineligible potential donors include those who exhibit one or more of the following conditions or behaviors.

- Persons who have had a medical diagnosis of *T. cruzi* infection based on symptoms and/or laboratory results.
- Persons who have tested positive or reactive for *T. cruzi* antibodies using an FDA-licensed or investigational *T. cruzi* donor screening test (Ref. 1).

B. Donor Testing

1. You must test blood specimens from all HCT/P donors for antibodies to *T. cruzi* using an FDA-licensed donor screening test (21 CFR 1271.80(c)).

2. Any HCT/P donor whose specimen tests negative (or non-reactive) for antibodies to *T. cruzi* may be considered to be negative (or non-reactive) for purposes of making a donor eligibility determination.

3. Any HCT/P donor whose specimen tests positive (or reactive) for antibodies to *T. cruzi* is ineligible to be a donor (21 CFR 1271.80(d)(1)).

V. REFERENCES

1. Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), August 2007. http://www.fda.gov/cber/tissue/docs.htm

2. Dorn, P. L., L. Perniciaro, M. J. Yabsley, D. M. Roellig, G. Balsamo, J. Diaz and D. Wesson (2007). "Autochthonous transmission of *Trypanosoma cruzi*, Louisiana." Emerg Infect Dis 13(4): 605-7.

3. WHO Expert Committee on the Control of Chagas Disease (2000: Brasilia, Brazil), Control of Chagas Disease: second report of the WHO expert committee, 2002.

4. Bellotti, G., E. A. Bocchi, A. V. de Moraes, M. L. Higuchi, M. Barbero-Marcial, E. Sosa, A. Esteves-Filho, R. Kalil, R. Weiss, A. Jatene and F. Pileggi (1996). "In vivo detection of *Trypanosoma cruzi* antigens in hearts of patients with chronic Chagas' heart disease." Am Heart J 131(2): 301-7.

5. Vago, A. R., A. M. Macedo, S. J. Adad, D. D. Reis and R. Correa-Oliveira (1996). "PCR detection of *Trypanosoma cruzi* DNA in oesophageal tissues of patients with chronic digestive Chagas' disease." Lancet 348(9031): 891-2.

6. Añez, N., H. Carrasco, H. Parada, G. Crisante, A. Rojas, C. Fuenmayor, N. Gonzalez, G. Percoco, R. Borges, P. Guevara and J. L. Ramirez (1999). "Myocardial parasite persistence in chronic chagasic patients." Am J Trop Med Hyg 60(5): 726-32.

7. Jones, E.M., D. G. Colley, S. Tostes, E. R. Lopes, C. L. Vnencak-Jones, and T. L. McCurley (1993): "Amplification of a *Trypanosoma cruzi* DNA sequence from inflammatory lesions in human chagasic cardiomyopathy." Am J Trop Med Hyg 48(3): 348-357.

8. Vago, A. R., L. O. Andrade, A. A. Leite, D. d'Avila Reis, A. M. Macedo, S. J. Adad, S. Tostes Jr., M.C. V. Moreira, G. B. Filho, S. D. J. Pena (2000). "Genetic characterization of *Trypanosoma cruzi* directly from tissues of patients with chronic Chagas disease: Differential distribution of genetic types into diverse organs." American Journal of Pathology 156(5): 1805-1809.

9. Virreira, M., G. Serrano, L. Maldonado, and M. Svoboda (2006). "*Trypanosoma cruzi*: Typing of genotype (sub)lineages in megacolon samples from bolivian patients." Acta Tropica 100(3): 252-255.

10. da Silva Manoel-Caetano, F., C.M. Carareto, A. A. Borim, K. Miyazaki, and A.E. Silva (2008). "kDNA gene signatures of Trypanosoma cruzi in blood and oesophageal mucosa from chronic chagasic patients." Trans R Soc Trop Med Hyg 102(11): 1102-1107.

Contains Nonbinding Recommendations

Draft – Not for Implementation

11. Blood Products Advisory Committee, 74th Meeting, September 12, 2002 http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3892t1-03.pdf.

12. Blood Products Advisory Committee, 89th Meeting, April 26-27, 2007 http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4300M.pdf.

13. Leiby, D. A., R. M. Herron, Jr., E. J. Read, B. A. Lenes and R. J. Stumpf (2002). "*Trypanosoma cruzi* in Los Angeles and Miami blood donors: impact of evolving donor demographics on seroprevalence and implications for transfusion transmission." Transfusion 42(5): 549-55.

14. Strong, D. M. and K. Shoos-Lipton (2006). "Information Concerning Implementation of a Licensed Test for Antibodies to *Trypanosoma cruzi*." AABB Bulletin #06-08.

15. Saulnier Sholler, G. L., S. Kalkunte, C. Greenlaw, K. McCarten and E. Forman (2006). "Antitumor activity of nifurtimox observed in a patient with neuroblastoma." J Pediatr Hematol Oncol 28(10): 693-5.

16. Young, C., P. Losikoff, A. Chawla, L. Glasser and E. Forman (2007). "Transfusion-acquired *Trypanosoma cruzi* infection." Transfusion 47(3): 540-4.

17. Cimo, P. L., W. E. Luper and M. A. Scouros (1993). "Transfusion-associated Chagas' disease in Texas: report of a case." Tex Med 89(12): 48-50.

18. Leiby, D. A., B. A. Lenes, M. A. Tibbals and M. T. Tames-Olmedo (1999). "Prospective evaluation of a patient with *Trypanosoma cruzi* infection transmitted by transfusion." N Engl J Med 341(16): 1237-9.

19. Lane, D. J., G. Sher, B. Ward, M. Ndao, D. Leiby, B. Hewlett and E. Bow (2000). "Investigation of the second case of transfusion transmitted Chagas disease in Canada." 42nd Annual Meeting of the American Society of Hematology, San Francisco, CA.

20. CDC. C.F. Zayas, C. Perlino, A. Caliendo, D. Jackson, E. J. Martinez, P. Tso, T. G. Heffron, J. L. Logan, B. L. Herwaldt, et.al. (2002). "Chagas disease after organ transplantation--United States, 2001." MMWR Morb Mortal Wkly Rep 51(10): 210-2.

21. CDC. L. Mascola, B. Kubak, S. Radhakrishna, T. Mone, R. Hunter, D. A. Leiby, M. Kuehnert, A. Moore, F. Steurer, G. Lawrence and H. Kun (2006). "Chagas disease after organ transplantation--Los Angeles, California, 2006." MMWR Morb Mortal Wkly Rep 55(29): 798-800.

22. Leiby, D. A., F. J. Rentas, K. E. Nelson, V. A. Stambolis, P. M. Ness, C. Parnis, H. A. McAllister, Jr., D. H. Yawn, R. J. Stumpf and L. V. Kirchhoff (2000). "Evidence of *Trypanosoma cruzi* infection (Chagas' disease) among patients undergoing cardiac surgery." Circulation 102(24): 2978-82.

23. Leiby, D. A., E. J. Read, B. A. Lenes, A. J. Yund, R. J. Stumpf, L. V. Kirchhoff and R. Y. Dodd (1997). "Seroepidemiology of *Trypanosoma cruzi*, etiologic agent of Chagas' disease, in US blood donors." J Infect Dis 176(4): 1047-52.

24. Kirchhoff, L. V., P. Paredes, A. Lomelí-Guerrero, M. Paredes-Espinoza, C. S. Ron-Guerrero, M. Delgado-Mejia and J. G. Peña-Muñoz (2006). "Transfusion-associated Chagas disease (American trypanosomiasis) in Mexico: implications for transfusion medicine in the United States." Transfusion 46(2): 298-304.

25. Schmunis, G. A. (1999). "Prevention of transfusional Trypanosoma cruzi infection in Latin America." Mem Inst Oswaldo Cruz 94 (Suppl 1): 93-101).

26. Bern, C., S. P. Montgomery, L. Katz, S. Caglioti and S. L. Stramer (2008). "Chagas disease and the US blood supply." Curr Op Infect Dis 21:476–482.

27. Ben Younès-Chennoufi, A., M. Hontebeyrie-Joskowicz, V. Tricottet, H. Eisen, M. Reynes and G. Said (1988). "Persistence of *Trypanosoma cruzi* antigens in the inflammatory lesions of chronically infected mice." Trans R Soc Trop Med Hyg 82 (1): 77-83.

28. Buckner, F. S., A. J. Wilson and W. C. Van Voorhis (1999). "Detection of live *Trypanosoma cruzi* in tissues of infected mice by using histochemical stain for ß-galactosidase." Infect Immun 67(1): 403-9.

29. Morocoima, A., M. Rodriguez, L. Herrera and S. Urdaneta-Morales (2006). "*Trypanosoma cruzi*: experimental parasitism of bone and cartilage." Parasitol Res 99(6): 663-8.

30. Herrera, L., C. Martínez, H. Carrasco, A. M. Jansen and S. Urdaneta-Morales (2007). "Cornea as a tissue reservoir of *Trypanosoma cruzi*." Parasitol Res 100(6): 1395-9.

31. Shippey, S. H., 3rd, C. M. Zahn, M. M. Cisar, T. J. Wu and A. J. Satin (2005). "Use of the placental perfusion model to evaluate transplacental passage of *Trypanosoma cruzi*." Am J Obstet Gynecol 192(2): 586-91.

32. CDC. S. L. Stramer, R. Y. Dodd, D. A. Leiby, R. M. Herron,L. Mascola, L. J. Rosenberg, S. Caglioti, E. Lawaczeck, R. H. Sunenshine, M. J. Kuehnert, S. Montgomery, C. Bern, A. Moore, B. Herwaldt, H. Kun and J. R. Verani (2007). "Blood donor screening for Chagas disease--United States, 2006-2007." MMWR Morb Mortal Wkly Rep 56(7): 141-3.

33. Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments, October 2006, http://www.fda.gov/cber/gdlns/devbld.htm.

別紙様式第2-1

No. 9

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. 4. 15	該当なし		
一般的名称	人赤血球濃厚液						
販売名（企業名）	赤血球濃厚液-LR「日赤」(日本赤十字社) 照射赤血球濃厚液-LR「日赤」(日本赤十字社)		研究報告の公表状況	Nóbrega AA, Garcia MH, Tatto E, Obara MT, Costa E, Sobel J, Araujo WN. Emerg Infect Dis. 2009 Apr;15(4):653-5.	公表国	ブラジル	

研究報告の概要	○ブラジルにおけるアサイー果実摂取によるシャーガス病の経口伝播 2006年1月～11月にブラジルアマゾンのパラー州で、急性シャーガス病合計178症例が報告され、このうち一部でアサイー果実の摂取による経口伝播の可能性が判明した。 Barcarenaで発症した11例は、血液スメア検体の観察で原虫が確認された。後方視的コホート試験および症例対照試験を実施した。輸血歴、臓器移植歴、森林地帯での滞在、サシガメに刺されたことについては全員が否定した。11名中5名は、9月15日に行われた会合で同じものを食べており、アサイーのペーストやジュースの摂取が共通の暴露要因だった。アサイー果実を潰す際に、原虫を媒介するサシガメの排泄物が混入した可能性が考えられた。
報告企業の意見	ブラジルで発生したシャーガス病のアウトブレイクにおいて、アサイー果実の摂取による経口伝播の可能性が判明したとの報告である。
今後の対応	日本赤十字社は、輸血感染症対策として献血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、シャーガス病の既往がある場合には献血不適としている。日本在住の中南米出身献血者については、厚生労働科学研究「献血血の安全性確保と安定供給のための新興感染症等に対する検査スクリーニング法等の開発と献血制限に関する研究」班と共同して検討する予定である。今後も引き続き情報の収集に努める。
使用上の注意記載状況・その他参考事項等	赤血球濃厚液-LR「日赤」 照射赤血球濃厚液-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

(3)

Oral Transmission of Chagas Disease by Consumption of Açaí Palm Fruit, Brazil

Aglaêr A. Nóbrega, Marcio H. Garcia, Erica Tatto, Marcos T. Obara, Elenild Costa, Jeremy Sobel, and Wildo N. Araujo

In 2006, a total of 178 cases of acute Chagas disease were reported from the Amazonian state of Pará, Brazil. Eleven occurred in Barcarena and were confirmed by visualization of parasites on blood smears. Using cohort and case–control studies, we implicated oral transmission by consumption of açaí palm fruit.

Chagas disease (American trypanosomiasis) chronically infects ≈10 million persons in Latin America (*1*). The etiologic agent is *Trypanosoma cruzi*, which is transmitted by bloodsucking triatomine insects. Other modes of transmission are transfusional, congenital, and oral (foodborne) (*2*). Oral transmission occurs by consumption of foods contaminated with triatomines or their feces or by consumption of raw meat from infected mammalian sylvatic hosts (*3*). The precise stage of food handling at which contamination occurs is unknown. The first outbreak of orally transmitted Chagas disease in Brazil was reported in 1965 (*4*). Two outbreaks were associated with consumption of sugar cane juice (*5,6*). In these outbreaks, the incubation period was ≈22 days, compared with 4–15 days for vectorial transmission and 30–40 days for transfusional transmission (*7*).

Chagas disease has not been considered endemic in the Brazilian Amazon region. The first Amazonian outbreak of acute Chagas disease was reported in 1968; oral transmission was suspected (*8*). During 1968–2005, a total of 437 cases of acute Chagas disease were reported in this region. Of these cases, 311 were related to 62 outbreaks in which the suspected mode of transmission was consumption of açaí (*9*).

Açaí is the fruit of a palm of the family *Aracaceae* (Figure 1, panel A); it is crushed to produce a paste or beverage. Most of the Amazonian population consumes açaí juice daily. Contamination is believed to be caused by triatomine stools on the fruit or insects inadvertently crushed during processing (*10*). There are no reports of collection of açaí for laboratory testing during an outbreak of acute Chagas disease. Because outbreaks with high attack rates occur in small groups whose members all consume the same foods, açaí has not been epidemiologically implicated in transmission of this disease.

During January–November 2006, a total of 178 cases of acute Chagas disease were reported in Pará State, Brazil, in the Amazon basin (Ministry of Health, unpub. data). Eleven of these cases occurred in Barcarena (population 63,268) (*11*) (Figure 1, panel B). All patients had symptom onset in September and October. Of the 11 case-patients, 5 were staff members at a health post who shared a meal at a staff meeting on September 15. We attempted to identify risk factors for illness.

The Study

We conducted a retrospective cohort study of staff members at the health post who participated in the meeting on September 15. A case-patient was any person who participated in the meeting and had a positive direct parasitologic examination for *T. cruzi* or positive serologic results and clinical evidence of acute Chagas disease. A non-case was any person who participated in the meeting and had negative test results for *T. cruzi*. We also conducted a 1:3 case–control study (11 case-patients and 34 controls matched by sex and age) that included patients with laboratory confirmed cases from Barcarena. A case-patient was any person in whom during September 1–October 15 *T. cruzi* was found by direct parasitologic examination, irrespective of signs or symptoms of disease, or who had positive serologic results and clinical evidence of disease. This interval was based on date of symptom onset of the first and last case-patient and a reported incubation period of 3–22 days for orally transmitted disease. Controls were age- and sex-matched residents of case-patient neighborhoods who had negative serologic results for *T. cruzi*.

Parasitologic examinations were conducted for case-patients by using quantitative buffy coat test, thick blood smear, or buffy coat test (the latter 2 tests included Giemsa staining). Serologic tests were conducted by using indirect hemagglutination test, ELISA, or indirect immunofluorescent test. An immunoglobulin (Ig) M titer ≥40 was considered positive. Controls had nonreactive IgM and IgG titers. We ruled out leishmaniasis in all persons with positive serologic results for *T. cruzi* by using an immunofluorescent test for IgM to *Leishmania* spp. (*12*).

We conducted an entomologic investigation during December 11–16, 2006, at the homes of 5 case-patients and in forested areas near the homes of 2 case-patients; at the commercial establishment where açaí consumed by the case-patients linked to the health post was prepared and served; at an açaí juice production and sale establishment reported to be frequented by other case-patients; and at the river dock market where açaí delivered to Barcarena is unloaded. At this market, we searched baskets used to transport açaí in river boats. We applied an insect-displacing compound (piridine; Pirisa, Taquara, Brazil) to the interior and exterior of buildings at investigation sites and placed traps (*13*) to obtain triatomines.

Data were analyzed by using Epi Info version 6.04d (Centers for Disease Control and Prevention, Atlanta, GA, USA). We measured relative risk in the cohort study and matched odds ratios in the matched case–control study, with 95% confidence intervals and $\alpha = 5\%$. Fisher exact, McNemar, Mantel-Haenszel, and Kruskall-Wallis tests were used as needed. Study power $(1 - \beta)$ was 5%.

All case-patients had positive results for *T. cruzi* by direct examination of blood (Figure 2). Nine (82%) patients were female; median age was 39 years (range 7–70 years). Eight (73%) patients resided in urban areas, 7 (64%) in brick dwellings, and 3 (27%) in mixed brick and wooden dwellings. All patients denied having had blood transfusions or organ transplants, having slept in rural or sylvatic areas, and having been bitten by triatomines.

The epidemic curve for the 11 patients is shown in Figure 1, panel C. Main signs and symptoms were fever, weakness, facial edema, myalgia, arthralgia, and peripheral edema (Table 1). No deaths occurred, and median time from symptom onset to treatment initiation was 22 days.

The cohort consisted of 12 persons who attended the staff meeting. Of these persons, 6 shared a meal, 5 (83%) of whom were case-patients. The remaining persons were seronegative for *T. cruzi*. Exposures associated with infection were consumption of thick açaí paste and drinking açaí juice at the health post; consumption of chilled açaí was protective (Table 2). This shared meal was the only common exposure among cohort members. No other foods consumed at the meal were associated with illness (Table 2). Among exposures tested, drinking açaí juice on September 15 and at the health post were significantly associated with illness ($p<0.02$ and $p<0.001$, respectively; matched odds ratio not determined). Other exposures were not associated with illness. No triatomine insects were identified at any sites of the entomologic investigation.

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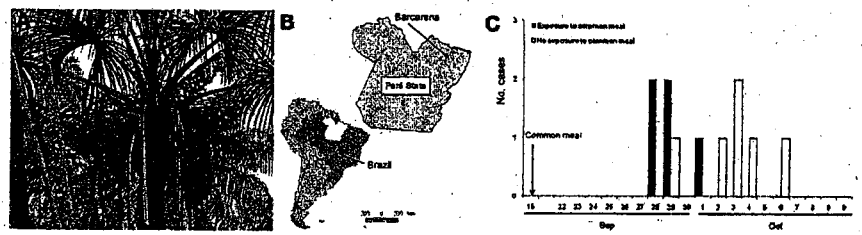

Figure 1. A) Açaí palm and açaí fruit. B) Location of Barcarena in Pará State, Brazil. C) Epidemic curve for 11 case-patients with acute Chagas disease, Barcarena, Brazil, September–October 2006.

Figure 2. *Trypanosoma cruzi* (arrow) in a peripheral blood smear of a patient at a local health facility in a rural area of Pará State, Brazil (Giemsa stain, magnification ×100). Image provided by Adriana A. Oliveira, Brazilian Field Epidemiology Training Program, Brasília, Brazil.

Table 1. Signs and symptoms in 11 patients with laboratory-confirmed acute Chagas disease, Barcarena, Brazil, 2006

Sign or symptom	No. (%) patients
Fever	11 (100)
Fatigue	11 (100)
Facial edema	11 (100)
Headache	10 (91)
Myalgia	9 (82)
Arthralgia	9 (82)
Peripheral edema	9 (82)
Shortness of breath	7 (64)
Tachycardia	7 (64)
Nausea/vomiting	7 (64)
Jaundice	5 (46)
Epigastric pain	5 (46)
Retroorbital pain	5 (46)

Table 2. Food exposures in a cohort study of 5 case-patients with acute Chagas disease, Barcarena, Brazil, 2006*

Exposure†	Ill, no. (%)	Not ill, no. (%)	RR	95% CI	p value‡
Açaí, thick paste	3 (100)	0	4.5	1.3–15.3	0.04
Açaí juice at health post	3 (100)	0	4.5	1.3–15.3	0.04
Chilled açaí juice	1 (12)	7 (88)	0.1	0.02–0.8	0.02
Charque	3 (75)	2 (25)	5.3	0.8–35.1	0.09
Cupuaçu	2 (100)	0	3.3	1.3–8.6	0.15
Biribá	1 (50)	1 (50)	1.3	0.3–6.1	0.68
Muruci	1 (100)	0	2.3	1.3–6.0	0.42
Any raw food	4 (67)	2 (33)	4.0	0.6–26.1	0.12

*RR, relative risk; CI, confidence interval.
†Charque is dried, salted meat; cupuaçu, biribá, and muruci are fruits.
‡By Fisher exact test.

Conclusions

Our study findings implicated açaí in an outbreak of acute Chagas disease. Oral transmission of this disease in the Amazon region has been reported since the 1960s. Açaí has long been the principal suspected food vehicle, but characteristics of outbreaks, small groups with universal exposure and high attack rates, have precluded epidemiologic implication of this food. There are no reports of timely collection of açaí for laboratory testing in an outbreak.

In this outbreak, vectorborne, transfusional, transplant-associated, and transplacental transmission were excluded. Incubation periods of cohort case-patients were compatible with those of previous reports. A shared meal was the only event linking case-patients, and cohort and case–control studies demonstrated an association between açaí consumption at this meal and infection. These findings indicate an outbreak of orally transmitted disease from contaminated açaí.

Limitations of this study are possible recall bias caused by delay between illness and investigation and failure to collect food samples for testing. Studies are needed to determine viability of *T. cruzi* in açaí, along with the tree-to-bowl continuum of açaí, to identify sources of contamination. Because açaí is a major dietary component in the Amazon region and a component of the local economy, identifying practical prevention measures is essential.

Ms Nóbrega is supervisor of the Field Epidemiology Training Program of the Brazilian Ministry of Health in Brasília, Brazil. Her research interests include the epidemiology of infectious diseases and outbreak investigations.

References

1. Bilate AM, Cunha-Net E. Chagas disease cardiomyopathy: current concepts of an old disease. Rev Inst Med Trop São Paulo. 2008;50:67–74. DOI: 10.1590/S0036-46652008000200001
2. Amato Neto V, Lopes M, Umezawa ES, Aveiro Ruocco MS, Dias JC. Outras formas de transmissão do *Trypanosoma cruzi*. Revista de Patologia Tropical. 2000;29(Suppl):115–29.
3. Dias JC. Notas sobre o *Trypanosoma cruzi* e suas caracteristicas bio-ecológicas, como agente de enfermidades transmitidas por alimentos. Rev Soc Bras Med Trop. 2006;39:370–5. DOI: 10.1590/S0037-86822006000400010
4. da Silva NN, Clausell DT, Nóbilis H, de Mello AL, Ossanai J, Rapone T, et al. Epidemic outbreak of Chagas disease probably due to oral contamination [in Portuguese]. Rev Inst Med Trop São Paulo. 1968;10:265–76.
5. Shikanai-Yasuda MA, Marcondes CB, Guedes LA, Siqueira GS, Barone AA, Dias JC, et al. Possible oral transmission of acute Chagas disease in Brazil. Rev Inst Med Trop São Paulo. 1991;33:351–7.
6. Tatto E, Menezes JA, Kitagawa BY, Freitas DR, Dimech GS, Wada MY, et al. Acute Chagas disease (ACD) outbreak related to sugar cane drunk in Santa Catarina State, south Brasil. In: Abstracts of the 56th Meeting of the American Society of Tropical Medicine and Hygiene; 2007 Nov 4–8; Philadelphia. Philadelphia: The Society; 2007. Abstract 997.
7. Brasil Ministério da Saúde, Secretaria de Vigilância em Saúde. Doença de Chagas aguda: manual prático de subsídio à notificação obrigatória no Sinan. Brasília: Ministério da Saúde, Sistema de Informação de Agravos de Notificação (Sinan); 2004.
8. Shaw J, Lainson R, Frailha H. Epidemiology of the first autochthonous case of Chagas' disease recorded in Belém, Pará, Brazil [in Portuguese]. Rev Saude Publica. 1969;3:153–7. DOI: 10.1590/S0034-89101969000200005
9. Valente SA, Valente VC, Pinto AY. Epidemiologia e transmissão oral da doença de Chagas no Amazônia brasileira. In: Informe de la consulta técnica em epidemiologia, prevención y manejo de la transmision de la enfermidad de chagas como enfermidad transmitida por alimentos (ETA). Washington: Organizacion Panamericana de La Salud/Organizacion Mundial de La Salud; 2006. p. 21–6.
10. Valente SA, Valente VC, Frailha Neto H. Transmissão da doença de Chagas: como estamos? Rev. Soc Bras Med Trop. 1999;32(Suppl II):51–5. DOI: 10.1590/S0037-86821999000500023
11. Instituto Brasileiro de Geografia e Estatística [cited 2009 Jan 6]. Available from http://www.ibge.gov.br
12. Ministério da Saúde, Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Doenças infecciosas e parasitarias: guia de bolso. Brasília: Ministério da Saúde; 2005.
13. Noireau F, Abad-Franch F, Valente SA, Dias-Lima A, Lopes CM, Cunha V, et al. Trapping triatominae in silvatic habitats. Mem Inst Oswaldo Cruz. 2002;97:61–3. DOI: 10.1590/S0074-02762002000100009

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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	
				2009. 4. 9	該当なし			
一般的名称	人赤血球濃厚液		研究報告の公表状況	ProMED 20090406.1328, 2009 Apr 6. 情報源: El Universal, 2009 Apr 5.	公表国	ベネズエラ	使用上の注意記載状況・その他参考事項等	
販売名（企業名）	赤血球濃厚液-LR「日赤」(日本赤十字社) 照射赤血球濃厚液-LR「日赤」(日本赤十字社)						赤血球濃厚液-LR「日赤」 照射赤血球濃厚液-LR「日赤」	
研究報告の概要	○食品介在性トリパノソーマ症 - ベネズエラ、グアバジュース ベネズエラ北部のバルガス州西部Chichiriviche de la Costaの住民らに被害が出ている疾患は、シャーガス病であることが確認された。汚染されたグアバジュースの摂取により伝播され、同じ学校に通う児童47名と教師3名が感染するアウトブレイクが発生した。4週間以上続く流行で患者数は増加しており、7、9、12歳の3名の児童が死亡した。児童35名は未だ入院中で、重症患者もいる。既に対策が取られ、感染拡大の危険はない。						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					
	ベネズエラで、グアバジュースの摂取によるシャーガス病のアウトブレイクが発生し、同じ学校に通う児童47名と教師3名が感染、児童3名が死亡したとの報告である。		日本赤十字社は、輸血感染症対策として献血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、シャーガス病の既往がある場合には献血不適としている。日本在住の中南米出身献血者については、厚生労働科学研究「献血血の安全性確保と安定供給のための新興感染症等に対する検査スクリーニング法等の開発と献血制限に関する研究」班と共同して検討する予定である。今後も引き続き情報の収集に努める。					

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Archive Number 20090406.1328
Published Date 06-APR-2009
Subject PRO/AH/EDR> Trypanosomiasis, foodborne - Venezuela: (Vargas), guava juice

TRYPANOSOMIASIS, FOODBORNE - VENEZUELA: (VARGAS), GUAVA JUICE
****
A ProMED-mail post
<http://www.promedmail.org>
ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

Date: 5 Apr 2009
Source: El Universal [trans by Mod.MPP, edited]
<http://www.eluniversal.com/2009/04/05/grccs_art_confirman-chagas-en_1338174.s

Chagas confirmed on the west coast of Vargas

Ministry of Health [MINSA] reiterates the lifting of epidemiologic siege

Yesterday the Minister of Health, Jesus Mantilla, confirmed that Chagas disease is the disease that is attacking the population of Chichiriviche de la Costa, in the western part of the state of Vargas.

The head of the Ministry of Health was in the area and stated that it was transmitted through the ingestion of contaminated guava juice, producing the outbreak of illness in the area, that affected 47 students and three teachers from the morning shift of the Romulo Monasterios state school.

Similarly, the minister reiterated the statements made yesterday [4 Apr 2009 -- see prior ProMED-mail posting Undiagnosed fatalities - Venezuela (02): (Vargas) Chagas susp, RFI 20090404.1305 - Mod.MPP] by the governor of Vargas, Jorge Garcia Carneiro, the epidemiologic "fence" erected to stop the epidemic that occurred in the area, because, as noted, there is no risk of spread.

For this disease, which for over 4 weeks was affecting the population and increasing numbers of patients, killing 3 children ages 7, 9 and 12 years.

However, 35 other children remain hospitalized in the La Guaira Social Security [hospital], the Pariata Periferico [health facility], the Perez Carreno [health facility] and the University Clinic. Doctors from this hospital reported that 15 patients from the area have been admitted, and that the problem is present from [the events surrounding carnaval - Mardis Gras - Mod.MPP]. It was learned that there is a patient in serious condition.

Although the possibility of transmission in the zone was ruled out, the residents of Chichiriviche reported that the usual vacationers to the zone have not arrived. [The affected area is a beach resort frequented by vacationers. The week ending in Easter Sunday is known as Semana Santa in Latin American countries. It is a vacation week, and locations such as Chichiriviche are usually filled with vacationers coming for the week. - Mod.MPP]

[Byline: Anthony Rangel]

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Communicated by:
ProMED-mail <promed@promedmail.org>

[The above newswire is confirmation of the suspicion that the previously undiagnosed outbreak in Venezuela (see prior ProMED-mail postings listed below) is due to ingestion of a juice that was contaminated with _Triatoma infestans_ intestinal contents.

This is now the 7th outbreak of foodborne transmission of trypanosomiasis in the Americas reported by ProMED-mail (see prior postings listed below). As mentioned in the 1st report of this current outbreak (Undiagnosed fatalities - Venezuela: (Vargas), Chagas, susp, RFI 20090402.1279), the 1st reported outbreak of foodborne transmission of trypanosomiasis was reported in Santa Catarina Brazil in 2005 (see prior ProMED-mail postings listed below). This outbreak was associated with ingestion of sugar cane juice that was found to be contaminated with crushed _Triatoma infestans_, the vector of trypanosomiasis in Brazil. Since reporting of outbreaks of foodborne transmitted trypanosomiasis began, there were 6 prior documented outbreaks associated with contaminated juices -- 4 in Brazil (involving 4 states in the country), one in Venezuela, and one in Colombia. The prior outbreak in Venezuela involved 128 cases at a school in metropolitan Caracas, and was associated with contaminated fruit juice. This current outbreak has involved approximately 50 cases at a school in a small beachside town/village outside of Caracas, and is also associated with contaminated fruit juice.

One wonders how new a phenomenon foodborne transmission of trypanosomiasis really is, or is it just that we are now looking more carefully as the standard of housing in these countries has improved, and exposure to the _Triatoma infestans_ in the household has decreased. Or perhaps, there is improved recognition and investigation of acute outbreaks in general in the region.

For the interactive HealthMap/ProMED map of Chichiriviche with links to other recent ProMED-mail postings in surrounding areas, see <http://healthmap.org/r/008y>. - Mod.MPP]

[see also:
Undiagnosed fatalities - Venezuela (02): (Vargas) Chagas susp, RFI 20090404.1305
Undiagnosed fatalities - Venezuela: (Vargas), Chagas, susp, RFI 20090402.127
Trypanosomiasis - Colombia: (SAN), foodborne susp. 20090121.0259
2007

Trypanosomiasis, foodborne - Venezuela: (Caracas) (02) 20071231.4192
Trypanosomiasis, foodborne - Venezuela: (Caracas) 20071226.4141
Trypanosomiasis, foodborne - Brazil (Amazonia) 20070821.2732
2006

Trypanosomiasis, foodborne - Brazil (PA) 20060728.2085
2005

Trypanosomiasis, foodborne - Brazil (Santa Catarina) (05) 20050401.0940
Trypanosomiasis - Brazil (Amapa) 20050331.0929
Trypanosomiasis, foodborne - Brazil (Santa Catarina) (04) 20050330.0917
Trypanosomiasis, foodborne - Brazil (Santa Catarina) (03) 20050327.0884
Trypanosomiasis, foodborne - Brazil (Santa Catarina) (02) 20050325.0870
Trypanosomiasis, foodborne - Brazil (Santa Catarina) 20050324.0847
1997

Chagas disease - Latin America 19970114.0066
Chagas disease vector (05) 19970118.0105
1996

Trypanosomes, New World, Symposium - Guyana 1996 19960830.1493]
.....mpp

医薬品
医薬部外品　研究報告　調査報告書
化粧品

別紙様式第 2-1
番号 9

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	厚生労働省処理欄
				2009 年 5 月 25 日	該当なし	
一般的名称	人ハプトグロビン		研究報告の公表状況	The NEW ENGLAND JOURNAL of MEDICINE 2009; 360(20): 2099-2107	公表国 アメリカ	
販売名（企業名）	ハプトグロビン静注 2000 単位「ベネシス」（ベネシス）					

研究報告の概要

New York の 62 才男性は，シカダニウイルスに感染したシカダニの咬傷後，髄膜脳炎で死亡した。手術および剖検で採取された組織標本の解析で、広範囲にわたる壊死性髄膜脳炎であることが明らかになった。ホルマリン固定組織から核酸が抽出され、シカダニウイルスの存在がフラビウイルス特異的 PCR 測定法で確認された。

シカダニウイルスは、フラビウイルスのダニ媒介脳炎群であり、ポワッサンウイルスと密接に関係がある。ダニ媒介脳炎ウイルスとポワッサンウイルスを含めて、フラビウイルスのダニ媒介脳炎群のいくつかは、人および動物で脳炎を起こす。ダニ媒介脳炎ウイルスは最も重大な大発生を起こしている。これらのウイルスは抗原性において密接に関連し、主に北半球で見つかっている。ダニ媒介脳炎ウイルスによる感染は軽度あるいは無症候性、または、髄膜炎と脳炎が起こる可能性がある。

米北東部および北中央部の一定の地域で、シカのシカダニウイルスの保有率は高い。しかし、ヒト感染は過去に報告されていない。これは、このウイルスが容易に人に感染しない、あるいは、それが特に病原性でないことを示唆する。脳炎症状患者においてポワッサンウイルスの診断検査は通常実施されない。

そのため、ヒト発生率は、過小評価される可能性がある。

シカダニはライム病、ヒト・バベシア症やヒト顆粒球アナプラズマ症を含むいくつかのダニ媒介疾患を伝染させる。この症例は、シカダニウイルスが致命的脳炎の原因でありえることを立証する。

報告企業の意見	今後の対応
シカダニウイルスがヒトに感染した初めての報告であり、また、このウイルスが致命的脳炎の原因であり得とする報告である。 シカダニウイルスは、フラビウイルス科フラビウイルス属に属し、ビリオンは球形で、直径 40～50nm のエンベロープ有する RNA ウイルスである。万一、原料血漿にシカダニウイルスが混入しても、BVD をモデルウイルスとしたウイルスバリデーション試験成績から、製造工程において十分に不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意

(1) 本剤の原材料となる献血者の血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体、抗 HTLV-I 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人ハプトグロビンを濃縮・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膜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。

BRIEF REPORT

Fatal Case of Deer Tick Virus Encephalitis

Norma P. Tavakoli, Ph.D., Heng Wang, M.A., Michelle Dupuis, B.Sc., Rene Hull, B.A., Gregory D. Ebel, Sc.D., Emily J. Gilmore, M.D., and Phyllis L. Faust, M.D., Ph.D.

SUMMARY

Deer tick virus is related to Powassan virus, a tickborne encephalitis virus. A 62-year-old man presented with a meningoencephalitis syndrome and eventually died. Analyses of tissue samples obtained during surgery and at autopsy revealed a widespread necrotizing meningoencephalitis. Nucleic acid was extracted from formalin-fixed tissue, and the presence of deer tick virus was verified on a flavivirus-specific polymerase-chain-reaction (PCR) assay, followed by sequence confirmation. Immunohistochemical analysis with antisera specific for deer tick virus identified numerous immunoreactive neurons, with prominent involvement of large neurons in the brain stem, cerebellum, basal ganglia, thalamus, and spinal cord. This case demonstrates that deer tick virus can be a cause of fatal encephalitis.

From the Wadsworth Center, New York State Department of Health (N.P.T., H.W., M.D., R.H.), and the Department of Biomedical Sciences, School of Public Health, University at Albany (N.P.T.) — both in Albany; the Department of Pathology, University of New Mexico School of Medicine, Albuquerque (G.D.E.); and the Departments of Neurology (E.J.G.) and Pathology and Cell Biology (P.L.F.), Columbia University, and New York Presbyterian Hospital (E.J.G., P.L.F.) — both in New York. Address reprint requests to Dr. Tavakoli at the Empire State Plaza, P.O. Box 509, Albany, NY 12201, or at norma.tavakoli@wadsworth.org.

N Engl J Med 2009;360:2099-107.

DEER TICK VIRUS IS A MEMBER OF THE TICKBORNE ENCEPHALITIS GROUP of flaviviruses and is closely related to Powassan virus. Deer tick virus was first isolated from *Ixodes scapularis* ticks in 1997 in North America.[1] The complete sequence of the deer tick virus has been determined.[2] The viral genome is 10.8 kb in length and shares 84% nucleotide sequence identity and 94% amino acid sequence identity with the Powassan virus genome. The two viruses are antigenically related,[3] and it has been suggested that they share a common origin and represent two viral lineages related to Powassan virus in North America.[2] Ebel et al.[4] refer to deer tick virus as Powassan virus lineage II, and in this report we use the same terminology.

Several members of the tickborne encephalitis group of flaviviruses, including tickborne encephalitis virus and Powassan virus, cause encephalitis in humans and animals, with tickborne encephalitis virus causing the most serious outbreaks. These viruses are closely related antigenically and are found predominantly in the northern hemisphere. In Europe, tickborne encephalitis occurs mainly in eastern and central regions and affects approximately 50 to 199 persons per 100,000 inhabitants annually.[5] The seroprevalence of antibodies to Powassan virus is estimated to be 0.5 to 4.0% in areas in which the disease is endemic.[6]

Infection with tickborne encephalitis virus can be mild or asymptomatic, or it can result in meningitis and encephalitis. Powassan virus can be pathogenic in human beings and can cause severe encephalitis with a fatality rate of up to 60% and long-term neurologic sequelae in survivors.[7] In contrast, Central European encephalitis that is caused by tick bites typically produces mild or silent infection. Other disease-causing flaviviruses include West Nile virus, St. Louis encephalitis virus, dengue virus, and yellow fever virus.[8] These viruses are transmitted by mosquitoes and cause a spectrum of diseases including meningitis, encephalitis, dengue fever, and yellow fever.

In certain locations of the northeastern and north central United States, the prevalence of deer tick virus in adult deer ticks is high,[9,10] but human infection has not been reported previously. This could indicate that the virus does not easily infect humans or that it is not particularly pathogenic. Diagnostic testing for Powassan virus is not routinely performed for patients with symptoms of encephalitis. Human incidence may thus be currently underestimated.

CASE REPORT

In late spring, a 62-year-old man was admitted to a local New York State hospital with a 4-day history of fatigue, fever, bilateral maculopapular palmar rash, and an onset of diplopia, dysarthria, and weakness in the right arm and leg. He was a native of New York State and had no history of recent travel. He owned horses and spent time outdoors in a wooded area. Reports of Lyme disease were common in his county of residence, indicating tick activity in the area. His medical history included chronic lymphocytic leukemia–small lymphocytic lymphoma (CLL–SLL), which had been diagnosed 4 years earlier and had initially been treated with fludarabine. He was not taking corticosteroids. On admission, he was given nonsteroidal antiinflammatory medication and an oral antibiotic (amoxicillin–clavulanate), which had been prescribed by his primary care physician for a recent exacerbation of chronic sinusitis that had been recurrent for more than a year. His baseline white-cell count was 15,000 cells per cubic millimeter and had increased to 70,000 cells per cubic millimeter during the past 6 to 8 months. He was started on broad-spectrum antibiotics and acyclovir (700 mg administered intravenously every 8 hours) for presumed infection of the central nervous system. The differential diagnosis included cerebral ischemia, possibly related to leukostasis, infection (viral, bacterial, or fungal), and lymphoma.

Initial laboratory results were notable for a markedly elevated peripheral-blood white-cell count (144,200 cells per cubic millimeter) and cerebrospinal fluid with normal glucose, minimally elevated protein, no white cells, and a negative Gram's stain (Table 1). The erythrocyte sedimentation rate was 4, blood cultures were sterile, and antibody titers were negative for *Borrelia burgdorferi* and *Anaplasma phagocytophilum*. The neurologic symptoms progressed, and after 2 days he was transferred to another hospital. At the time of transfer, the peripheral-blood white-cell count was 174,800 per cubic millimeter (with 4% neutrophils and 94% lymphocytes) (Table 1).

Findings on flow cytometry were characteristic of CLL–SLL. Bacterial and fungal blood cultures were sterile. Sputum cultures for tuberculosis and legionella species were negative. No serum antibodies to *Bartonella henselae* or leptospira or brucella species were detected. One day after admission, a repeat spinal tap showed an elevated protein level of 192 mg per deciliter, lymphocytic pleocytosis with 891 cells per cubic millimeter (with 1% neutrophils and 93% lymphocytes), and a normal glucose level (Table 1). Flow cytometry of the cerebrospinal fluid demonstrated a predominantly reactive T-cell population (98% of CD45+ cells were CD3+/CD5+ small T cells), with no evidence of CLL–SLL. Bacterial culture and Gram's staining of the cerebrospinal fluid were negative. India-ink staining, cryptococcus antigen test, and PCR analyses for herpes simplex virus types 1 and 2 and JC–BK virus were negative in cerebrospinal fluid.

Magnetic resonance imaging (MRI) performed after transfer (hospital day 1) revealed abnormal T_2-weighted and fluid-attenuated inversion recovery (FLAIR) images, with hyperintensities most prominent in the superior cerebellum, left pons, and bilateral basal ganglia (Fig. 1A, 1B, and 1C). An axial diffusion-weighted image and apparent-diffusion-coefficient sequences revealed restricted diffusion in the superior cerebellum, suggesting an ischemic process (Fig. 1D). The patient remained febrile (maximum temperature, 104.5°F [40.3°C]), and antimicrobial coverage was broadened to include an antifungal agent. His neurologic function deteriorated, which necessitated intubation, and his function did not improve despite maximal medical therapy.

On hospital day 4, his fever abated, and computed tomographic imaging revealed a mild obstructive hydrocephalus, leading to placement of an external ventricular drain. On hospital day 5, repeat MRI revealed worsening of signal abnormalities and markedly increased hydrocephalus. He was taken urgently to the operating room for decompression with a suboccipital craniotomy, at which time cerebellar biopsy was performed. Analysis of the biopsy specimen revealed severe meningoencephalitis with a dense meningeal lymphoid infiltrate containing mainly reactive CD4+ T cells, lymphocytic venous invasion and destruc-

tion, widespread loss of cerebellar Purkinje cells, occasional microglial nodules, and marked Bergmann gliosis (Fig. 1A to 1H in the Supplementary Appendix, available with the full text of this article at NEJM.org). The parenchyma was infiltrated by activated microglia–macrophages and predominantly CD8+ T cells (Fig. 1I and 1J in the Supplementary Appendix). All biopsy cultures were negative, and staining of biopsy tissue was negative for bacterial, fungal, and mycobacterial organisms and viral antigens (including herpes simplex virus 1 and 2, varicella–zoster virus, cytomegalovirus, influenza A, parainfluenza 3, adenovirus, and parvovirus).

MRI of the brain on hospital day 7 revealed progression of signal abnormalities, new lesions in the right thalamus and bilateral cerebral hemispheres, and persistent hydrocephalus (Fig. 2 in the Supplementary Appendix). By hospital day 11, there was no improvement in his status. Life support was withdrawn, and he died 17 days after the onset of symptoms. An autopsy was performed.

METHODS

CLINICAL SPECIMENS

A surgical biopsy of the cerebellum was fixed in formalin and embedded in paraffin. After autopsy, the brain was formalin-fixed for 2 weeks, and standard tissue blocks were paraffin-embedded. Unembedded, formalin-fixed brain tissue from the midbrain, cerebellum, pons, and spinal cord was submitted for PCR testing. (For details on viruses and control samples that were used, see the Methods section in the Supplementary Appendix.)

REVERSE-TRANSCRIPTASE–PCR AND SEQUENCE ANALYSIS

Nucleic acid was extracted from formalin-fixed tissue with the use of the WaxFree DNA extraction kit (TrimGen). This kit coextracts RNA. Ten microliters of extracted nucleic acid was reverse-transcribed to complementary DNA (cDNA) with the use of the iScript cDNA synthesis kit (Bio-Rad). Heminested reverse-transcriptase PCR (RT-PCR) for the detection of flavivirus with the use of universal primers was performed as described previously.[11,12] (In the Supplementary Appendix, additional information on the PCR primers is listed in Table A, and details regarding the PCR methods, sequence, and histologic and immunohistochemical analyses are listed in the Methods section.)

Table 1. Results of Analysis of Cerebrospinal Fluid and Blood of the Patient.*

Variable	First Hospitalization	Day 1 after Transfer to Second Hospital	Normal Range
Cerebrospinal fluid			
Glucose level (mg/dl)	59	47	40–70
Protein level (mg/dl)	64	192	15–45
White-cell count (cells/mm³)	0	891	0–5
Neutrophils (%)		1	0
Lymphocytes (%)		93	70
Complete blood count			
White-cell count (cells/mm³)	144,200	174,800	3500–9100
Neutrophils (%)	2	4	38–80
Lymphocytes (%)	98	94	15–40

* To convert the values for glucose to millimoles per liter, multiply by 0.05551.

RESULTS

The general autopsy revealed diffuse lymphadenopathy and splenomegaly and infiltration of liver and kidney by CLL–SLL. The brain weight was 1810 g (normal range in adults, 1300 to 1350), consistent with marked edema. On sectioning, there was marked softening and grayish discoloration throughout the brain stem and cerebellum.

Histologic examination of the brain revealed widespread meningopolioencephalitis and meningopoliomyelitis; there was no evidence of infiltration by CLL–SLL. A mild meningeal lymphocytic infiltrate persisted, and dense perivascular infiltrates were still identified in the parenchyma (Fig. 3C to 3K in the Supplementary Appendix). Throughout the brain, multinodular to patchy mononuclear infiltrates and confluent areas of necrosis were identified, along with microglial nodules and neuronophagia. This was most accentuated in large motor neurons of the brain stem (including cranial nerve nuclei), spinal anterior horns, cerebellum, basal ganglia, and thalamus (Fig. 2, and Fig. 3 in the Supplementary Appendix). Microglia–macrophage infiltration was greatest in gray-matter regions but also involved white-matter tracts to a lesser degree (Fig. 3A in the Supplementary Appendix).

As in the surgical biopsy, lymphocytic infiltrates in leptomeninges and perivascular spaces contained predominantly CD4+ helper T cells, whereas those in the parenchyma were predominantly CD8+ cytotoxic T cells (Fig. 4 in the Supplementary Appendix). CD8+ T cells were also

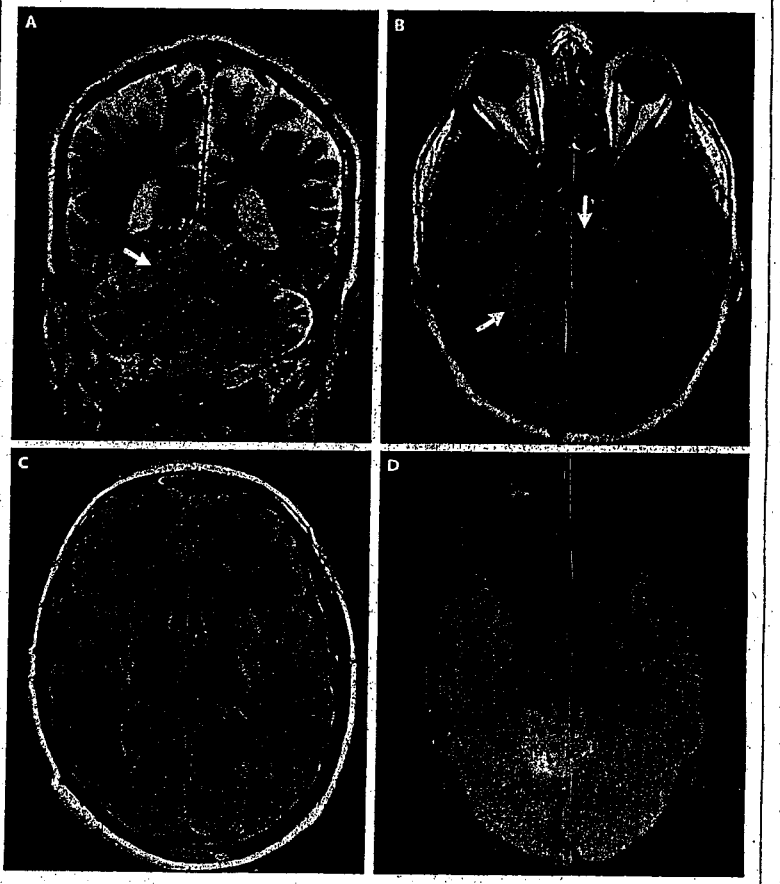

Figure 1. Magnetic Resonance Imaging (MRI) of the Brain on Hospital Admission.
MRI scanning that was performed on hospital day 1 revealed abnormal T_2-weighted signaling in the superior cerebellum (Panel A, arrow) and abnormal T_2-weighted fluid-attenuated inversion recovery images with hyperintensities in the cerebellum and left pons (Panel B, arrows) and in the bilateral basal ganglia (Panel C). The superior cerebellum was bright on diffusion-weighted imaging (Panel D) and dark on apparent-diffusion-coefficient sequences, which suggested an ischemic process.

more frequently identified in close apposition to surviving neurons (Fig. 2C, and Fig. 4A, 4B, and 4E in the Supplementary Appendix).

On the extracted nucleic acid from the formalin-fixed brain tissue, the following analyses were performed: a PCR panel including real-time PCR assays for the detection of herpes simplex viruses 1 and 2, Epstein–Barr virus, cytomegalovirus, human herpesvirus type 6, varicella–zoster virus, and adenovirus; real-time RT-PCR assays for the de-

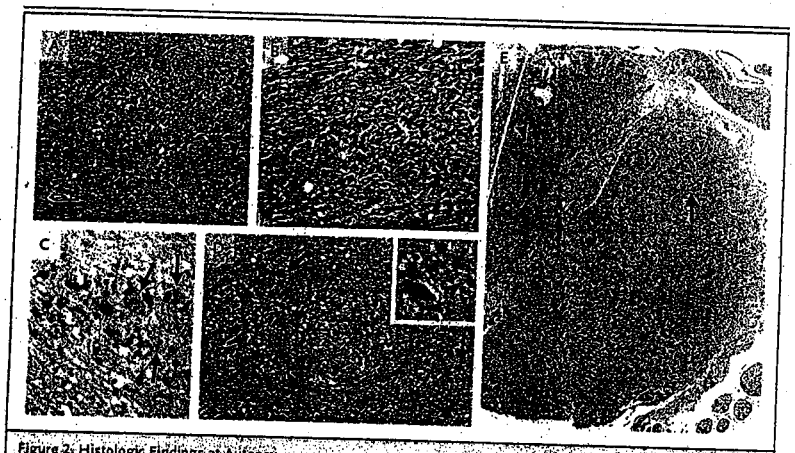

Figure 2. Histologic Findings at Autopsy.

In Panel A, microglial nodules and lymphocytic infiltrates in the pons are visible in basal pontine nuclei (arrowheads), with less prominent involvement of descending fiber tracts (arrow) and pontocerebellar fibers. In Panel B, confluent foci of parenchymal necrosis can be seen in pontine basal nuclei. In Panel C, CD8+ immunostaining of the basis pontis shows a cytotoxic T-cell infiltrate and a close association with surviving neurons (arrows). In Panel D, nearly complete neuronal loss is seen in the substantia nigra with rare surviving neurons (arrows); in the inset, an eosinophilic dying neuron and remaining neuromelanin pigment are engulfed in macrophages or free in the parenchyma (arrowheads). In Panel E, phosphoglucomutase 1 immunostaining of lumbar spinal cord shows marked infiltration by microglia–macrophages and in the anterior horn and focal microglial nodules in the lateral corticospinal tract (arrow) and posterior column (arrowhead). In Panels A, B, and D, paraffin sections were stained with hematoxylin and eosin.

tection of West Nile virus and eastern equine encephalitis virus; a real-time PCR assay using a cDNA template for the detection of enterovirus; a group-specific RT-PCR assay for the detection of alphaviruses[13]; and conventional PCR assays using a cDNA template for the detection of St. Louis encephalitis, California serogroup, and Cache Valley viruses. PCR assays for the detection of borrelia species, including *B. burgdorferi*, and of *A. phagocytophilum* were performed on DNA extracts from the cerebellum and spinal cord. All results were negative. A group-specific RT-PCR assay for the detection of flaviviruses gave PCR products of the expected size for both the first-round PCR and the nested PCR.[11] The PCR products of approximately 250 bp and 220 bp were purified from the gel and sequenced. A search with the use of the nucleotide Basic Local Alignment Search Tool (BLAST) algorithm posted on the Web site of the National Center for Biotechnology Information identified a 220-bp sequence sharing 97% of the sequence of deer tick virus strains CTB30 (accession number, AF311056.1), and IPS001 (accession number, AF310947.1) and Powassan virus strain R59266 (accession number, AF310948.1). To confirm the lineage of the virus, sequencing was performed with the use of previously published and newly designed primer sets from the envelope coding region, NS5, and sequences in the 3′ untranslated region[1,4] (Table A in the Supplementary Appendix).

With a total of 23 primer sets used, two regions of the virus were sequenced: 2748 bp, spanning part of the RNA polymerase coding sequence and the 3′ untranslated region of the virus, and 1180 bp of the envelope coding sequence. Phylogenetic analyses of these fragments indicated that the virus, named DT-NY-07, was most closely related to the deer tick virus (Fig. 3).[14-16]

To confirm that deer tick virus antigens were detectable in brain tissue from the patient, two polyclonal mouse antibody reagents were generated against whole deer tick virus and recombinant deer tick virus E protein (rEDTV). Both antiserum samples showed similar immunohistochemical specificity in both the cerebellar biopsy and autopsy specimens, although generally a larger number of neurons and viral antigens in macrophages were labeled with the whole-virus serum (Fig. 4, and Fig. 5 in the Supplementary Appendix). The whole-virus antiserum labeled neuronal-cell bodies, dendrites, and axons. The rEDTV serum and rarely the whole-virus serum also labeled rounded, granular-to-tubular profiles within the neuronal cytoplasm of large motor neurons, with a cellular distribution highly reminiscent of the Golgi apparatus in some neurons (Fig. 4A, and Fig. 6 in the Supplementary Appendix). Alternatively, the structures may represent viral particles within the lysosomal–endosomal system. A segmental distribution of labeled neurons was prominent in the hippocampus (Fig. 4B). In isocortical regions, occasional labeled neurons and a focus of infected cells consistent with oligodendrocytes were also identified (Fig. 4D).

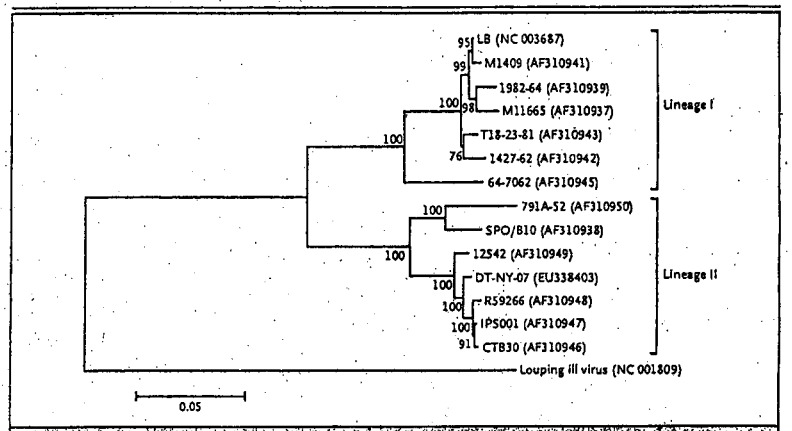

Figure 3. Phylogenetic Tree Showing the Relationship between the Virus (DT-NY-07) Detected in Tissue Sections from the Brain of the Patient and Other Powassan Viruses.

This phylogenetic tree was constructed from 2304 nucleotide sequences of the NS5 region; GenBank accession numbers are in parentheses. The evolutionary history was inferred with the use of the neighbor-joining method.[14] The optimal tree with the sum of branch length equaling 0.60849744 is shown. The percentage of replicate trees in which the associated taxa are clustered together in the bootstrap test (1000 replicates) is shown next to each branch. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to construct the phylogenetic tree. To root the dendrogram, louping ill virus was used as the outgroup. The evolutionary distances were computed with the use of the maximum composite likelihood method[15] and are expressed in the units of the number of base substitutions per site. All positions containing gaps and missing data were eliminated from the data set. Phylogenetic analyses were conducted with the use of Molecular Evolutionary Genetics Analysis (MEGA) software, version 4.0.[16]

DISCUSSION

Strains of Powassan virus lineages I and II are distinct and are maintained in separate enzootic cycles because of differences in transmission vectors and geographic distribution. Lineage I strains are transmitted by ticks and have been reported in North America (mainly in New York State and Canada) and in eastern Russia, whereas lineage II strains have been isolated in the Atlantic Coast of the United States and in Wisconsin.[4] Lineage I strains appear to be associated with *I. cookei* and groundhogs (*Marmota monax*), whereas lineage II strains are associated with deer ticks and white-footed mice (*Peromyscus leucopus*).[7] In addition, lineage II strains have not previously been associated with human disease, whereas a number of infections in humans associated with lineage I strains have been documented.[17-21] From these re-

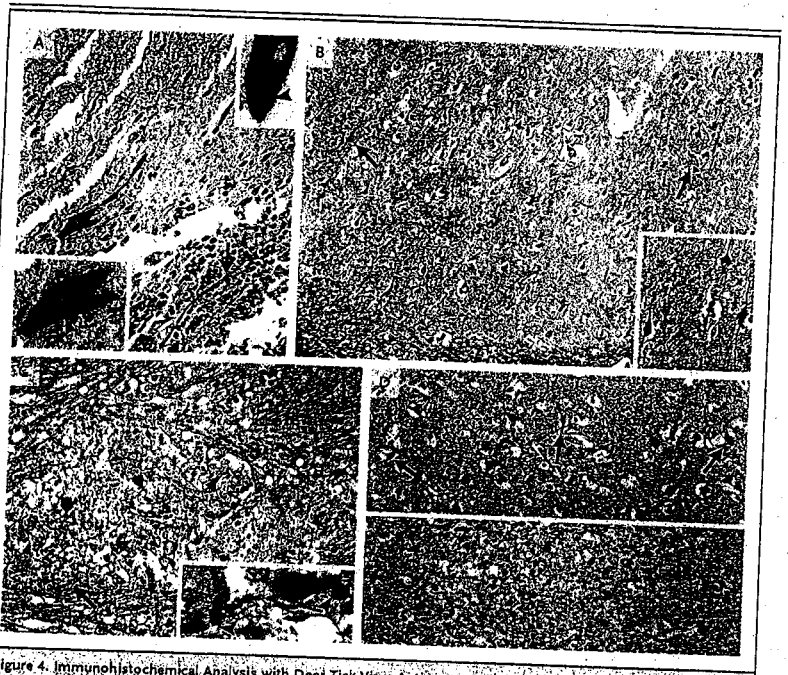

Figure 4. Immunohistochemical Analysis with Deer Tick Virus Antiserum Samples.

Paraffin sections of cerebellar samples obtained from the patient on biopsy (Panel A) and samples from the hippocampus (Panel B), pons (Panel C), and temporal cortex (Panel D), obtained at autopsy were stained either with antibody against whole deer tick virus (Panel A, upper inset, and Panels B and C) or with antibody against recombinant deer tick virus E protein (rEDTV) (Panel A, Panel A, lower inset, and Panel D). In Panel A, in the cerebellar biopsy sample, both types of antiserum recognized surviving Purkinje cells, with prominent filling of their dendrites in the molecular layer and occasional identification of axons in the granule-cell layer (arrow); in the insets, several Purkinje cells were identified with immunoreactive granular-to-tubular profiles (arrowheads). In Panel B, many hippocampal pyramidal neurons were immunolabeled in a segmental distribution (in area surrounding arrows), with prominent decoration of apical and basal processes (inset). In Panel C, many surviving immunolabeled neurons in the basis pontis are visible. The whole deer tick virus antibody also recognized viral antigens engulfed in macrophages (arrow; inset, arrowheads), whereas the rEDTV antibody did not have such recognition. In Panel D, in temporal cortex, immunoreactive neurons that were not associated with inflammatory reaction were occasionally identified (upper panel, arrows). In the temporal white matter, a focus of labeled cells consistent with oligodendrocytes was seen (lower panel). (For more details, see Fig. 5 and 6 in the Supplementary Appendix.)

ports, it appears that lineage I Powassan encephalitis is characterized by respiratory distress, fever, vomiting, convulsions, and occasionally paralysis.[17,19] Studies in the northern Ontario region of Canada show an antibody prevalence rate of as much as 3.2%, indicating that infection does not always cause severe disease.[22] In a phylogenetic study of Powassan-related viruses of North America, a lineage II strain (ON97) was reportedly isolated from human brain tissue.[2] However, no other information regarding the case was provided.

Confirmation of infection with a lineage I strain of Powassan virus has been made principally by serologic methods. Because of serologic cross-reactivity, these methods do not necessarily distinguish lineage I from lineage II strains. Neutralization assays are required for confirmation; molecular detection and sequence determination, as performed in our investigation, allowed for definitive classification of the virus.

In this study, we detected deer tick virus by both molecular and immunohistochemical methods in the central nervous system of a patient with encephalitis. The neurotropism seen in this case, with involvement of both gray and white matter, matches the pattern of central nervous system infection for arboviruses, which may be highly neuroinvasive.[23]

The patient was known to have frequented wooded areas, although no specific contact with ticks had been reported. He presented in late spring, which suggested that transmission was probably from nymphal deer ticks, which are most active during spring and summer months. In addition, since nymphal deer ticks are small in size (1.5 mm in diameter), it is not uncommon for their bites to remain undetected. It is possible that the patient's underlying condition (CLL–SLL) predisposed him to particularly serious disease. Reports of elderly and immunocompromised patients being at a greater risk for severe encephalitis caused by West Nile virus are well documented.[24,25]

Our immunohistochemical studies with newly generated deer tick virus antibodies demonstrated prominent labeling of neuronal-cell bodies and their processes; a focus of apparent oligodendroglial infection was also identified (Fig. 4). In addition, some neurons contained rounded granular-to-tubular profiles. A segmental distribution of immunolabeling was evident in the hippocampus, as was seen in cerebellum infected by central European tickborne encephalitis virus, as described previously.[26] The parenchymal lymphocytic infiltrates in this case and in previous pathological studies of tickborne encephalitis virus[26,27] were predominantly CD8+ cytotoxic T cells, which were also seen in close apposition to surviving neurons, further indicating that immunologic mechanisms may have contributed to nerve-cell destruction in tickborne encephalitides.

Diagnostic testing for Powassan virus is not routinely performed in patients with encephalitis. More extensive testing for arboviruses, including Powassan virus, might reveal that arboviral infections are more widespread than previously reported. For Powassan virus, testing is especially important during the summer months and in regions where infected ticks are prevalent. Deer ticks transmit several tickborne diseases, including Lyme disease, human babesiosis, and human granulocytic anaplasmosis.[28] This report of deer tick virus resulting in a fatal case of encephalitis emphasizes the significance of deer ticks in transmitting a variety of infections. There are limited data on the prevalence of infection with deer tick virus among adult deer ticks, although a rate of 0.6 to 1.3% in limited geographic areas in the United States has been reported.[9] Because no specific antiviral therapy is available for Powassan infection, the best strategy remains prevention (i.e., avoidance of contact with the arthropod vector). Studies to elucidate the prevalence and relative pathogenic features of Powassan lineages I and II are warranted.

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The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the CDC.

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REFERENCES

1. Telford SR III, Armstrong PM, Katavolos P, et al. A new tick-borne encephalitis-like virus infecting New England deer ticks, *Ixodes dammini*. Emerg Infect Dis 1997;3:165-70.
2. Kuno G, Artsob H, Karabatos N, Tsuchiya KR, Chang GJJ. Genomic sequencing of deer tick virus and phylogeny of Powassan-related viruses of North America. Am J Trop Med Hyg 2001;65:671-6.
3. Beasley DWC, Suderman MT, Holbrook MR, Barrett ADT. Nucleotide sequencing and serological evidence that the recently recognized deer tick virus is a genotype of Powassan virus. Virus Res 2001;79:81-9.
4. Ebel GD, Spielman A, Telford SR III. Phylogeny of North American Powassan virus. J Gen Virol 2001;82:1657-65.
5. Charrel RN, Attoui H, Butenko AM, et al. Tick-borne virus diseases of human interest in Europe. Clin Microbiol Infect 2004;10:1040-55.
6. Artsob H. Powassan encephalitis. In: Monath TP, ed. The arboviruses: epidemiology and ecology. Boca Raton, FL: CRC Press, 1988:29-49.
7. Gritsun TS, Nuttall PA, Gould EA. Tick-borne flaviviruses. Adv Virus Res 2003;61:317-71.
8. Burke DS, Monath TP. Flaviviruses. In: Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, eds. Fields virology. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2001:1043-126.
9. Ebel GD, Campbell BN, Goethert HK,

Spielman A, Telford SR III. Enzootic transmission of deer tick virus in New England and Wisconsin sites. Am J Trop Med Hyg 2000;63:36-42.
10. Ebel GD, Foppa I, Spielman A, Telford SR III. A focus of deer tick virus transmission in the northcentral United States. Emerg Infect Dis 1999;5:570-4.
11. Scaramozzino N, Crance J-M, Jouan A, DeBriel DA, Stoll F, Garin D. Comparison of flavivirus universal primer pairs and development of a rapid, highly sensitive heminested reverse transcription-PCR assay for detection of flavivirus targeted to a conserved region of the NS5 gene sequences. J Clin Microbiol 2001;39:1922-7.
12. Tavakoli NP, Tobin EH, Wong SJ, et al. Identification of dengue virus in respiratory specimens from a patient who had recently traveled from a region where dengue virus is endemic. J Clin Microbiol 2007;45:1523-7.
13. Pfeffer M, Proebster B, Kinney RM, Kaaden O-R. Genus-specific detection of alphaviruses by a semi-nested reverse transcription-polymerase chain reaction. Am J Trop Med Hyg 1997;57:709-18.
14. Saitou N, Nei M. The neighbor-joining method: a new method for reconstructing phylogenetic trees. Mol Biol Evol 1987;4:406-25.
15. Tamura K, Nei M, Kumar S. Prospects for inferring very large phylogenies by using the neighbor-joining method. Proc Natl Acad Sci U S A 2004;101:11030-5.
16. Tamura K, Dudley J, Nei M, Kumar S. MEGA4: Molecular Evolutionary Genetics Analysis (MEGA) software version 4.0. Mol Biol Evol 2007;24:1596-9.
17. Gholam BA, Puksa S, Provias JP. Powassan encephalitis: a case report with neuropathology and literature review. CMAJ 1999;161:1419-22.
18. Embil JA, Camfield P, Artsob H, Chase DP. Powassan virus encephalitis resembling herpes simplex encephalitis. Arch Intern Med 1983;143:341-3.
19. Wilson MS, Wherrett BA, Mahday MS. Powassan virus meningoencephalitis: a case report. Can Med Assoc J 1979;121:320-3.
20. Goldfield M, Austin SM, Black HC, Taylor BF, Altman R. A non-fatal human case of Powassan virus encephalitis. Am J Trop Med Hyg 1973;22:78-81.
21. McLean DM, Donohue WL. Powassan virus: isolation of virus from a fatal case of encephalitis. Can Med Assoc J 1959;80:708-11.
22. McLean DM, McQueen EJ, Petite HE, MacPherson LW, Scholten TH, Ronald K. Powassan virus: field investigations in northern Ontario, 1959 to 1961. CMAJ 1962;86:971-4.
23. Love S, Wiley CA. Viral infections. In: Love S, Louis DW, Ellison DW, eds. Greenfield's neuropathology. 8th ed. London: Hodder Arnold, 2008:1323-33.
24. Penn RG, Guarner J, Sejvar JJ, et al. Persistent neuroinvasive West Nile virus infection in an immunocompromised patient. Clin Infect Dis 2006;42:680-3.
25. Ravindra KV, Freifeld AG, Kalil AC, et al. West Nile virus-associated encephalitis in recipients of renal and pancreas transplants: case series and literature review. Clin Infect Dis 2004;38:1257-60.
26. Gelpi E, Preusser M, Garzuly F, Holzmann H, Heinz FX, Budka H. Visualization of Central European tick-borne encephalitis infection in fatal human cases. J Neuropathol Exp Neurol 2005;64:506-12.
27. Gelpi E, Preusser M, Laggner U, et al. Inflammatory response in human tick-borne encephalitis: analysis of postmortem brain tissue. J Neurovirol 2006;12:322-7.
28. Thompson C, Spielman A, Krause PJ. Coinfecting deer-associated zoonoses: Lyme disease, babesiosis, and ehrlichiosis. Clin Infect Dis 2001;33:676-85.

医薬品　研究報告　調査報告書

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一般的名称	テクネチウム大凝集人血清アルブミン（^{99m}Tc）		研究報告の公表状況	Plos pathogens May 2009, vol.4, Issue.5,e100455	公表国		
販売名（企業名）	テクネ MAA キット（富士フイルムＲＩファーマ株式会社）				ザンビア、南アフリカ		
研究報告の概要	要約：南アフリカでのアレナウイルス関連の新規の出血熱である Lujo ウイルスの遺伝子検出及び特徴づけ 2008 年に南アフリカで発生した致死性出血熱のアウトブレークにおいて、新規の旧世界アレナウイルスが分離された。旧世界の出血熱関連のアレナウイルスとしては 30 年ぶりの発見である。Unbiased pyrosequencing により、アウトブレークの検体者からの検体を受領してから 72 時間以内の識別と系統発生学的な特徴づけが可能であった。遺伝子解析により、他の旧世界アレナウイルスと明らかに異なる、固有のものであること、旧世界アレナウイルスと新世界アレナウイルスとのおよそ等距離にあること等が判明した。このウイルスが確認された場所の地名（Lusaka, Johannesburg）より Lujo virus（以下、LUJV）と命名した。この発見は、LUJV の宿主や地理的な分布、病原性の調査に使用される試薬の開発を可能にするとともに、病原体の発見や公衆衛生にとっての unbiased high throughput pyrosequencing の有用性を確認することができた。			使用上の注意記載状況・その他参考事項等 特になし
報告企業の意見			今後の対応				
Lujo ウイルスの新規性については、従来確認されていた他のアレナウイルスとはかなり異なる固有のものであること、また、患者５人中４人が死亡していることから、高病原性であることが判明しており、新規・重大な感染症に関する報告と評価する。			ヒト血液を原料とする血漿分画製剤とは直接関連しないことから、現時点で当該生物由来製品に関し、措置等を行う必要はないと判断する。				

Genetic Detection and Characterization of Lujo Virus, a New Hemorrhagic Fever–Associated Arenavirus from Southern Africa

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Abstract

Lujo virus (LUJV), a new member of the family *Arenaviridae* and the first hemorrhagic fever–associated arenavirus from the Old World discovered in three decades, was isolated in South Africa during an outbreak of human disease characterized by nosocomial transmission and an unprecedented high case fatality rate (80%; 4/5 cases). Unbiased pyrosequencing of RNA extracts from serum and tissues of outbreak victims enabled identification and detailed phylogenetic characterization within 72 hours of sample receipt. Full genome analyses of LUJV showed it to be unique and branching off the ancestral node of the Old World arenaviruses. The virus's glycoprotein sequence was highly diverse and almost equidistant from that of other Old World and New World arenaviruses, consistent with a potential distinctive receptor tropism. LUJV is a novel genetic species of highly pathogenic arenavirus.

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Competing Interests: SKH and ME are employees of 454 Life Sciences, Inc., a Roche Company.

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Introduction

Members of the genus *Arenavirus*, comprising currently 22 recognized species (http://www.ictvonline.org/virusTaxonomy.asp?version=2008), are divided into two complexes based on serologic, genetic, and geographic relationships [1,2]: the New World (NW) or Tacaribe complex, and the Old World (OW) or Lassa-Lymphocytic choriomeningitis complex that includes the ubiquitous arenavirus type-species *Lymphocytic choriomeningitis virus* (LCMV; [3]). The RNA genome of arenaviruses is bi-segmented, comprising a large (L) and a small (S) segment that each codes for two proteins in ambisense coding strategy [4,5]. Despite this coding strategy, the *Arenaviridae* are classified together with the families *Orthomyxoviridae* and *Bunyaviridae* as segmented single-strand, negative sense RNA viruses.

The South American hemorrhagic fever viruses Junin (JUNV; [6,7]), Machupo (MACV; [8]), Guanarito (GTOV; [9]) and Sabia virus (SABV, [10]), and the African Lassa virus (LASV [11]), are restricted to biosafety level 4 (BSL-4) containment due to their associated aerosol infectivity and rapid onset of severe disease. With the possible exception of NW Tacaribe virus (TCRV; [12]), which has been isolated from bats (*Artibeus* spp.), individual arenavirus species are commonly transmitted by specific rodent species wherein the capacity for persistent infection without overt disease suggests long evolutionary adaptation between the agent and its host [1,13–16]. Whereas NW arenaviruses are associated with rodents in the *Sigmodontinae* subfamily of the family *Cricetidae*, OW arenaviruses are associated with rodents in the *Murinae* subfamily of the family *Muridae*.

Humans are most frequently infected through contact with infected rodent excreta, commonly via inhalation of dust or aerosolized virus-containing materials, or ingestion of contaminated foods [13]; however, transmission may also occur by inoculation with infected body fluids and tissue transplantation [17–19]. LCMV, which is spread by the ubiquitous *Mus musculus* as host species and hence found world-wide, causes symptoms in humans that range from asymptomatic infection or mild febrile illness to meningitis and encephalitis [13]. LCMV infection is only rarely fatal in immunocompetent adults; however, infection during pregnancy bears serious risks for mother and child and frequently results in congenital abnormalities. The African LASV, which has its reservoir in rodent species of the *Mastomys* genus, causes an estimated 100,000–500,000 human infections per year in West African countries (Figure 1). Although Lassa fever is typically subclinical or associated with mild febrile illness, up to 20% of cases may have severe systemic disease culminating in fatal outcome [20,21]. Three other African arenaviruses are not known to cause human disease: Ippy virus (IPPYV; [22,23]), isolated from

Author Summary

In September and October 2008, five cases of undiagnosed hemorrhagic fever, four of them fatal, were recognized in South Africa after air transfer of a critically ill index case from Zambia. Serum and tissue samples from victims were subjected to unbiased pyrosequencing, yielding, within 72 hours of sample receipt, multiple discrete sequence fragments that represented approximately 50% of a prototypic arenavirus genome. Thereafter, full genome sequence was generated by PCR amplification of intervening fragments using specific primers complementary to sequence obtained by pyrosequencing and a universal primer targeting the conserved arenaviral terminii. Phylogenetic analyses confirmed the presence of a new member of the family *Arenaviridae*, provisionally named Lujo virus (LUJV) in recognition of its geographic origin (Lusaka, Zambia, and Johannesburg, South Africa). Our findings enable the development of specific reagents to further investigate the reservoir, geographic distribution, and unusual pathogenicity of LUJV and confirm the utility of unbiased, high-throughput pyrosequencing for pathogen discovery and public health investigation.

Arvicanthis spp. and Mobala virus (MOBV; [24]) isolated from *Praomys* spp. in the Central African Republic (CAR); and Mopeia virus (MOPV) that like LASV is associated with members of the genus *Mastomys*, and was reported from Mozambique [25] and Zimbabwe [26], although antibody studies suggest that MOPV and LASV may also circulate in CAR [27] where the geographies of these viruses appear to overlap (Figure 1). Up to present, there have been no published reports of severe human disease associated with arenaviruses isolated from southern Africa.

In September 2008 an outbreak of unexplained hemorrhagic fever was reported in South Africa [28]. The index patient was airlifted in critical condition from Zambia on September 12 to a clinic in Sandton, South Africa, after infection from an unidentified source. Secondary infections were recognized in a paramedic (case 2) who attended the index case during air transfer from Zambia, in a nurse (case 3) who attended the index case in the intensive care unit in South Africa, and in a member of the hospital staff (case 4) who cleaned the room after the index case died on September 14. One case of tertiary infection was recorded in a nurse (case 5) who attended case 2 after his transfer from Zambia to Sandton on September 26, one day before barrier nursing was implemented. The course of disease in cases 1 through 4 was fatal; case 5 received ribavirin treatment and recovered. A detailed description of clinical and epidemiologic data, as well as immunohistological and PCR analyses that indicated the presence of an arenavirus, are reported in a parallel communication (Paweska et al., Emerg. Inf. Dis., submitted). Here we report detailed genetic analysis of this novel arenavirus.

Results/Discussion

Rapid identification of a novel pathogen through unbiased pyrosequencing

RNA extracts from two post-mortem liver biopsies (cases 2 and 3) and one serum sample (case 2) were independently submitted for unbiased high-throughput pyrosequencing. The libraries yielded between 87,500 and 106,500 sequence reads. Alignment of unique singleton and assembled contiguous sequences to the GenBank database (http://www.ncbi.nlm.nih.gov/Genbank) using the Basic Local Alignment Search Tool (blastn and blastx; [29]) indicated coverage of approximately 5.6 kilobases (kb) of sequence distributed along arenavirus genome scaffolds: 2 kb of S segment sequence in two fragments, and 3.6 kb of L segment sequence in 7 fragments (Figure 2). The majority of arenavirus sequences were obtained from serum rather than tissue, potentially reflecting lower levels of competing cellular RNA in random amplification reactions.

Full genome characterization of a newly identified arenavirus

Sequence gaps between the aligned fragments were rapidly filled by specific PCR amplification with primers designed on the pyrosequence data at both, CU and CDC. Terminal sequences were added by PCR using a universal arenavirus primer, targeting the conserved viral termini (5′-CGC ACM GDG GAT CCT AGG C, modified from [30]) combined with 4 specific primers positioned near the ends of the 2 genome segments. Overlapping primer sets based on the draft genome were synthesized to facilitate sequence validation by conventional dideoxy sequencing. The accumulated data revealed a classical arenavirus genome structure with a bi-segmented genome encoding in an ambisense strategy two open reading frames (ORF) separated by an intergenic stem-loop region on each segment (Figure 2) (GenBank Accession numbers FJ952384 and FJ952385).

Our data represent genome sequences directly obtained from liver biopsy and serum (case 2), and from cell culture isolates obtained from blood at CDC (case 1 and 2), and from liver biopsies at NICD (case 2 and 3). No sequence differences were uncovered between virus detected in primary clinical material and virus isolated in cell culture at the two facilities. In addition, no changes were detected between each of the viruses derived from these first three cases. This lack of sequence variation is consistent with the epidemiologic data, indicating an initial natural exposure of the index case, followed by a chain of nosocomial transmission among subsequent cases.

Lujo virus (LUJV) is a novel arenavirus

Phylogenetic trees constructed from full L or S segment nucleotide sequence show LUJV branching off the root of the OW arenaviruses, and suggest it represents a highly novel genetic lineage, very distinct from previously characterized virus species and clearly separate from the LCMV lineage (Figure 3A and 3B). No evidence of genome segment reassortment is found, given the identical placement of LUJV relative to the other OW arenaviruses based on S and L segment nucleotide sequences. In addition, phylogenetic analysis of each of the individual ORFs reveals similar phylogenetic tree topologies. A phylogenetic tree constructed from deduced L-polymerase amino acid (aa) sequence also shows LUJV near the root of the OW arenaviruses, distinct from characterized species, and separate from the LCMV branch (Figure 3C). A distant relationship to OW arenaviruses may also be inferred from the analysis of Z protein sequence (Figure S1). The NP gene sequence of LUJV differs from other arenaviruses from 36% (IPPYV) to 43% (TAMV) at the nucleotide level, and from 41% (MOBV/LASV) to 55% (TAMV) at the aa level (Table S1). This degree of divergence is considerably higher than both, proposed cut-off values within (<10–12%), or between (>21.5%) OW arenavirus species [31,32], and indicates a unique phylogenitic position for LUJV (Figure 3D). Historically, phylogenetic assignments of arenaviruses have been based on portions of the NP gene [1,33], because this is the region for which most sequences are known. However, as more genomic sequences have become available, analyses of full-length GPC sequence have revealed evidence of possible relationships between OW and NW

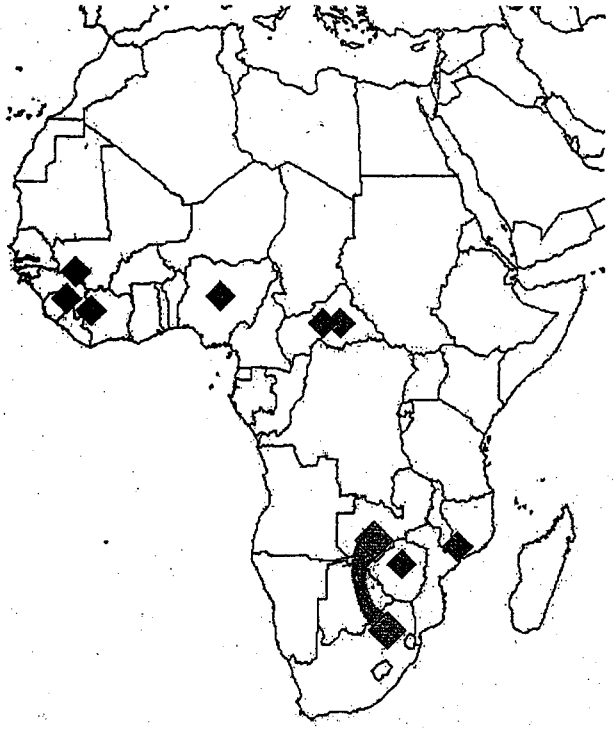

Figure 1. Geographic distribution of African arenaviruses. MOBV, MOPV, and IPPYV (blue) have not been implicated in human disease; LASV (red) can cause hemorrhagic fever. The origin of the LUJV index and secondary and tertiary cases linked in the 2008 outbreak are indicated in gold.
doi:10.1371/journal.ppat.1000455.g001

arenaviruses not revealed by NP sequence alone [34]. Because G1 sequences are difficult to align some have pursued phylogenetic analyses by combining the GPC signal peptide and the G2 sequence for phylogenetic analysis [16]. We included in our analysis the chimeric signal/G2 sequence (Figure 3E) as well as the receptor binding G1 portion (Figure 3F); both analyses highlighted the novelty of LUJV, showing an almost similar distance from OW as from NW viruses.

Protein motifs potentially relevant to LUJV biology

Canonical polymerase domains pre-A, A, B, C, D, and E [35–37] are well conserved in the L ORF of LUJV (256 kDa, pI = 6.4; Figure 4). The Z ORF (10.5 kDa, pI = 9.3) contains two late domain motifs like LASV; however, in place of the PTAP motif found in LASV, that mediates recognition of the tumor susceptibility gene 101, Tsg101 [38], involved in vacuolar protein sorting [39,40], LUJV has a unique Y_{77}REL motif that matches the YXXL motif of the retrovirus equine infectious anemia virus [41], which interacts with the clathrin adaptor protein 2 (AP2) complex [42]. A Tsg101-interacting motif, P_{90}SAP, is found in LUJV in position of the second late domain of LASV, PPPY, which acts as a Nedd4-like ubiquitin ligase recognition motif [43]. The RING motif, containing conserved residue W_{44} [44], and the conserved myristoylation site G_2 are present [45–47] (Figure 4). The NP of LUJV (63.1 kDa, pI = 9.0) contains described aa motifs that resemble mostly OW arenaviruses [48], including a cytotoxic T-lymphocyte (CTL) epitope reported in LCMV (GVYMGNL; [49]), corresponding to G_{122}VYRGNL in LUJV, and a potential antigenic site reported in the N-terminal portion of LASV NP (RKSKRND; [50]), corresponding to R_{55}KDKRND in LUJV (Figure 4).

The GPC precursor (52.3 kDa, pI = 9.0) is cotranslationally cleaved into the long, stable signal peptide and the mature glycoproteins G1 and G2 [51–54]. Based on analogy to LASV [55] and LCMV [56], signalase would be predicted to cleave between D_{58} and S_{59} in LUJV. However, aspartate and arginine

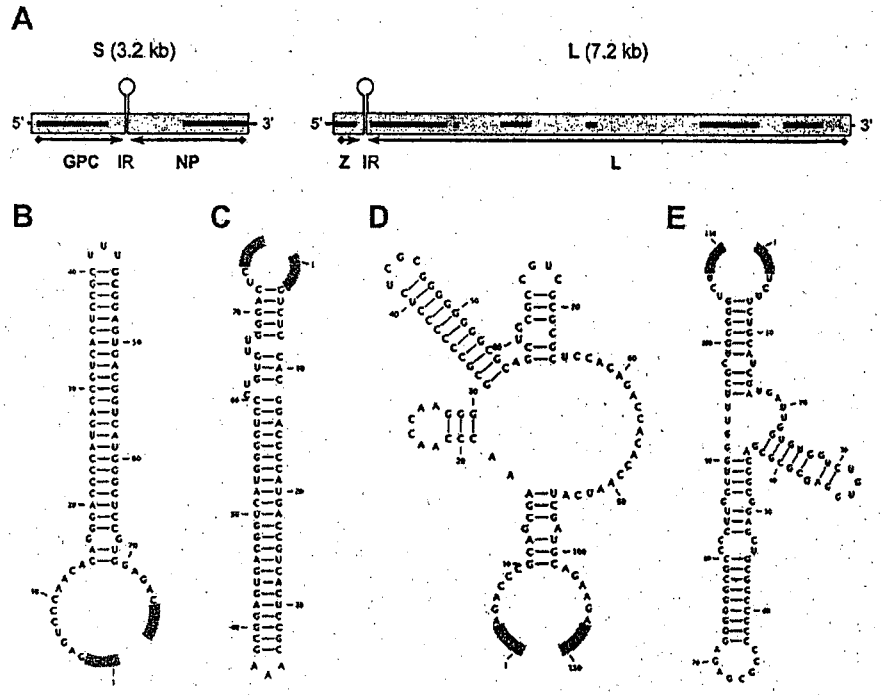

Figure 2. LUJV genome organization and potential secondary structure of intergenic regions. Open reading frames (ORF) for the glycoprotein precursor GPC, the nucleoprotein NP, the matrix protein analog Z, and the polymerase L, and their orientation are indicated (A); blue bars represent sequences obtained by pyrosequencing from clinical samples. Secondary structure predictions of intergenic regions (IR) for S (B, C) and L segment sequence (D, E) in genomic (B, D) and antigenomic orientation (C, E) were analyzed by mfold; shading indicates the respective termination codon (opal, position 1), and its reverse-complement, respectively.
doi:10.1371/journal.ppat.1000455.g002

residues in the −1 and −3 positions, respectively, violate the (−3,−1)-rule [57]; thus, cleavage may occur between S_{59} and S_{60} as predicted by the SignalP algorithm. The putative 59 aa signal peptide of LUJV displays a conserved G_2, implicated in myristoylation in JUNV [58], however, it is followed in LUJV by a non-standard valine residue in position +4, resembling non-standard glycine residues found in Oliveros virus (OLVV [59]) and Latino virus (LATV; http://www2.ncid.cdc.gov/arbocat/catalog-listing.asp?VirusID = 263&SI = 1). Conservation is also observed for aa residues P_{12} (except Amapari virus; AMAV [60]), E_{17} [61](except Pirital virus; PIRV [62]), and N_{20} in hydrophobic domain 1, as well as I_{32}KGVFNLYK$_{40}$SG, identified as a CTL epitope in LCMV WE (I_{32}KAVYNFATCG; [63]) (Figure 4).

Analogous to other arenaviruses, SKI-1/S1P cleavage C-terminal of $RKLM_{221}$ is predicted to separate mature G1 (162 aa, 18.9 kDa, pI = 6.4) from G2 (293 aa, 26.8 kDa, pI = 9.5) [52,53,64]. G2 appears overall well conserved, including the strictly conserved cysteine residues: 6 in the luminal domain, and 3 in the cytoplasmic tail that are included in a conserved zinc finger motif reported in JUNV [65] (Figure 4). G2 contains 6 potential glycosylation sites, including 2 strictly conserved sites, 2 semi-conserved sites N_{335} (absent in LCMVs and Dandenong virus; DANV [19]) and N_{252} (absent in LATV), and 2 unique sites in the predicted cytoplasmic tail (Figure 4). G1 is poorly conserved among arenaviruses [16], and G1 of LUJV is no exception, being highly divergent from the G1 of the other arenaviruses, and shorter than that of other arenaviruses. LUJV G1 contains 6 potential glycosylation sites in positions comparable to other arenaviruses, including a conserved site N_{93}HS (Figure 4), which is shifted by one aa in a motif that otherwise aligns well with OW arenaviruses and NW arenavirus clade A and C viruses. There is no discernable homology to other arenavirus G1 sequences that would point to usage of one of the two identified arenavirus receptors; Alpha-dystroglycan (α-DG) [66] that binds OW arenaviruses LASV and LCMV, and NW clade C viruses OLVV and LATV [67], or transferrin receptor 1 (TfR1) that binds pathogenic NW arenaviruses JUNV, MACV, GTOV, and SABV [68] (Figure S2).

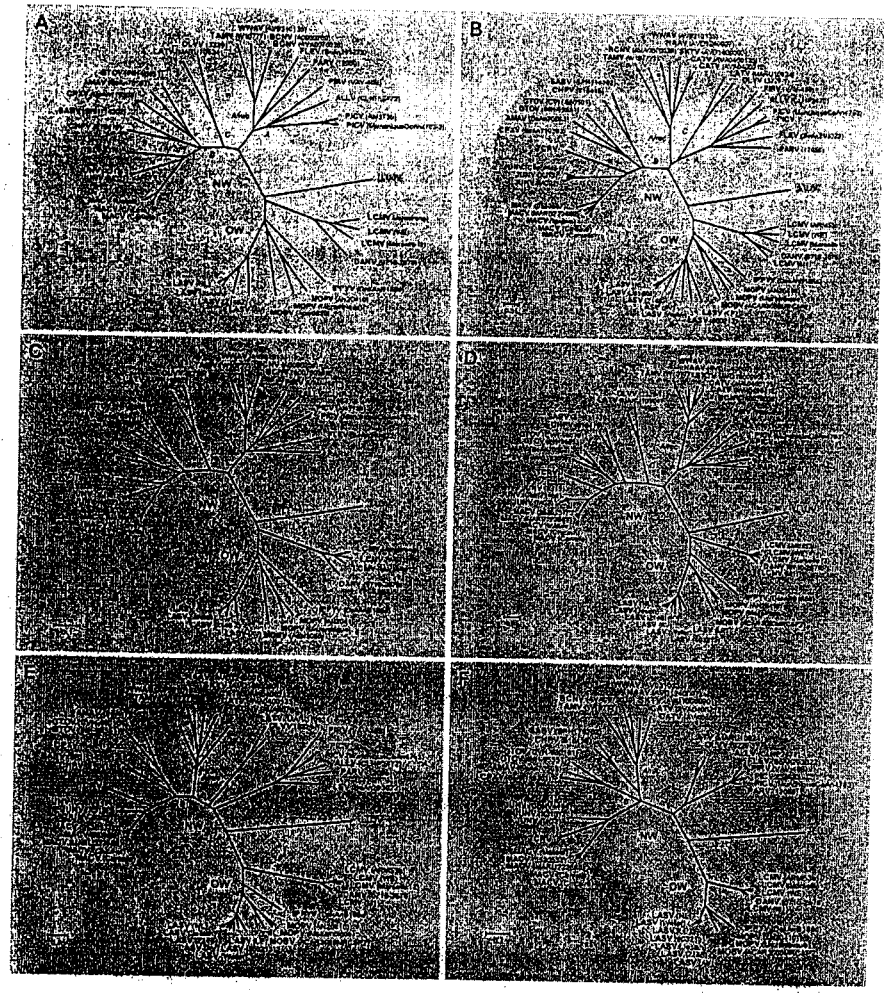

Figure 3. Phylogenetic analyses of LUJV. Phylogenetic relationships of LUJV were inferred based on full L (A) and S segment nucleotide sequence (B), as well as on deduced amino acid sequences of L (C), NP (D), Signal/G2 (E) and G1 (F) ORF's. Phylogenies were reconstructed by neighbor-joining analysis applying a Jukes-Cantor model; the scale bar indicates substitutions per site; robust boostrap support for the positioning of LUJV was obtained in all cases (>98% of 1000 pseudoreplicates). GenBank Accession numbers for reference sequences are: ALLV CLHP2472 (AY216502, AY012687); AMAV BeAn70563 (AF512834); BCNV AVA0070039 (AY924390, AY922491), A0060209 (AY216503); CATV AVA0400135 (DQ865244), AVA0400212 (DQ865245); CHPV 810419 (EU, 260464, EU260463); CPXV BeAn119303 (AY216519, AF512832); DANV 0710-2678 (EU136039, EU136038); FLEV BeAn293022 (EU627611, AF512831); GTOV INH-95551 (AY358024, AF485258), CVH-960101 (AY497548); IPPYV DakAnB188d (DQ328878, DQ328877); JUNV MC2 (AY216507, D10072), XJ13 (AY358022, AY358023), CbalV4454 (DQ272266); LASV LP (AF181853), 803213 (AF181854), Weller (AY628206), AV (AY179171, AF246121), Z148 (AY628204, AY628205), Josiah (U73034, J043204), NL (AY179172, AY179173); LATV MARU10924 (EU627612, AF485259); LCMV Armstrong (AY847351), ARM53b (M20869), WE (AF004519, M22138), Marseille12 (DQ286932, DQ286931), M1 (AB261991); MACV Carvallo (AY619642, AY619643), Chicava (AY624354, AY624355), Mallele (AY619644, AY619645), MARU222688 (AY922407), 9530537 (AY571959); MOBV ACAR3080MRC5P2 (DQ328876, AY342390); MOPV AN20410 (AY772169, AY772170), Mozambique (DQ328875, DQ328874); NAAV AVD1240007 (EU123329); OLVV 3229-1 (AY216514, U34248); PARV 12056 (EU627613, AF485261); PICV (K02734), MunchiqueCoAn4763 (EF529745, EF529744), AN3739 (AF427517); PIRV VAV-488 (AY216505, AF277659); SABV SPH114202 (AY358026, U41071); SKTV AVD1000090 (EU123328); TAMV W10777 (EU627614, AF512828); TCRV (J04340, M20304); WWAV AV9310135 (AY924395, AF228063).
doi:10.1371/journal.ppat.1000455.g003

In summary, our analysis of the LUJV genome shows a novel virus that is only distantly related to known arenaviruses. Sequence divergence is evident across the whole genome, but is most pronounced in the G1 protein encoded by the S segment, a region implicated in receptor interactions. Reassortment of S and L segments leading to changes in pathogenicity has been described in cultured cells infected with different LCMV strains [69], and between pathogenic LASV and nonpathogenic MOPV [70]. We find no evidence to support reassortment of the LUJV L or S genome segment (Figure 3A and 3B). Recombination of glycoprotein sequence has been recognized in NW arenaviruses [14,16,33,34,71–73], resulting in the division of the complex into four sublineages: lineages A, B, C, and an A/recombinant lineage that forms a branch of lineage A when NP and L sequence is considered (see Figure 3C and 3D), but forms an independent branch in between lineages B and C when glycoprotein sequence is considered (see Figure 3D). While recombination cannot be excluded in case of LUJV, our review of existing databases reveals no candidate donor for the divergent GPC sequence. To our knowledge is LUJV the first hemorrhagic fever-associated arenavirus from Africa identified in the past 3 decades. It is also the first such virus originating south of the equator (Figure 1). The International Committee on the Taxonomy of Viruses (ICTV) defines species within the *Arenavirus* genus based on association with a specific host, geographic distribution, potential to cause human disease, antigenic cross reactivity, and protein sequence similarity to other species. By these criteria, given the novelty of its presence in southern Africa, capacity to cause hemorrhagic fever, and its genetic distinction, LUJV appears to be a new species.

Materials and Methods

Sequencing

Clinical specimens were inactivated in TRIzol (liver tissue, 100 mg) or TRIzol LS (serum, 250 µl) reagent (Invitrogen, Carlsbad, CA, USA) prior to removal from BSL-4 containment. Total RNA extracts were treated with DNase I (DNA-free, Ambion, Austin, TX, USA) and cDNA generated by using the Superscript II system (Invitrogen) and 100–500 ng RNA for reverse transcription primed with random octamers that were linked to an arbitrary, defined 17-mer primer sequence [74]. The resulting cDNA was treated with RNase H and then randomly amplified by the polymerase chain reaction (PCR; [75]); applying a 9:1 mixture of a primer corresponding to the defined 17-mer sequence, and the random octamer-linked 17-mer primer, respectively [74]. Products >70 base pairs (bp) were selected by column purification (MinElute, Qiagen, Hilden, Germany) and ligated to specific linkers for sequencing on the 454 Genome Sequencer FLX (454 Life Sciences, Branford, CT, USA) without fragmentation of the cDNA [19,76,77]). Removal of primer sequences, redundancy filtering,

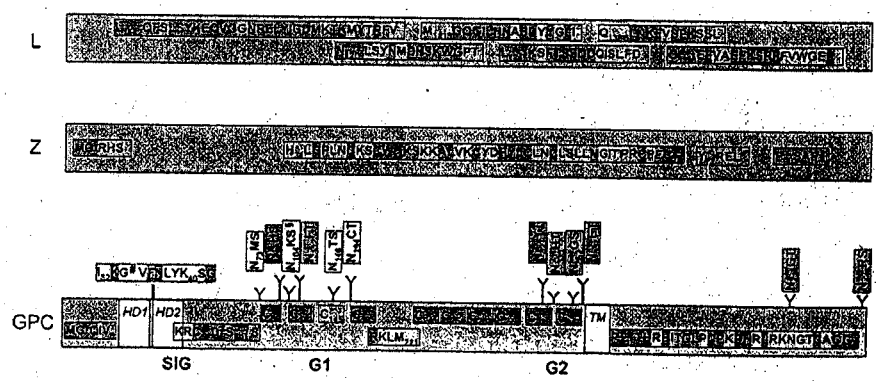

Figure 4. Schematic of conserved protein motifs. Conservation of LUJV amino acid motifs with respect to all other (green highlight), to OW (yellow highlight), or to NW (blue highlight) arenaviruses is indicated; grey highlight indicates features unique to LUJV. Polymerase motifs pre-A (L_{1142}), A (N_{1209}), B (M_{1313}), C (L_{1345}), D (Q_{1386}), and E (C_{1398}) are indicated for the L ORF; potential myristoylation site G_2, the RING motif H_{34}/C_{76}, and potential late domains YXXL an PSAP are indicated for the Z ORF; and myristoylation site G_2, posttranslational processing sites for signalase (S_{59}/S_{60}) and S1P cleavage ($RKLM_{221}$), CTL epitope (I_{32}), zinc finger motif P_{415}/G_{440}, as well as conserved cysteine residues and glycosylations sites (Y) are indicated for GPC. * late domain absent in NW viruses and DANV; † PSAP or PTAP in NW viruses, except in PIRV and TCRV (OW viruses: PPPY); # G in all viruses except LCMV (= A); ‡ D in NW clade A only; § conserved with respect to OW, and NW clade A and C; *HD*, hydrophobic domain; *TM*, transmembrane anchor.
doi:10.1371/journal.ppat.1000455.g004

and sequence assembly were performed with software programs accessible through the analysis applications at the GreenePortal website (http://156.145.84.111/Tools).

Conventional PCRs at CU were performed with HotStar polymerase (Qiagen) according to manufacturer's protocols on PTC-200 thermocyclers (Bio-Rad, Hercules, CA, USA): an enzyme activation step of 5 min at 95°C was followed by 45 cycles of dehaturation at 95°C for 1 min, annealing at 55°C for 1 min, and extension at 72°C for 1 to 3 min depending on the expected amplicon size. A two-step RT-PCR protocol was also followed at CDC using Invitrogen's Thermoscript RT at 60 degrees for 30 min followed by RNase H treatment for 20 min. cDNA was amplified using Phusion enzyme with GC Buffer (Finnzymes, Espoo, Finland) and 3% DMSO with an activation step at 98°C for 30 sec, followed by the cycling conditions of 98°C for 10 sec, 58°C for 20 sec, and 72°C for 1 min for 35 cycles and a 5 min extension at 72°C. Specific primer sequences are available upon request. Amplification products were run on 1% agarose gels, purified (MinElute, Qiagen), and directly sequenced in both directions with ABI PRISM Big Dye Terminator 1.1 Cycle Sequencing kits on ABI PRISM 3700 DNA Analyzers (Perkin-Elmer Applied Biosystems, Foster City, CA).

Sequence analyses

Programs of the Wisconsin GCG Package (Accelrys, San Diego, CA, USA) were used for sequence assembly and analysis; percent sequence difference was calculated based on Needleman-Wunsch alignments (gap open/extension penalties 15/6.6 for nucleotide and 10/0.1 for aa alignments; EMBOSS [78]), using a Perl script to iterate the process for all versus all comparison. Secondary RNA structure predictions were performed with the web-based version of mfold (http://mfold.bioinfo.rpi.edu); data were exported as .ct files and layout and annotation was done with CLC RNA Workbench (CLC bio, Århus, Denmark). Protein topology and targeting predictions were generated by employing SignalP, and NetNGlyc, TMHMM (http://www.cbs.dtu.dk/services), the web-based version of TopPred (http://mobyle.pasteur.fr/cgi-bin/portal.py?form=toppred), and Phobius (http://phobius.sbc.su.se/). Phylogenetic analyses were performed using MEGA software [79].

References

1. Bowen MD, Peters CJ, Nichol ST (1997) Phylogenetic analysis of the Arenaviridae: patterns of virus evolution and evidence for cospeciation between arenaviruses and their rodent hosts. Mol Phylogenet Evol 8: 301–316.
2. Moncayo AC, Hice CL, Watts DM, Travassos de Rosa AP, Guzman H, et al. (2001) Allpahuayo virus: a newly recognized arenavirus (arenaviridae) from arboreal rice rats (oecomys bicolor and oecomys paricola) in northeastern peru. Virology 284: 277–286.
3. Armstrong C, Lillie RD (1934) Experimental lymphocytic choriomeningitis of monkeys and mice produced by a virus encountered in studies of the 1933 St. Louis encephalitis epidemic. Public Health Rep 49: 1019–1027.
4. Auperin DD, Romanowski V, Galinski M, Bishop DH (1984) Sequencing studies of pichinde arenavirus S RNA indicate a novel coding strategy, an ambisense viral S RNA. J Virol 52: 897–904.
5. Salvato MS, Shimomaye EM (1989) The completed sequence of lymphocytic choriomeningitis virus reveals a unique RNA structure and a gene for a zinc finger protein. Virology 173: 1–10.
6. Parodi AS, Greenway DJ, Rugiero HR, Frigerio M, De La Barrera JM, et al. (1958) [Concerning the epidemic outbreak in Junin.]. Dia Med 30: 2300–2301.
7. Pirosky I, Zuccarini J, Molinelli EA, Di Pietro A, Barrera Oro JG, et al. (1959) Virosis hemorragica del Noroeste Bonaerense. Orientacion Medica 8: 303–311.
8. Johnson KM, Wiebenga NH, Mackenzie RB, Kuns ML, Taurason NM, et al. (1965) Virus Isolations from Human Cases of Hemorrhagic Fever in Bolivia. Proc Soc Exp Biol Med 118: 113–118.
9. Salas R, de Manzione N, Tesh RB, Rico-Hesse R, Shope RE, et al. (1991) Venezuelan haemorrhagic fever. Lancet 338: 1033–1036.
10. Coimbra TLM, Nassar ES, Burattini MN, de Souza LTM, Ferreira IB, et al. (1994) New arenavirus isolated in Brazil. Lancet 343: 391–392.
11. Buckley SM, Casals J (1970) Lassa fever, a new virus disease of man from West Africa. 3. Isolation and characterization of the virus. Am J Trop Med Hyg 19: 680–691.
12. Downs WG, Anderson CR, Spence L, Aitken THG, Greenhall AH (1963) Tacaribe virus, a new agent isolated from Artibeus bats and mosquitoes in Trinidad, West Indies. Am J Trop Med Hyg 12: 640–646.
13. Buchmeier MJ, de la Torre JC, Peters CJ (2007) Arenaviridae: the viruses and their replication. In: Knipe DM, Howley PM, eds. Fields Virology. Philadelphia, PA, USA: Wolter Kluwer Lippincott Williams & Wilkins. pp 1791–1827.
14. Fulhorst CF, Bowen MD, Ksiazek TG, Rollin PE, Nichol ST, et al. (1996) Isolation and characterization of Whitewater Arroyo virus, a novel North American arenavirus. Virology 224: 114–120.
15. Hugot JP, Gonzalez JP, Denys C (2001) Evolution of the Old World Arenaviridae and their rodent hosts: generalized host-transfer or association by descent? Infect Genet Evol 1: 13–20.
16. Charrel RN, de Lamballerie X, Emonet S (2008) Phylogeny of the genus Arenavirus. Curr Opin Microbiol 11: 362–368.
17. Fischer SA, Graham MB, Kuehnert MJ, Kotton CN, Srinivasan A, et al. (2006) Transmission of lymphocytic choriomeningitis virus by organ transplantation. N Engl J Med 354: 2235–2249.
18. Amman BR, Pavlin BI, Albarino CG, Comer JA, Erickson BR, et al. (2007) Pet rodents and fatal lymphocytic choriomeningitis in transplant patients. Emerg Infect Dis 13: 719–725.
19. Palacios G, Druce J, Du L, Tran T, Birch C, et al. (2008) A new arenavirus in a cluster of fatal transplant-associated diseases. N Engl J Med 358: 991–998.
20. Ogbu O, Ajuluchukwu E, Uneke CJ (2007) Lassa fever in West African sub-region: an overview. J Vector Borne Dis 44: 1–11.

Supporting Information

Figure S1 Phylogenetic tree based on deduced Z amino acid sequence. In contrast to phylogenetic trees obtained with the other ORFs (Figure 2), poor bootstrap support (43% of 1,000 pseudoreplicates) for the branching of LUJV off the LCMV clade was obtained with Z ORF sequence. For GenBank accession numbers see Figure 2.
Found at: doi:10.1371/journal.ppat.1000455.s001 (0.44 MB TIF)

Figure S2 Pairwise sliding-window distance analysis of GPC sequence. LUJV and members of the OW (LASV, MOPV, IPPYV, LCMV, DANV) and NW (GTOV, CPXV, BNCV, PIRV, OLVV, SABV, MACV) arenavirus complex were compared using LASV NL (A) or GTOV CVH (B) as query (10 aa step; 80 aa window).
Found at: doi:10.1371/journal.ppat.1000455.s002 (4.21 MB TIF)

Table S1 Pairwise nucleotide and amino acid differences between LUJV and other OW and NW arenaviruses. * NAAV, North American arenavirus. † Values <30% (amino acid) or <33% (nucleotide) are highlighted in green.
Found at: doi:10.1371/journal.ppat.1000455.s003 (0.20 MB DOC)

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Author Contributions

Conceived and designed the experiments: TB WIL. Performed the experiments: TB JTP LKM SKH GP MLK JW. Analyzed the data: TB LKM SKH CS GP MLK ME STN WIL. Contributed reagents/materials/analysis tools: JTP CS JW BS ME. Wrote the paper: TB JTP BS STN WIL.

21. Khan SH, Goba A, Chu M, Roth C, Healing T, et al. (2008) New opportunities for field research on the pathogenesis and treatment of Lassa fever. Antiviral Res 78: 103–115.
22. Swanepoel R, Leman PA, Shepherd AJ, Shepherd SP, Kiley MP, et al. (1985) Identification of Ippy as a Lassa-fever-related virus. Lancet 1: 639.
23. Meunier DY, McCormick JB, Georges AJ, Georges MC, Gonzalez JP (1985) Comparison of Lassa, Mobala, and Ippy virus reactions by immunofluorescence test. Lancet 1: 873–874.
24. Gonzalez JP, McCormick JB, Saluzzo JF, Herve JP, Georges AJ, et al. (1983) An arenavirus isolated from wild-caught rodents (Praomys species) in the Central African Republic. Intervirology 19: 105–112.
25. Wulff H, McIntosh BM, Hamner DB, Johnson KM (1977) Isolation of an arenavirus closely related to Lassa virus from Mastomys natalensis in south-east Africa. Bull World Health Organ 55: 441–444.
26. Johnson KM, Taylor P, Elliot LH, Tomori O (1981) Recovery of a Lassa-related arenavirus in Zimbabwe. Am J Trop Med Hyg 30: 1291–1293.
27. Georges AJ, Gonzalez JP, Abdul-Wahid S, Saluzzo JF, Meunier DM, et al. (1985) Antibodies to Lassa and Lassa-like viruses in man and mammals in the Central African Republic. Trans R Soc Trop Med Hyg 79: 78–79.
28. National Institute for Communicable Diseases (2008) Arenavirus outbreak, South Africa. Communicable Diseases Communique 7: 1–3. http://www.nicd.ac.za.
29. Altschul SF, Gish W, Miller W, Myers EW, Lipman DJ (1990) Basic local alignment search tool. J Mol Biol 215: 403–410.
30. Clegg JC, Wilson SM, Oram JD (1991) Nucleotide sequence of the S RNA of Lassa virus (Nigerian strain) and comparative analysis of arenavirus gene products. Virus Res 18: 151–164.
31. Bowen MD, Rollin PE, Ksiazek TG, Hustad HL, Bausch DG, et al. (2000) Genetic diversity among Lassa virus strains. J Virol 74: 6992–7004.
32. Emonet S, Lemasson JJ, Gonzalez JP, de Lamballerie X, Charrel RN (2006) Phylogeny and evolution of old world arenaviruses. Virology 350: 251–257.
33. Bowen MD, Peters CJ, Nichol ST (1996) The phylogeny of New World (Tacaribe complex) arenaviruses. Virology 219: 285–290.
34. Albarino CG, Posik DM, Ghiringhelli PD, Lozano ME, Romanowski V (1998) Arenavirus phylogeny: a new insight. Virus Genes 16: 39–46.
35. Poch O, Sauvaget I, Delarue M, Tordo N (1989) Identification of four conserved motifs among the RNA-dependent polymerase encoding elements. EMBO J 8: 3867–3874.
36. Delarue M, Poch O, Tordo N, Moras D, Argos P (1990) An attempt to unify the structure of polymerases. Protein Eng 3: 461–467.
37. Müller R, Poch O, Delarue M, Bishop DH, Bouloy M (1994) Rift Valley fever virus L segment: correction of the sequence and possible functional role of newly identified regions conserved in RNA-dependent polymerases. J Gen Virol 75(Pt 6): 1345–1352.
38. Perez M, Craven RC, de la Torre JC (2003) The small RING finger protein Z drives arenavirus budding: implications for antiviral strategies. Proc Natl Acad Sci U S A 100: 12978–12983.
39. Garrus JE, von Schwedler UK, Pornillos OW, Morham SG, Zavitz KH, et al. (2001) Tsg101 and the vacuolar protein sorting pathway are essential for HIV-1 budding. Cell 107: 55–65.
40. VerPlank L, Bouamr F, LaGrassa TJ, Agresta B, Kikonyogo A, et al. (2001) Tsg101, a homologue of ubiquitin-conjugating (E2) enzymes, binds the L domain in HIV type 1 Pr55(Gag). Proc Natl Acad Sci U S A 98: 7724–7729.
41. Puffer BA, Parent LJ, Wills JW, Montelaro RC (1997) Equine infectious anemia virus utilizes a YXXL motif within the late assembly domain of the Gag p9 protein. J Virol 71: 6541–6546.
42. Puffer BA, Watkins SC, Montelaro RC (1998) Equine infectious anemia virus Gag polyprotein late domain specifically recruits cellular AP-2 adapter protein complexes during virion assembly. J Virol 72: 10218–10221.
43. Staub O, Dho S, Henry P, Correa J, Ishikawa T, et al. (1996) WW domains of Nedd4 bind to the proline-rich PY motifs in the epithelial Na+ channel deleted in Liddle's syndrome. EMBO J 15: 2371–2380.
44. Joazeiro CA, Wing SS, Huang H, Leverson JD, Hunter T, et al. (1999) The tyrosine kinase negative regulator c-Cbl as a RING-type, E2-dependent ubiquitin-protein ligase. Science 286: 309–312.
45. Perez M, Greenwald DL, de la Torre JC (2004) Myristoylation of the RING finger Z protein is essential for arenavirus budding. J Virol 78: 11443–11448.
46. Strecker T, Maisa A, Daffis S, Eichler R, Lenz O, et al. (2006) The role of myristoylation in the membrane association of the Lassa virus matrix protein Z. Virol J 3: 93.
47. Capul AA, Perez M, Burke E, Kunz S, Buchmeier MJ, et al. (2007) Arenavirus Z-glycoprotein association requires Z myristoylation but not functional RING or late domains. J Virol 81: 9451–9460.
48. Gonzalez JP, Bowen MD, Nichol ST, Rico-Hesse R (1996) Genetic characterization and phylogeny of Sabia virus, an emergent pathogen in Brazil. Virology 221: 318–324.
49. Whitton JL, Tishon A, Lewicki H, Gebhard J, Cook T, et al. (1989) Molecular analyses of a five-amino-acid cytotoxic T-lymphocyte (CTL) epitope: an immunodominant region which induces nonreciprocal CTL cross-reactivity. J Virol 63: 4303–4310.
50. Gonzalez JP, Sanchez A, Rico-Hesse R (1995) Molecular phylogeny of Guanarito virus, an emerging arenavirus affecting humans. Am J Trop Med Hyg 53: 1–6.
51. Lenz O, ter Meulen J, Klenk HD, Seidah NG, Garten W (2001) The Lassa virus glycoprotein precursor GP-C is proteolytically processed by subtilase SKI-1/S1P. Proc Natl Acad Sci U S A 98: 12701–12705.
52. Beyer WR, Popplau D, Garten W, von Laer D, Lenz O (2003) Endoproteolytic processing of the lymphocytic choriomeningitis virus glycoprotein by the subtilase SKI-1/S1P. J Virol 77: 2866–2872.
53. Rojek JM, Lee AM, Nguyen N, Spiropoulou CF, Kunz S (2008) Site 1 protease is required for proteolytic processing of the glycoproteins of the South American hemorrhagic fever viruses Junin, Machupo, and Guanarito. J Virol 82: 6045–6051.
54. Burns JW, Buchmeier MJ (1991) Protein-protein interactions in lymphocytic choriomeningitis virus. Virology 183: 620–629.
55. Eichler R, Lenz O, Strecker T, Garten W (2003) Signal peptide of Lassa virus glycoprotein GP-C exhibits an unusual length. FEBS Lett 538: 203–206.
56. Burns JW, Buchmeier MJ (1993) Glycoproteins of the arenaviruses. In: Salvato MS, ed. The Arenaviridae. New York: Plenum Press. pp 17–33(35).
57. von Heijne G (1984) How signal sequences maintain cleavage specificity. J Mol Biol 173: 243–251.
58. York J, Romanowski V, Lu M, Nunberg JH (2004) The signal peptide of the Junin arenavirus envelope glycoprotein is myristoylated and forms an essential subunit of the mature G1–G2 complex. J Virol 78: 10783–10792.
59. Bowen MD, Peters CJ, Mills JN, Nichol ST (1996) Oliveros virus: a novel arenavirus from Argentina. Virology 217: 362–366.
60. Pinheiro FP, Shope RE, de Andrade AHP, Bensabath G, Cacios GV, et al. (1966) Amapari, a new virus of the Tacaribe group from rodents and mites of Amapa Territory, Brazil. Proc Soc Exp Biol Med 122: 531–535.
61. York J, Nunberg JH (2006) Role of the stable signal peptide of Junin arenavirus envelope glycoprotein in pH-dependent membrane fusion. J Virol 80: 7775–7780.
62. Fulhorst CE, Bowen MD, Salas RA, de Manzione NM, Duno G, et al. (1997) Isolation and characterization of pirital virus, a newly discovered South American arenavirus. Am J Trop Med Hyg 56: 548–553.
63. Fircher H, Moskophidis D, Rohrer U, Burki K, Hengartner H, et al. (1990) Viral escape by selection of cytotoxic T cell-resistant virus variants in vivo. Nature 346: 629–633.
64. Lenz O, ter Meulen J, Feldmann H, Klenk HD, Garten W (2000) Identification of a novel consensus sequence at the cleavage site of the Lassa virus glycoprotein. J Virol 74: 11418–11421.
65. York J, Nunberg JH (2007) A novel zinc-binding domain is essential for formation of the functional Junin virus envelope glycoprotein complex. J Virol 81: 13385–13391.
66. Cao W, Henry MD, Borrow P, Yamada H, Elder JH, et al. (1998) Identification of alpha-dystroglycan as a receptor for lymphocytic choriomeningitis virus and Lassa fever virus. Science 282: 2079–2081.
67. Spiropoulou CF, Kunz S, Rollin PE, Campbell KP, Oldstone MB (2002) New World arenavirus clade C, but not clade A and B viruses, utilizes alpha-dystroglycan as its major receptor. J Virol 76: 5140–5146.
68. Radoshitzky SR, Abraham J, Spiropoulou CF, Kuhn JH, Nguyen D, et al. (2007) Transferrin receptor 1 is a cellular receptor for New World haemorrhagic fever arenaviruses. Nature 446: 92–96.
69. Riviere Y, Ahmed R, Southern PJ, Buchmeier MJ, Oldstone MB (1985) Genetic mapping of lymphocytic choriomeningitis virus pathogenicity: virulence in guinea pigs is associated with the L RNA segment. J Virol 55: 704–709.
70. Lukashevich IS, Patterson J, Carrion R, Moshkoff D, Ticer A, et al. (2005) A live attenuated vaccine for Lassa fever made by reassortment of Lassa and Mopeia viruses. J Virol 79: 13934–13942.
71. Archer AM, Rico-Hesse R (2002) High genetic divergence and recombination in Arenaviruses from the Americas. Virology 304: 274–281.
72. Charrel RN, de Lamballerie X, Fulhorst CF (2001) The Whitewater Arroyo virus: natural evidence for genetic recombination among Tacaribe serocomplex viruses (family Arenaviridae). Virology 283: 161–166.
73. Charrel RN, Feldmann H, Fulhorst CF, Khelifi R, de Chesse R, et al. (2002) Phylogeny of New World arenaviruses based on the complete coding sequences of the small genomic segment identified an evolutionary lineage produced by intrasegmental recombination. Biochem Biophys Res Commun 296: 1118–1124.
74. Palacios G, Quan PL, Jabado OJ, Conlan S, Hirschberg DL, et al. (2007) Panmicrobial oligonucleotide array for diagnosis of infectious diseases. Emerg Infect Dis 13: 73–81.
75. Saiki RK, Scharf S, Faloona F, Mullis KB, Horn GT, et al. (1985) Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia. Science 230: 1350–1354.
76. Margulies M, Egholm M, Altman WE, Attiya S, Bader JS, et al. (2005) Genome sequencing in microfabricated high-density picolitre reactors. Nature 437: 376–380.
77. Cox-Foster DL, Conlan S, Holmes EC, Palacios G, Evans JD, et al. (2007) A metagenomic survey of microbes in honey bee colony collapse disorder. Science 318: 283–287.
78. Rice P, Longden I, Bleasby A (2000) EMBOSS: the European Molecular Biology Open Software Suite. Trends Genet 16: 276–277.
79. Kumar S, Tamura K, Nei M (2004) MEGA3: Integrated software for Molecular Evolutionary Genetics Analysis and sequence alignment. Brief Bioinform 5: 150–163.

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 2009年2月2日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称	別紙のとおり		研究報告の公表状況	ProMED-mail, 20090129.0400	公表国 スウェーデン	
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：ユンガンウイルスがヒトにおける子宮内胎児死亡に関連していることが示唆された。 ユンガンウイルス（パレコウイルス属、ピコルナウイルス科）は、実験用マウスにおいて胎児の死亡や奇形を起こすことが知られている。研究データ及び疫学的データからこのウイルスがヒトにおける子宮内胎児死亡に関連していることが示唆された。 このウイルスは、スウェーデン中央部のユンガン川の近くに生息するハタネズミ（野生齧歯類宿主の一種）から分離された。ユンガンウイルスは、米国の野生の齧歯類においても確認されている。また、同様に齧歯類を主な宿主とするカルディオウイルス属やピコルナウイルス属と関係があるとされている。 実験用マウスでの研究では、妊娠中にユンガンウイルスに感染し、ストレスにさらされた母親の半数以上は周産期に死産した。その中には、水頭症や無脳症といった中枢神経系の奇形が認められた子マウスもいた。 スウェーデンでの最近の研究で、子宮内胎児死亡があったヒトの胎盤及び組織において、免疫組織化学的手法及びリアルタイム PCR によってユンガンウイルスが検出された。コントロールとした正常妊婦の胎盤からはウイルスは検出されなかった。子宮内胎児死亡の発生と周期的な齧歯類の密度との間に興味ある関連が認められている。米国の子宮内胎児死亡例においても、ユンガンウイルスが確認されている。	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。

MedDRA/J ver.11.1

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乾燥ペプシン処理人免疫グロブリン、⑥乾燥スルホ化人免疫グロブリン、⑦乾燥スルホ化人免疫グロブリン*、⑧乾燥濃縮人活性化プロテインC、⑨乾燥濃縮人血液凝固第Ⅷ因子、⑩乾燥濃縮人血液凝固第Ⅸ因子、⑪乾燥抗破傷風人免疫グロブリン、⑫抗 HBs 人免疫グロブリン、⑬トロンビン、⑭フィブリノゲン加第ⅩⅢ因子、⑮乾燥濃縮人アンチトロンビンⅢ、⑯ヒスタミン加人免疫グロブリン製剤、⑰人血清アルブミン*、⑱人血清アルブミン*、⑲乾燥ペプシン処理人免役グロブリン*、⑳乾燥人血液凝固第Ⅸ因子複合体*、㉑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献血静注グロブリン“化血研”、⑥献血ベニロンーⅠ、⑦ベニロン*、⑧注射用アナクトC2,500単位、⑨コンファクトF、⑩ノバクトM、⑪テタノセーラ筋注用250単位、⑫ヘパトセーラ、⑬トロンビン“化血研”、⑭ボルヒール、⑮アンスロビンP、⑯ヒスタグロビン、⑰アルブミン20%化血研*、⑱アルブミン5%化血研*、⑲静注グロブリン*、⑳ノバクトF*、㉑アンスロビンP1500注射用
報告企業の意見	ユンガンウイルスが属するパレコウイルス属は、9つあるピコルナウイルス科の属の1つで、他にヒトパレコウイルスが属している。ピコルナウイルス科ウイルスは、一本のプラス鎖 RNA を核酸として持ち、直径22～30nm でエンベロープを持たない。ヒトパレコウイルスは呼吸器官と消化器官で増殖する。幼児を中心として感染するが、ほとんどが無症候性と見られている。呼吸器感染や下痢症に加え、中枢神経系の感染症も報告されている。ユンガンウイルスは野ネズミから分離されているが、情報は少ない。 本研究報告はユンガンウイルスの垂直感染に関する報告であり、ヒト血液を原材料とする本剤に直ちに影響があるものではない。仮に、ウイルスが原材料に混入していたとしても、本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及び不活化工程が存在しているので、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。今回報告したユンガンウイルスは、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HAVまたはEMCV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、本剤の製造工程がこれらのウイルスの除去・不活化効果を有することを確認している。また、これまでに本剤によるユンガンウイルスの感染の報告例は無い。 以上の点から、本剤はユンガン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

Archive Number 20090129.0400
Published Date 29-JAN-2009
Subject PRO/AH/EDR> Ljungan virus, intrauterine fetal death - Sweden

LJUNGAN VIRUS, INTRAUTERINE FETAL DEATH - SWEDEN
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A ProMED-mail post
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International Society for Infectious Diseases
<http://www.isid.org>

Date: Wed 28 Jan 2009
From: Bo Niklasson <bo.niklasson@medcellbiol.uu.se>

Ljungan virus associated with intrauterine fetal death in humans (Sweden)

Ljungan virus (genus _Parechovirus_, family _Picornaviridae_) has been shown to cause fetal death and malformations in laboratory mice. The virus now has been associated with intrauterine fetal deaths in humans based on both laboratory and epidemiological evidence. This virus was isolated from one of its wild rodent reservoirs, the bank vole (_Myodes glareolus_), near the Ljungan River in central Sweden (1, 2). Ljungan virus also has been identified in wild rodents in the USA (3, 4). Ljungan virus is related to cardioviruses, picornaviruses which also have rodents as their main reservoir hosts.

Cardioviruses and their role as potential human pathogens recently were discussed on ProMED — see ProMED archive refs. below.

Studies with laboratory mice showed that more than half of the dams infected with Ljungan virus during pregnancy and then exposed to stress gave birth to pups that died during the perinatal period (5). Malformations of the central nervous system, including hydrocephaly [water on the brain] and anencephaly [lack of brain], were seen in some of these offspring.

Recent studies in Sweden found Ljungan virus in placenta and tissue from human cases of intrauterine fetal death (IUFD) using both immunohistochemistry and real time RT-PCR (6, 7). Placentas from normal pregnancies have been used as controls and found to be Ljungan virus-negative. An intriguing association between the incidence of IUFD and cyclic rodent density has been observed. Ljungan virus also was found in one IUFD case in the United States.

References:

1. Niklasson B, Kinnunen L, Hornfeldt B, Horling J, Benemar C, Hedlund KO, et al. A new picornavirus isolated from bank voles (Clethrionomys glareolus). Virology 1999 Mar 1;255(1):86-93.
2. Niklasson B, Nyholm E, Feinstein RE, Samsioe A, Hornfeldt B. Diabetes and myocarditis in voles and lemmings at cyclic peak densities--induced by Ljungan virus? Oecologia 2006 Nov;150(1):1-7.
3. Main AJ, Shope RE, Wallis RC. Characterization of Whitney's Clethrionomys gapperi virus isolates from Massachusetts. J Wildl Dis 1976 Apr;12(2):154-64.
4. Whitney E, Roz AP, Rayner GA. Two viruses isolated from rodents (Clethrionomys gapperi and Microtus pennsylvanicus) trapped in St. Lawrence County, New York. J Wildl Dis 1970 Jan;6(1):48-55.
5. Samsioe A, Feinstein R, Saade G, Sjoholm A, Hornfeldt B, Fundele R, et al. Intrauterine death, fetal malformation, and delayed pregnancy in Ljungan virus-infected mice: Birth Defects Res B Dev Reprod Toxicol 2006 Aug;77(4):251-6.
6. Samsioe A, Papadogiannakis N, Hultman T, Sjoholm A, Klitz W, Niklasson B. Ljungan virus present in intrauterine fetal death diagnosed by both immunohistochemistry and PCR. Birth Defects Res A Clin Mol Teratol 2009 Jan 9.
7. Niklasson B, Samsioe A, Papadogiannakis N, Kawecki A, Hornfeldt B, Saade GR, et al. Association of zoonotic Ljungan virus with intrauterine fetal deaths. Birth Defects Res A Clin Mol Teratol 2007 Jun;79(6):488-93.

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[The genus _Parechovirus_ is one of the 9 genera comprising the family _Picornaviridae_ and includes 2 species, _Human parechovirus_ and _Ljungan virus_. According to Virus Taxonomy (The Eighth Report of the International Committee on Taxonomy of Viruses), the human parechoviruses replicate in the respiratory and gastrointestinal tracts. Infection is particularly prevalent in young children but is probably mostly asymptomatic. In addition to respiratory infections and diarrhea, infections of the central nervous system have been reported occasionally. The cytopathology may be unusual in including changes in granularity and chromatin distribution in the nucleus when viewed by the electron microscope. Isolates of Ljungan virus appear to infect predominantly rodents. The predicted protein sequences of parechoviruses are highly divergent, with no protein having a greater than 30 percent level of identity compared with corresponding proteins of any other member of the family _Picornaviridae_. The American and Swedish isolates of Ljungan virus show some divergence.

*****Professor Niklasson has indicated that he is seeking collaborators to pursue these observations in greater depth. Anyone with an interest or involvement in the field should contact Professor Niklasson directly.*****
- Mod.CP]

[see also:
2008

Cardioviruses, human (02): global presence 20080911.2845
Cardioviruses, human: 1st report 20080910.2824
1998

Myocarditis, rodent vector - Sweden 19980720.1371]
.....chc/cp/msp/jw
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医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	総合機構処理欄
				2009. 4. 15	該当なし	
一般的名称	人赤血球濃厚液	研究報告の公表状況	CDC. Available from: http://www.cdc.gov/ncidod/dvbid/westnile/surv&controlCaseCount08_detailed.htm.		公表国 米国	
販売名(企業名)	赤血球濃厚液-LR「日赤」(日本赤十字社) 照射赤血球濃厚液-LR「日赤」(日本赤十字社)					

研究報告の概要

○2008年米国におけるウエストナイルウイルスの流行状況

米国疾病対策センターが発表した2008年の米国におけるウエストナイルウイルスの流行状況である。症例数は、2008年1月1日から12月31日までに発生し、2009年4月10日までに州や地方の保健当局からArboNETを通じて米国疾病対策センターに報告された軽症例及び重症例の合計である。46の州から1356例の感染例が報告され、うち687例(51%)で脳炎や髄膜炎を発症、624例(46%)で発熱、45例(3%)が他の症状/詳細不明だった。死亡に至ったのは44例だった。

神経侵襲性疾患が多く報告されているのは、軽症例より重症例の方が報告されやすいというサーベイランスの報告バイアスによるものである。また、サーベイランスシステムは無症候感染を検出するようには設計されていない。人口調査データからは、ウエストナイルウイルスに感染した人(無症候感染を含む)のうち、神経侵襲性疾患を発症するのは1%未満であることが示唆されている。

使用上の注意記載状況・その他参考事項等

赤血球濃厚液-LR「日赤」
照射赤血球濃厚液-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

2008年、米国におけるウエストナイルウイルス感染症例は46州から1356例が報告され、うち687例で脳炎や髄膜炎を発症、死亡に至ったのは44例だったとの報告である。

今後の対応

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、ウエストナイルウイルス感染の国内発生に備え、平成17年10月25日付血液対策課発事務連絡に基づき緊急対応の準備を進めているほか、厚生労働科学研究「献血血の安全性確保と安定供給のための新興感染症等に対する検査スクリーニング法等の開発と献血制限に関する研究」班と共同して対応について検討している。今後も引き続き情報の収集に努める。

⑧

West Nile Virus Basics
- Fact Sheet
- Q&A

Specific Topics
- Maps & Human Cases
- Clinical Guidance
- Lab Guidance
- Workplace Safety
- Background
- Ecology/Virology
- Education/Training

Resources
- In the News
- Publications
- Conferences
- R...d Links
- St... & Local Government Sites
- Guidelines for Surveillance, Prevention, & Control PDF (254 KB/77 pages)

West Nile Virus Home > Statistics, Surveillance, and Control >

Esta página en Español

Statistics, Surveillance, and Control

Maps and Data | Surveillance Program | Guidelines | Case Definition | See Also

Final 2008 West Nile Virus Activity in the United States

State	Encephalitis/ Meningitis	Fever	Other Clinical/Unspecified	Total	Fatali...
Alabama	11	7	0	18	0
Arizona	62	43	9	114	7
Arkansas	7	2	0	9	0
California	292	149	4	445	15
Colorado	17	54	0	71	1
Connecticut	5	2	1	8	0
Delaware	0	0	1	1	0
District of Columbia	4	1	3	8	0
Florida	3	0	0	3	0
Georgia	4	3	1	8	0
Idaho	2	31	6	39	1
Illinois	12	4	4	20	1
Indiana	3	0	1	4	0
Iowa	3	0	3	6	1
Kansas	14	17	0	31	0
Kentucky	3	0	0	3	0
Louisiana	18	31	0	49	1
Maryland	6	7	1	14	0
Massachusetts.	1	0	0	1	0
Michigan	11	4	2	17	0
Minnesota	2	8	0	10	0
Mississippi	22	43	0	65	2
Missouri	12	3	0	15	1
Montana	0	3	2	5	0
Nebraska	7	40	0	47	1
Nevada	9	5	2	16	0
New Jersey	6	4	0	10	2
New Mexico	5	3	0	8	0
New York	32	14	0	46	6
North Carolina	2	0	1	3	0
North Dakota	2	35	0	37	0

Ohio	14	1	0	15	1
Oklahoma	4	5	0	9	0
Oregon	3	13	0	16	0
Pennsylvania	12	2	0	14	1
Rhode Island	1	0	0	1	0
South Carolina	0	1	0	1	0
South Dakota	11	28	0	39	0
Tennessee	12	7	0	19	1
Texas	40	24	0	64	1
Utah	6	18	2	26	0
Virginia	0	0	1	1	0
Washington	2	1	0	3	0
West Virginia	1	0	0	1	0
Wisconsin	4	3	1	8	1
Wyoming	0	8	0	8	0
Totals	**687**	**624**	**45**	**1356**	

West Nile encephalitis and West Nile meningitis are forms of severe disease that affect a person's nervous system. Encephalitis refers to an inflammation of the brain, meningitis is an inflammation of the membrane around the brain and the spinal cord.
Click here for further explanation of WN meningitis and/or encephalitis.

West Nile fever refers to typically less severe cases that show no evidence of neuroinvasion. WN fever is considered a notifiable disease, however the number of cases reported (as with all diseases) may be limited by whether persons affected seek care, whether laboratory diagnosis is ordered and the extent to which cases are reported to health authorities by the diagnosing physician.

Other Clinical includes persons with clinical manifestations other than WN fever, WN encephal or WN meningitis, such as acute flaccid paralysis. **Clinical/Unspecified** cases are those for wh sufficient clinical information was not provided.

See the **case definition** (2004) for Neuroinvasive and Non-Neuroinvasive Domestic Arbovira Diseases. From the CDC Epidemiology Program Office.

Total Human Cases Reported to CDC: These numbers reflect both mild and severe humar disease cases occurring between January 1, 2008 to December 31, 2008 as reported through A 10, 2009 to ArboNET by state and local health departments. ArboNET is the national, electron surveillance system established by CDC to assist states in tracking West Nile virus and other mosquito-borne viruses. Information regarding 2008 virus/disease activity is posted when suc cases are reported to CDC.

Of the 1356 cases, 687 (51%) were reported as West Nile meningitis or encephalitis (neuroinvasive disease), 624 (46%) were reported as West Nile fever (milder disease), and 4 (3%) were clinically unspecified at this time. Please refer to state health department web sites further details regarding state case totals.

Note: The high proportion of neuroinvasive disease cases among reported cases of West Nile v disease reflects surveillance reporting bias. Serious cases are more likely to be reported than n cases. Also, the surveillance system is not designed to detect asymptomatic infections. Data fr population-based surveys indicate that among all people who become infected with West Nile v (including people with asymptomatic infections) less than 1% will develop severe neuroinvasi disease. See: Mostashari F, Bunning ML, Kitsutani PT, et al. Epidemic West Nile Encephalitis, N York, 1999: Results of a household-based seroepidemiological survey. Lancet 2001;358:261-2

For Case Information:
1999|2000|2001|2002|2003|2004|2005|2006|2007|2008

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Division of Vector Borne Infectious Diseases
National Center for Zoonotic, Vector-Borne, and Enteric Diseases

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別紙様式第2-1

No. 8

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. 3. 15	該当なし	
一般的名称	解凍人赤血球濃厚液		研究報告の公表状況	New York City Department of Health and Mental Hygiene, 2009 Feb 23. Available from: http://www.nyc.gov/html/doh/downloads/pdf/cd/2009/09md05.pdf	公表国 米国	
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社)					

研究報告の概要

○ニューヨーク市における輸血関連バベシア症の増加

2008年9月以降6ヵ月間でニューヨーク市民の輸血関連バベシア症7例が確認され、これまでの年平均1～2症例と比べて急増した。輸血を受ける患者は免疫抑制状態など基礎疾患を有する場合が多く、医療従事者はバベシア症を疑わない可能性がある。

バベシア症は、赤血球に寄生する原虫*Babesia microti*を原因とする、重症あるいは死亡に至るダニ媒介疾患である。健常宿主では無症候または軽症の場合が多く、未治療では1年以上感染が持続することがある。自然感染は、ニューヨーク市近隣に生息する*Ixodes scapularis*(クロアシダニ)によって起こる。若虫の数が多い春と夏の間、伝播リスクは最大となる。

ニューヨーク市民のバベシア症症例数は、1989年以降徐々に増加しており、近隣地域でも同様の傾向が認められた。これは、輸血関連症例の増加によることが考えられる。2002年には16例、2008年の暫定データでは39例が報告されている。

輸血関連バベシア症は、赤血球(新鮮、凍結)と血小板による症例のみが報告されている。FDAによると、1979年以降80例以上が報告されており、ほとんどは最近10年間の症例であった。現在、供血血液のバベシア感染スクリーニング検査はない。発熱やバベシア感染の既往歴のある供血者は供血延期となるが、低レベルの寄生虫血症を生じた無症候性感染者の供血は回避できない。

ニューヨーク市の臨床医は、過去3ヵ月以内に輸血歴または臓器移植歴がある原因不明の発熱および(または)溶血性貧血の患者には、輸血関連バベシア症を考慮するべきである。潜伏期間は、ダニ媒介性バベシア症で1～4週間、輸血関連バベシア症で2～9週間と考えられる。疑わしい症例に対してはバベシア症検査を実施し、陽性の場合はニューヨーク市衛生局ならびにニューヨーク州保健局(NYSDOH)に報告しなければならない。

報告企業の意見	今後の対応
2008年9月以降の6ヵ月間、ニューヨーク市において輸血関連バベシア症の報告が急増し、ニューヨーク市衛生局は、医療従事者に対し、3ヵ月以内に輸血または臓器移植の既往歴があり、発熱および(または)溶血性貧血を有する患者の鑑別診断にバベシア症を考慮するよう勧告したとの報告である。	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。

使用上の注意記載状況・その他参考事項等

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

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

(9)

NEW YORK CITY DEPARTMENT OF HEALTH AND MENTAL HYGIENE
Thomas R. Frieden, MD, MPH
Commissioner

Health

Health Advisory #5:
Increase in Transfusion-associated Babesiosis in NYC

- **Seven cases of transfusion-associated babesiosis have been identified among New York City (NYC) residents since September 2008; this is a notable increase over baseline as previously an average of one to two transfusion-associated cases were reported annually;**
- **The NYC Health Department is asking providers to consider babesiosis in the differential diagnosis of patients with fever and/or hemolytic anemia who have a history of transfusion or organ transplant within the preceding 3 months;**
- **Suspected cases should be tested for babesiosis (see below for details), and laboratory positive cases should be reported to the NYC Health Department as well as the New York State Department of Health (NYSDOH) Blood and Tissue Resources Program (see contact information below).**

Please distribute to staff in the Departments of Internal Medicine, Pediatrics, Family Medicine, Infection Control, Infectious Disease, Emergency Medicine, Critical Care, Hematology/Oncology, Pharmacy, Blood Bank and Laboratory Medicine.

February 23, 2009

Dear Colleagues,

Reported cases of transfusion-associated babesiosis among New Yorkers have increased during the previous 6 months. In the past, an average of 1-2 reports of transfusion-associated babesiosis was received by the Department annually; since September 2008, 7 cases have been identified. Patients receiving transfusions often have underlying illnesses, including immunosuppressive conditions, and providers may not suspect babesiosis, especially during winter months when travel to endemic areas is less common. This alert reminds providers to consider babesiosis in the differential diagnosis for patients with febrile illnesses and/or hemolytic anemia who have received blood components or transplanted organs in the preceding 3 months.

Babesiosis is a rare, sometimes severe or fatal tick-borne disease caused by *Babesia microti*, a parasite that infects red blood cells. Symptoms occur most frequently in elderly, asplenic or immunocompromised individuals and may include fever, hemolytic anemia, thrombocytopenia, diarrhea, acute renal failure, DIC and ARDS. In healthy hosts, infection is often asymptomatic, or causes mild illness with fever, headache, myalgia and malaise. Untreated infections can persist for up to a year or longer.

Naturally acquired *Babesia* is transmitted by infected *Ixodes scapularis*, or blacklegged ticks, which are also known to transmit *Borrelia burgdorferi* (Lyme disease) and *Anaplasma phagocytophilum* (anaplasmosis). The blacklegged tick is only rarely found in NYC; however it is present in nearly all areas surrounding the City. Highly endemic areas for *Babesia microti* near NYC include Long Island (especially Fire and Shelter Islands), Connecticut, New Jersey and Massachusetts. Transmission risk is greatest during spring and summer, when nymphal ticks are abundant.

The number of cases of babesiosis reported among NYC residents has gradually risen since 1989 when 2 cases were reported. This trend has been seen in the surrounding region as well. This may in part explain the increased number of transfusion-associated cases. In 2002, 16 cases were reported, and provisional data for 2008 has 39 cases reported to date, see Table 1).

Table 1. Reported Cases of Babesiosis in NYC 2002-2008

2002	2003	2004	2005	2006	2007	2008
16	25	16	18	38	25	39

Transmission through blood transfusion can occur when blood components collected from a parasitemic donor are transfused to a susceptible recipient. To date, transmission has been reported only with red blood cells (both fresh and frozen) and platelets. According to the FDA, since 1979 over 80 cases of transfusion-associated babesiosis have been reported in the US, the majority of which occurred during the past decade[1]. Currently, there is no laboratory screening of the blood supply for evidence of infection with *Babesia*. Donors are deferred if they have a fever at the time of donation or report a history of *Babesia* infection, but this practice alone is unable to prevent asymptomatic individuals with low levels of parasitemia from serving as donors.

Clinicians in NYC should consider transfusion-associated babesiosis in any patient presenting with unexplained febrile illness and/or hemolytic anemia who received blood components or organ transplantation in the preceding three months. The incubation period for tick-associated babesiosis can range from 1 to 4 weeks; for transfusion-associated babesiosis, 2 to 9 weeks.

Diagnosis can be made by identifying ring forms (which closely resemble *Plasmodium falciparum*) and tetrad forms within red blood cells on a Giemsa or Wright stained blood smear. *Babesia* polymerase chain reaction (PCR) and serologic tests are available commercially to assist with the diagnosis. Confirmatory testing, including review of blood smears and submission to NYS for PCR, if deemed necessary, is available through the NYC Public Health Laboratory. A request form must be completed for specimen submissions. For more information, call the Parasitology Laboratory at (212) 447-2972 during business hours. Forms can be found online at http://www.nyc.gov/html/doh/html/labs/labs_forms.shtml .

Treatment is generally not recommended for asymptomatic or mild self-limiting infections. For patients in whom illness is more severe, combination drug therapy has been successful. While the combination of clindamycin and quinine for 7 days was used historically, side effects including tinnitus and gastroenteritis can be problematic. More recently, the combination of atovaquone and azithromycin has been favored as this regimen is equally effective and results in fewer side effects[2]. In rare instances, an exchange transfusion may be indicated. For additional information on treatment options, refer to the Medical Letter, Drugs for Parasitic Infections. See http://www.dpd.cdc.gov/dpdx/HTML/PDF_Files/MedLetter/Babesiosis.pdf.

Additional information is available on the DOHMH website at: http://www.nyc.gov/html/doh/html/cd/cdbab.shtml or the CDC website at: http://www.cdc.gov/ncidod/dpd/parasites/babesia/default.htm

Please call the Bureau of Communicable Disease at 212-788-9830 with any questions regarding testing, diagnosis, reporting or management of suspected cases of babesiosis. Cases of transfusion-associated babesiosis must also be reported to the NYSDOH Blood and Tissue Resources Program at 518-485-5341. A report must also be made to your hospitals' transfusion service so they can notify the blood center that supplied the blood components.

Cases can be reported to the DOHMH by telephone (212-788-9830) or facsimile transmission (212-788-4268) using the paper or electronic Universal Reporting form (URF). **The URF and instructions can be obtained from your hospital's Infection Control Practitioner or downloaded from the DOHMH website at http://home2.nyc.gov/html/doh/html/hcp/hcp-urf.shtml. Visit http://home2.nyc.gov/html/doh/html/hcp/hcp.shtml to join NYC-MED in order to submit a URF online.**

As always, we greatly appreciate your cooperation and collaboration in our efforts to detect, investigate and prevent infectious diseases in New York City.
Sincerely,

Sally Slavinski, DVM, MPH, ACVPM — *Annie Fine, MD*

Sally Slavinski, DVM, MPH, ACVPM, Assistant Director
Zoonotic, Influenza and Vectorborne Disease Unit (ZIVDU)
Bureau of Communicable Disease

Annie Fine, MD, Medical Director
ZIVDU
Bureau of Communicable Disease

[1] Gubernot D et al. Babesia Infection through Blood Transfusions: Reports Received by the US Food and Drug Administration, 1997-2007. CID 2009;48 (1 January):pps 25-30.
[2] Krause PJ et al. Atovaquone and azithromycin for the treatment of babesiosis. NEJM 2000 Nov 16;343(20):1454-8.

別紙様式第２
番号８

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5月14日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	人ハプトグロビン					
販売名（企業名）	ハプトグロビン静注2000単位「ベネシス」（ベネシス）	研究報告の公表状況	感染症学雑誌/；第83回日本感染症学会総会・学術講演会（2009.4.23.24） 2009；83(3)：214		公表国 日本	

研究報告の概要

平成20年8月、仙台市においてリケッチア症を疑う患者が発生した。発熱、全身倦怠感を主訴とし、受診時に発疹と刺し口が確認された。急性期の全血ならびに刺し口の生検材料、回復期の血清がリケッチア症の実験室診断に供され、Rickettsia japonicaに対する抗体価の有意な上昇を確認した。生検材料を用いたPCRにより、17KDa外膜蛋白遺伝子上のリケッチア属共通のプライマー（Rr17/Rr20）、R. japonica 極東アジアのロシアや中国の患者から報告されているR. heilongiangensisに一致したことから、9月に感染推定地域の現地調査を実施した。野鼠の捕獲とともにマダニ類の採集を行い、抗体測定、分離、17KDa のPCR とともにgltA、ompAを標的としたPCR を実施し、患者材料から得られたリケッチア遺伝子情報と比較検討した。3頭のドブネズミがR. heilongiangensisに対して高い抗体価を示し、3個体の Haemaphysalis concinaより17KDa、gltA、ompAの遺伝子領域において患者材料から得られた遺伝子配列と一致するものが検出されるとともに、同じ遺伝子配列を有するリケッチア（R. heilongiangensis）が分離された。以上のことから、国内にR. japonicaによる日本紅斑熱とは異なる紅斑熱リケッチア症が存在することが示され、H. concinaが生息する地域において同様の患者が発生している可能性が示唆された。今後、H. concinaの分布をより明確にするとともに、R. heilongiangensisなど保有するリケッチアの情報の蓄積と国内のリケッチア症に関する疫学をよりいっそう進めることが求められる。

報告企業の意見	今後の対応
国内にR. japonicaによる日本紅斑熱とは異なるR.heilongiangensisによる紅斑熱リケッチア症が存在することについての報告である。 リケッチア属のグラム陰性菌は0.3～0.5×0.8～2.0μmの大きさであり、万一Rickettsia Heilongiangensisが本剤の原料血漿に混入したとしても、除菌ろ過等の製造工程において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。

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意
(1) 本剤の原材料となる献血者の血液については、HBs抗原、抗HCV抗体、抗HIV-1抗体、抗HIV-2抗体、抗HTLV-I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人ハプトグロビンを濃縮・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。

(10)

G0904327

O-151 上天草地域に連続発生した日本紅斑熱の臨床的検討

上天草市立上天草総合病院
○廣岡亜矢，津郡孝則，原喜由香，和田正文，
糸永浩太郎，脇田喜雄，樋口定信

日本紅斑熱は1984年に馬原によって最初に報告された，発熱，全身の紅斑，肝機能障害を特徴とするダニ媒介性のリケッチア症で，感染症法の4類感染症に分類されている．重症例では播種性血管内凝固症候群に陥り，死亡例の報告もある．患者は西日本の太平洋側に多く，年間100名ほどが報告されている．熊本県では平成14年に八代市で80歳の男性の発生例が報告されてから平成17年までの報告例はなかった．我々の施設のある上天草市は八代市と有明海に囲まれた比較的温暖な環境である．天草地域における日本紅斑熱は平成18年に1例発症以後，平成19年には11例，平成20年10月現在までに6例が報告されている．熊本県下発症例すべてが天草地域に限局している．また鑑別疾患としてのツツガムシ病の報告は皆無である．今回我々は上天草地域に発生した症例について疫学調査を行った．患者の平均年齢は72.5歳（57～100歳）で，男女比はおおよそ2:3であった．初発症状は頭痛，発熱，倦怠感が多く，ダニ暴露から発症までは平均3日であった．身体所見上，全身に疼痛や掻痒を伴わない辺縁不整の紅斑と刺し口が見られ，検査所見上，CRPの上昇，血小板減少，低アルブミン血症が多くに認められた．全例，ミノサイクリンの投与で速やかに解熱し治癒した．日本紅斑熱には β-ラクタム剤が無効であるので，発疹を伴う発熱性疾患の鑑別疾患として重要であると考えられる．

X0980005

O-152 仙台市で確認された新しい紅斑熱リケッチア症

国立感染症研究所ウイルス第一部[1]，
仙台医療センター[2]，
大原総合病院附属大原研究所[3]，
福井大学医学部[4]，
国立感染症研究所細菌第一部[5]，
岐阜大学[6]
○安藤秀二[1]，黒澤昌弘[2]，坂田明子[1]，磯田博已[3]，
矢野泰弘[4]，高野　愛[5,6]，川端寛樹[5,6]，花岡　希[1]，
斉藤若奈[2]，岸本寿男[1]

平成20年8月，仙台市においてリケッチア症を疑う患者が発生した．発熱，全身倦怠感を主訴とし，受診時に発疹と刺し口が確認された．急性期の全血ならびに刺し口の生検材料，回復期の血清がリケッチア症の実験室診断に供され，*Rickettsia japonica*に対する抗体価の有意上昇を確認した．生検材料を用いたPCRにより，17KDa外膜蛋白遺伝子上のリケッチア属共通のプライマー（R1/R2），*R.japonica*を標的としたプライマー（R35/R10）で陽性であった．しかしながら，シークエンス解析により，*R.japonica*に極めて近縁であるが，極東アジアのロシアや中国の患者から報告されている*R.heilongjiangensis*に一致した．ことから，9月に感染推定地域の現地調査を実施した．野鼠の捕獲とともにマダニ類の採取を行い，抗体測定，分離，17KDaのPCRとともに*gltA*，*ompA*を標的としたPCRも実施し，患者材料から得られたリケッチア遺伝子情報と比較検討した．3頭のドブネズミが*R.heilongjiangensis*に対して高い抗体価を示し，3個体の*Haemaphysalis concinna*より17KDa，*gltA*，*ompA*の遺伝子領域において患者材料から得られた遺伝子配列と一致するものが検出されるとともに，同じ遺伝子配列を有するリケッチア（*R.heilongjiangensis*）が分離された．以上のことから，国内に*R.japonica*による日本紅斑熱とは異なる紅斑熱リケッチア症が存在することが示され，*H.concinna*が生息する地域において同様の患者が発生している可能性が示唆された．今後，*H.concinna*の分布をより明確にするとともに，*R.heilongjiangensis*など保有するリケッチアの情報の蓄積と国内のリケッチア症に関する啓発をよりいっそう進めることが求められる．

番号2

別紙3

研究報告調査報告書

識別番号・報告回数			第一報入手日 ：平成21年7月8日	新医薬品等の区分 ：該当なし	総合機構処理欄
一般的名称	－	研究報告の公表状況	－	公表国： 日本	
販売名（企業名）	－				使用上の注意記載状況等・その他参考事項等

研究報告の概要

50代後半の男性が，右母趾のウオの目をカッターで自己切除したところ黒く変色し，その範囲は徐々に拡大．後に右下肢の腫脹が出現し自力で動けず緊急搬送された．到着時体温38.8度，WBC 28,200/μl，CRP 24.1mg/dL，肝機能不全，血液凝固異常が認められた．右母趾に悪臭と壊疽を伴う重度の蜂巣炎がみられ，右下肢が発赤腫脹，X線所見で右大腿部までガス像が認められた．直ちに壊疽部切開後排膿を認め，下腿中央までの切開で膿が腓腹筋に沿って大量に存在していた．
入院直後に採取した右母趾由来膿よりC群レンサ球菌が検出され，Streptococcus dysgalactiae subsp. dysgalactiae による初めての人感染症例と考えられた．

報告企業の意見	今後の対応
本報告は，当該生物由来製品による感染症情報ではない． 本報告を“新規感染症”と考え，報告する．	今後も感染症情報の収集に努め，当該生物由来製品に係る情報を入手した場合には速やかに調査・報告を行い安全性の確保に努める．

MedDRA/J Ver. 12.0J

NMP2009-0003

Streptococcus dysgalactiae subsp. *dysgalactiae* による初めてのヒト侵襲性感染症例

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【序文】*Streptococcus dysgalactiae* subsp. *dysgalactiae* に起因する STSS を伴う壊死性筋膜炎症例について報告する．【症例】50 代後半の男性で半年前に右母趾のウオの目をカッターで自己切除．3 ヶ月前より右母趾が黒く変色しているのに気付きその範囲は徐々に拡大．1 週間前頃より右下肢の腫脹が出現し自力で動けず救急搬送される．到着時体温 38.8℃で WBC 28,200/μL，CRP 24.21 mg/dL，肝機能不全，血液凝固異常が認められた．また Glucose 226 mg/dL で糖尿病が判明．右母趾に悪臭と壊疽を伴う重度の蜂巣炎がみられ，右下肢が発赤腫脹，X 線所見で右大腿部までガス像が認められた．直ちに壊疽部切開後排膿を認め，下腿中央までの切開で膿が腓腹筋に沿って大量に存在しデブリードメント施行．翌日全身状態悪化の為右大腿遠位 1/3 以下の切断術が施行された．CMZ 次いで ABPC＋CLDM が投与され術後経過良好にて第 48 病日に転院．入院直後採取の右母趾由来膿よりラクトース非分解性，β 溶血性の C 群レンサ球菌及び同等数の *Proteus mirabilis* が検出され，腓腹筋由来膿からは優位な菌数をもって C 群レンサ球菌が検出された．本菌はストレプトキナーゼ陰性と 16S rDNA 解析から 99.2% の相同性で *S. dys. spp. dysgalactiae* と同定された．また，スーパー抗原遺伝子 *speG* 及び壊死性軟組織感染症発症の要因と考えられている病原遺伝子 *sagA* の保有が確認され，*emm* 遺伝子型 *stL1929.0* であった．【考察】*S. dysgalactiae* subsp. *equisimilis* による STSS 等のヒト侵襲性感染症の報告が増加しつつあるのに対し，*S. dys.* subsp. *dysgalactiae* は元来ヒト以外の動物由来株に接続されている亜種名で，ウシ STSS やイヌ菌血症などが報告されている．本報は *S. dys.* subsp. *dysgalactiae* による初めてのヒト感染症例と考えられるが，本菌のように新たな病原遺伝子を獲得することでヒトへの感染性を高めていく可能性を含め，本亜種についての研究の必要性が促される．

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
				2009. 3. 15	該当なし	
一般的名称	解凍人赤血球濃厚液		研究報告の公表状況	FDA, CBER. Available from: http://www.fda.gov/Cber/blood/fatal08.pdf.	公表国 米国	
販売名（企業名）	解凍赤血球濃厚液「日赤」（日本赤十字社） 照射解凍赤血球濃厚液「日赤」（日本赤十字社） 解凍赤血球-LR「日赤」（日本赤十字社） 照射解凍赤血球-LR「日赤」（日本赤十字社）					

研究報告の概要

○FDAに報告された供血後及び輸血後の死亡例 2008年度概要

2005年度から2008年度にかけて米国食品医薬品局（FDA）に報告された供血後及び輸血後の死亡例の概要である。

2008年度に、FDAは受血者72件、供血者10件の死亡報告を受領した。受血者死亡例の内訳は、46件が輸血に関連したもの、8件が死亡原因として輸血を排除できないもの、18件が輸血と関連しないものであった。輸血に関係した（または可能性のある）死亡報告は、2006年度の73件、2007年度の63件と比べて54件に減少した。

2005年度から2008年度の統合データ223件において、輸血関連急性肺障害（TRALI）による死亡報告がもっとも多く（51%）、次いで溶血性反応（25%）、微生物感染（13%）の順であった。TRALIは、過去4年間の死亡報告の半数以上を占めているが、2008年度は35%と大幅に少なくなった。

2008年度の微生物感染は7件で、このうちバベシア症が5件、*Staphylococcus aureus* 及び *Staphylococcus epidermidis* がそれぞれ1件であった。2005年度から2008年度の合計では、微生物感染28件のうち10件（36%）をバベシア症が占めている。

使用上の注意記載状況・その他参考事項等

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

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
2005年度から2008年度にかけて米国食品医薬品局（FDA）に報告された供血後及び輸血後の死亡例の概要である。	日本赤十字社では、薬事法及び関連法令に従い輸血副作用・感染症情報を収集し、医薬品医療機器総合機構を通じて国に報告している。今後も引き続き輸血副作用・感染症に関する情報の収集に努める。

(12)

Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2008

I. Background

As previously mentioned in the annual summary of fatalities reported to the FDA in Fiscal Years (FY) 2005, FY2006, and FY2007, the blood supply is safer today than at any time in history. Due to advances in donor screening, improved viral marker tests, automated data systems, and changes in transfusion medicine practices, the risks associated with blood transfusion continue to decrease. Overall, the number of transfusion related fatalities reported to the FDA remains small in comparison to the total number of transfusions. In 2006 there were approximately 30 million components transfused.[1] During the proximate period of FY2006, there were 73 reported transfusion related and potentially transfusion related fatalities, with subsequent decreases to 63 in FY2007 and 54 in FY2008.

CBER is distributing this summary of transfusion fatality reports received by the FDA to make public the data received in FY2008, to provide the combined data received over the last four fiscal years, and to compare the FY2008 reports to the fatality reports received in FY2007, FY2006, and FY2005. We also include information on the infrequent reports of post-donation fatalities. Throughout this report we note changes over time, but the reader should interpret these changes cautiously, given the small numbers of reports and inherent variations in reporting accuracy. The significance of shifts in numbers derived from small populations may appear to be greater than they really are.

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

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

1 Whitaker BI, Green J, et al. The 2007 Nationwide Blood Collection and Utilization Survey Report. Washington (DC): Department of Health and Human Services; 2008.
2 Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion, September, 2003. http://www.fda.gov/cber/gdlns/bldfatal.htm.

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

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

II. Results

During FY2008 (October 1, 2007, through September 30, 2008), we received a total of 82 fatality reports. Of these reports, 72 were transfusion recipient fatalities and 10 were post-donation fatalities.

Of the 72 transfusion recipient fatality reports, we concluded:
a) 46 of the fatalities were transfusion-related,
b) in 8 cases we were unable to rule out transfusion as the cause of the fatality,
c) 18 of the fatalities were unrelated to the transfusion.

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

A. Overall Comparison of Transfusion-Related Fatalities Reported from FY2005 through FY2008

In combined FY2005, FY2006, FY2007, and FY2008, Transfusion Related Acute Lung Injury (TRALI) caused the highest number of reported fatalities (51%), followed by hemolytic transfusion reactions (25%) due to non-ABO (15%) and ABO (10%) incompatibilities. Complications of microbial infection, Transfusion Associated Circulatory Overload (TACO),

and anaphylactic reactions each accounted for a smaller number of reported fatalities (Table 1 and Figure 1).

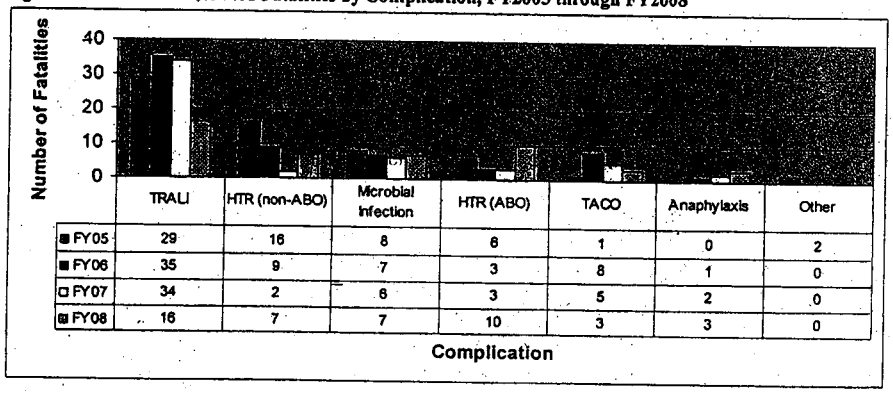
Table 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2008

Complication	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%
TRALI	29	47%	35	56%	34*	65%	16*	35%	114	51%
HTR (non-ABO)	16	26%	9	14%	2	4%	7	15%	34	15%
Microbial Infection	8	13%	7	11%	6	12%	7	15%	28	13%
HTR (ABO)	6	10%	3	5%	3	6%	10	22%	22	10%
TACO	1	2%	8	13%	5	10%	3	7%	17	8%
Anaphylaxis	0	0%	1	2%	2	4%	3	7%	6	3%
Other	2**	3%	0	0%	0	0%	0	0	2	1%
Totals	62	100%	63	100%	52	100%	46	100%	223	100%

*In FY2007, our review committee began using the Canadian Consensus Conference criteria[3,4] for evaluating TRALI cases – these numbers includes both "TRALI" and "possible TRALI" cases

**Other: Includes one case of Graft vs. Host Disease (GVHD) and one therapeutic plasma exchange (TPE) error (use of a treatment column contraindicated due to patient's medical history)

Figure 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2008



B. Transfusion Related Acute Lung Injury (TRALI)

[3] Goldman M, Webert KE, Arnold DM. et al. Proceedings of a consensus conference: towards an understanding of TRALI. Transfus Med Rev 2005;19:2-31.

[4] Kleinman S, Caulfield T, Chan P, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 2004;44:1774-1789.

While TRALI represented 51% of confirmed transfusion related fatalities reported to CBER over the last four fiscal years, in FY2008 fatalities due to TRALI decreased to 35% of confirmed transfusion related fatalities, compared to 65% in FY2007, 56% in FY2006, and 47% in FY2005. The number of TRALI fatalities associated with receipt of Fresh Frozen Plasma (FFP) decreased from 22 (63% of TRALI cases) in FY2006 to 12 (35% of TRALI cases) in FY2007 to 4 (25% of TRALI cases) in FY2008 (Figure 2). TRALI fatalities associated with receipt of Apheresis Platelets increased from 1 (3% of TRALI cases) in FY2007 to 5 (31% of TRALI cases) in FY2008. The percentage of FY2008 TRALI fatalities associated with receipt of Red Blood Cells (31% of TRALI cases) was comparable to that reported in FY2007 (35% of TRALI cases).

In Calendar Year 2006, transfused plasma products accounted for approximately 13% of all transfused components, apheresis platelets (using platelet concentrate equivalent units) – approximately 30%, and red blood cell-containing products – approximately 49%.[5] In comparison, for the combined fiscal years 2005-2008, FFP and other plasma accounted for 48% (55/114) of reported TRALI fatalities, apheresis platelets accounted for 10% (12/114), and RBC's accounted for 24% (27/114).

In FY2008, the 16 TRALI cases were temporally associated with products from 20 donors. Of these donors, 17 (85%) were tested for white blood cell (WBC) antibodies (Table 2). Antibody tests were negative in 18% of those tested. Of those tested, Human Leukocyte Antibodies (HLA) were present in 58% of donors. Human Neutrophil Antibodies (HNA) were present in 12% of donors, but these reactions were weak and non-specific. Some of the donors had multiple antibodies. Reporters who included patient testing data were able to match donor antibodies with recipient cognate antigens in 4 of the 16 cases, implicating 4 female donors. In two cases, reporters were able to identify **recipient** antibodies that matched or were a probable match to **donor** cognate antigens. In another case, both donor and recipient antibodies were identified which matched cognate antigens in the corresponding recipient and donor.

Of the 20 implicated donors, reports identified 13 females (65%) and 7 males (35%).

Although the transfusion community has taken voluntary measures to reduce the risk of TRALI, this complication of transfusion continues to be one of the leading causes of transfusion-related fatalities reported to the FDA. Data show that the largest percentage of fatal TRALI cases are associated with female donors with white blood cell antibodies, and recent literature describes efforts to selectively use plasma from male donors for transfusion.[6,7,8] In November, 2006, the American Association of Blood Banks (AABB) issued an Association Bulletin (#06-07), which included a recommendation that blood collection and transfusion facilities begin implementation of TRALI risk reduction measures for all high plasma-volume components. The measures include interventions to minimize the preparation of these components from donors known to

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

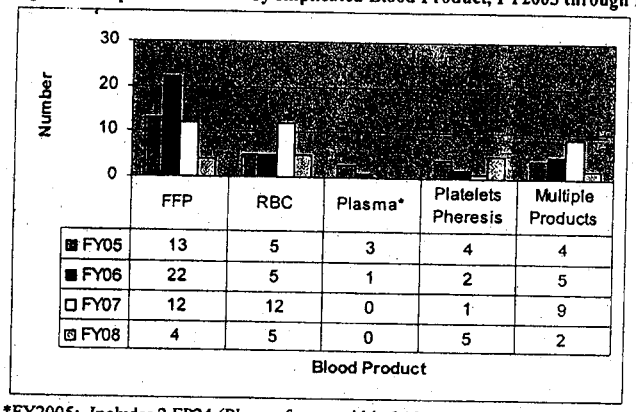
[6] Curtis, BR, Mcfarland JG. Mechanisms of transfusion-related acute lung injury (TRALI): anti-leukocyte antibodies. Crit Care Med 2006;34(5 Suppl):S118-S123.

[7] Eder AF, Herron R, Strupp A, et al. Transfusion-related lung injury surveillance (2003-2005) and the potential impact of the selective use of plasma from male donors in the American Red Cross. Transfusion 2007;47:599-607.

[8] Chapman CE, Williamson LM, Cohen H, et al. The impact of using male donor plasma on hemovigilance reports of transfusion-related acute lung injury (TRALI) in the UK (abstract). Vox Sang 2006;91(Suppl 3):227.

have white blood cell antibodies or who are at increased risk for developing these antibodies.[9] Some of the more current literature further describes efforts to reduce the use of plasma for transfusion prepared from female donors.[10,11]

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



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

Table 2: Donor Antibodies Identified in Association with TRALI, FY2007 and FY2008

Donor Leukocyte Antibodies	FY07 No.	FY07%	FY08 No.	FY08%
HLA Class I	18	17%	3	18%
HLA Class II	6	6%	2	12%
HLA Class I and II	15	14%	6	35%
HNA	17	16%	2	12%
HLA and HNA	6	6%	2	12%
Negative	42	41%	2	12%
Total Donors Tested	104	100%	17	100%

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

[9] Transfusion-related acute lung injury. AABB Association Bulletin (#06-07). Bethesda: American Association of Blood Banks;2006 Nov 3.
[10] Wright S, Athey S, Leaver A, et al. The effect of male-donor-only fresh frozen plasma on the incidence of acute lung injury following ruptured abdominal aortic aneurysm repair. Crit Care 2007;11:374.
[11] Chapman CE, Stainsby D, Jones H, et al. Ten years of hemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. Transfusion ;doi:10.1111/j.1537-2995.2008.01948.x

C. Hemolytic Transfusion Reactions

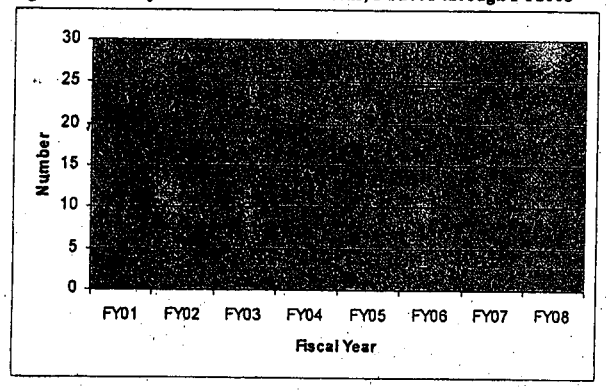
In FY2008, hemolytic transfusion reactions were the leading cause of transfusion related fatalities reported to CBER, representing 37% of confirmed transfusion related fatalities. The number of reported fatal hemolytic transfusion reactions increased to 17 in FY2008, as compared to 5 in FY2007, and 12 in FY2006. The recent increase is due to an increase in reports of ABO hemolytic reactions, with reports of 10 in FY2008, as compared to 3 in both FY2007 and FY2006. Reports of non-ABO hemolytic transfusion reactions also increased from 2 in FY2007 to 7 in FY2008 (Figure 1 and Table 3). Despite the FY2008 increase in the number of reported fatalities due to hemolytic transfusion reactions, we have seen an overall decrease in this number since FY2001 (Figure 3).

Table 3: Hemolytic Transfusion Reactions by Implicated Antibody, FY2005 through FY2008

Antibody	FY05 No.	FY05 %	FY06 No.	FY06 %	FY07 No.	FY07 %	FY08 No.	FY08 %	Total No.	Total %
ABO	6	27%	3	25%	3	60%	10	59%	22	39%
Multiple Antibodies*	6	27%	4	33%	1	20%	1	6%	12	21%
Jk^b	3	14%	0	0%	0	0%	2	12%	5	9%
Other**	3	14%	0	0%	0	0%	0	0%	3	5%
Kell	1	5%	1	8%	0	0%	2	12%	4	7%
Jk^a	1	5%	1	8%	1	20%	0	0%	3	5%
Fy^a	0	0%	1	8%	0	0%	2	12%	3	5%
Fy^b	0	0%	1	8%	0	0%	0	0%	1	2%
E	1	5%	0	0%	0	0%	0	0%	1	2%
I	1	5%	0	0%	0	0%	0	0%	1	2%
Js^a	0	0%	1	8%	0	0%	0	0%	1	2%
Totals	22	100%	12	100%	5	100%	17	100%	56	100%

*FY2005 antibody combinations included E+c, Fy^a+K, Fy^a+Jk^b, E+I+A_1, possible C+E+K; Wr^a+warm autoantibody.
*FY2006 antibody combinations included E+c, S+K, Jk^b+cold agglutinin, unidentified auto- and alloantibodies.
*FY2007: anti-M+C
*FY2008: anti-C+K+Fy^b+S+N+V+Js^a+Go^a+warm autoantibody.
**FY2005: Includes one report of non-immune hemolysis, one report of an unidentified antibody to a low incidence antigen, and one report of Cold Agglutinin Syndrome due to *Mycoplasma pneumonia* or Lymphoma.

Figure 3: Hemolytic Transfusion Reactions, FY2001 through FY2008



In FY2008, there were ten reports of fatal hemolytic transfusion reactions due to ABO-incompatible blood transfusions:

- 5 cases: recipient identification error at the time of transfusion
- 1 case: blood bank clerical error (incorrect sample used for testing)
- 3 cases: sample collected from incorrect patient[12]
- 1 case: transfusion of high-titer anti-B in group O Apheresis Platelets following group B bone marrow transplant

[12] MacIvor D, Triulzi DJ. Enhanced detection of blood bank sample collection errors with a centralized patient database. Transfusion 2009;49:40-43.

D. Microbial Infection

In FY2008, there were 7 reported fatalities attributed to microbial infection compared with reports of 6 in FY2007, 7 in FY2006, and 8 in FY2005. Two different bacteria were implicated in two fatalities, and five other fatalities resulted from Babesia transmission following Red Blood Cell transfusions from donors who subsequently tested positive for Babesia. The babesiosis cases accounted for 71% (5/7) of the microbial infections associated with transfusion fatalities in FY2008, as compared to 50% (3/6) in FY2007, 29% (2/7) in FY2006, and none reported in FY2005. Babesia accounted for 36% (10/28) of reported cases over the last four fiscal years, followed by *Staphylococcus aureus*, which accounted for 18% (5/28) (Table 4).

After seven years with no reported deaths due to transfusion-transmitted Babesiosis, CBER received reports of 10 transfusion-transmitted Babesiosis deaths during the four-year reporting period. For additional information, see the CBER article published in January 2009 describing fatal Babesiosis cases received by CBER from 1997-2007.[13]

There was one strict anaerobe, *Eubacterium limosum,* implicated in a fatal bacterial infection during the 4-year reporting period; this fatality occurred in FY2005. The remaining bacteria are facultative anaerobes.

Since FY2006, the number of reports of fatal microbial infections associated with apheresis platelets has remained unchanged (Figure 4). This finding is consistent with an overall decrease in the number of bacterial infections associated with apheresis platelets since FY2001 (Figure 5).

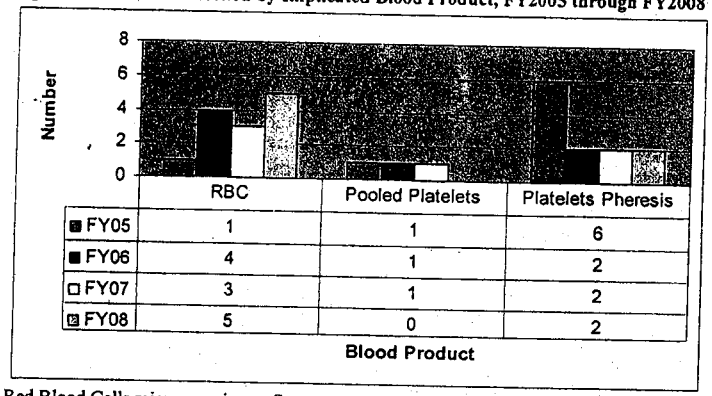
Table 4: Microbial Infection by Implicated Organism, FY2005 through FY2008

Organism	FY05	FY05	FY06	FY06	FY07	FY07	FY08	FY08	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%
*Babesia**	0	0%	2	29%	3	50%	5*	63%	10	36%
Staphylococcus aureus	3	37%	0	0%	1	17%	1	13%	5	18%
Escherichia coli	0	0%	3	43%	0	0%	0	0%	3	11%
Serratia marcescens	2	24%	0	0%	0	0%	0	0%	2	7%
Staphylococcus epidermidis	1	13%	0	0%	0	0%	1	13%	2	7%
Staphylococcus lugdunensis	1	13%	0	0%	0	0%	0	0%	1	4%
Eubacterium limosum	1	13%	0	0%	0	0%	0	0%	1	4%
Morganella morganii	0	0%	1	14%	0	0%	0	0%	1	4%
Yersinia enterocolitica	0	0%	1	14%	0	0%	0	0%	1	4%
Group C Streptococcus	0	0%	0	0%	1	17%	0	0%	1	4%
Klebsiella oxytoca	0	0%	0	0%	1	17%	0	0%	1	4%
Total	8	100%	7	100%	6	100%	7	100%	28	100%

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

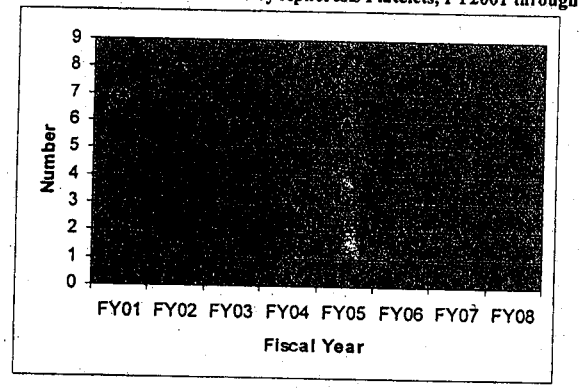
[13] Gubernot DM, Lucey CT, Lee KC et al. *Babesia* Infection through Blood Transfusions: Reports Received by the US Food and Drug Administration, 1997-2007. Clin Infect Dis 2009;48:000-000, electronically published, 26 November 2008.

Figure 4: Microbial Infection by Implicated Blood Product, FY2005 through FY2008



Red Blood Cells microorganisms: *S. marcescens (1), E. coli (1), Y. enterocolitica (1), B. microti (9), B. MO1(1)*
Pooled Platelets microorganisms: *S. aureus (1), E. coli (1), Streptococcus dysgalactiae (1)*
Platelets Pheresis microorganisms: *S. aureus (4), S. marcescens (1), S. lugdunensis (1), S. epidermidis (2), E. limosum (1), E. coli (1), M. morganii (1), K. oxytoca (1)*

Figure 5: Bacterial Infection by Apheresis Platelets, FY2001 through FY2008



E. Transfusion Not Ruled Out as Cause of Fatality

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

Combining the transfusion related fatalities with those that our medical officers could not rule out, there was a decrease in total reported fatalities from 63 in FY2007 to 55 in FY2008.

F. Not Transfusion Related

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

Table 5: Fatalities Not Related to Transfusion or Transfusion Not Ruled Out, FY2005 through FY2008

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

G. Post-Donation Fatalities

There was a small decrease in FY2008 in the number of reported fatalities following Source Plasma donation, and one fatality following donation of Apheresis Red Blood Cells (Table 6). In all of these cases, our medical reviewers concluded that, while there was a temporal link between the donations and the fatalities, there was no evidence to support a causal relationship between the donations and subsequent death of the donors.

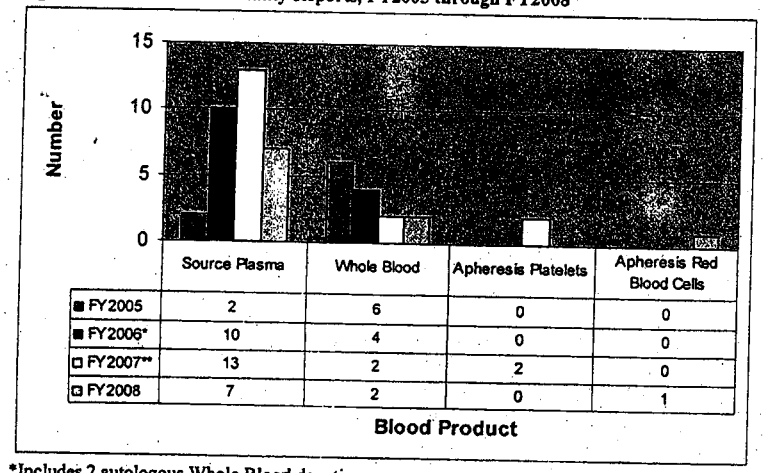
In FY2008, we received reports of two fatalities following Whole Blood donation collected by manual methods. In both cases, our medical reviewers found no evidence to support a causal relationship between the donation and subsequent death of the donor.

Table 6: Post-Donation Fatality Reports by Donated Product, FY2005 through FY2008

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

*Includes 2 autologous donations
**Autologous donations

Figure 6: Post-Donation Fatality Reports, FY2005 through FY2008



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

別紙様式第2-1

No. 27

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. 4. 15	該当なし	
一般的名称	人赤血球濃厚液		研究報告の公表状況	OIE – World Organisation for Animal Health. Available from: http://www.oie.int/eng/info/en_esbmonde.htm.	公表国	
販売名（企業名）	赤血球濃厚液-LR「日赤」（日本赤十字社） 照射赤血球濃厚液-LR「日赤」（日本赤十字社）				OIE	

研究報告の概要

○世界（英国を除く）の畜牛におけるウシ海綿状脳症（BSE）症例の報告数
1989年から2008年までに、世界各国から国際獣疫事務局（OIE）に報告されたウシ海綿状脳症の報告数である。2008年にBSE症例が報告されたのはカナダ（4頭）、フランス（8頭）、ドイツ（2頭）、アイルランド（23頭）、イタリア（1頭）、日本（1頭）、オランダ（1頭）、ポーランド（5頭）、ポルトガル（18頭）、スペイン（25頭）である。

報告企業の意見	今後の対応
1989年から2008年までに、世界各国（英国を除く）から国際獣疫事務局（OIE）に報告されたウシ海綿状脳症の報告数である。	日本赤十字社は、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴（旅行及び居住）を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より1980～96年に1日以上の英国滞在歴のある人の献血を制限している。今後もCJD等プリオン病に関する新たな知見及び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

赤血球濃厚液-LR「日赤」
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血液を介するウイルス、細菌、原虫等の感染
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(13)

= Number of cases in the United Kingdom
= Number of reported cases worldwide (excluding the United Kingdom) = Cases in imported animals only
= Annual incidence rate

Number of reported cases of bovine spongiform encephalopathy (BSE) in farmed cattle worldwide*(excluding the United Kingdom)

Country/Year	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Austria	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	2	2	1	0
Belgium	0	0	0	0	0	0	0	0	1	6	3	9	46	38	15	11	2	2	0	0
Canada	0	0	0	0	1(b)	0	0	0	0	0	0	0	0	0	2(a)	1	1	5	3	4
Czech Republic	0	0	0	0	0	0	0	0	0	0	0	0	2	2	4	7	8	3	2	0
Denmark	0	0	0	1(b)	0	0	0	0	0	0	0	1	6	3	2	1	1	0	0	0
Finland	0	0	0	0	0	0	0	0	0	0	0	0	1(a)	0	0	0	0	0	0	0
France	0	0	5	0	1	4	3	12	6	18	31(a)	161(d)	274(e)	239(f)	137(g)	54(h)	31	8	9	8
Germany	0	0	0	1(b)	0	3(b)	0	0	2(b)	0	0	7	125	106	54	65	32	16	4	2
Greece	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Ireland	15(a)	14(a)	17(a)	18(a)	16	19(a)	16(a)	73	80	83	91	149(d)	246(e)	333(f)	183(g)	126(h)	69(i)	41(j)	25(k)	23(l)
Israel	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Italy	0	0	0	0	0	2(b)	0	0	0	0	0	0	48	38(a)	29	7	8	7	2	1
Japan	0	0	0	0	0	0	0	0	0	0	0	0	3(e)	2	4(g)	5	7	10	3	1
Liechtenstein	0	0	0	0	0	0	0	0	0	2(a)	0	0	0	0	0	0	0	0	0	0
Luxembourg	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	1	0	0	0
Netherlands	0	0	0	0	0	0	0	0	2	2	2	2	20	24	19	6	3	2	2	1
Poland	0	0	0	0	0	0	0	0	0	0	0	0	0	4(f)	5	11	19	10	9	5
Portugal	0	1(b)	1(b)	1(b)	3(b)	12	15	31	30	127	159	149(a)	110	86	133	92(a)	46	33	14	18
Slovakia	0	0	0	0	0	0	0	0	0	0	0	0	5	6	2	7	3	0	1	0(l)
Slovenia	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	2(a)	1	1	1	0
Spain	0	0	0	0	0	0	0	0	0	0	0	2	82	127	167	137	98	68	36	25
Sweden	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0(l)
Switzerland	0	2	8	15	29	64	68	45	36	14	50	33(d)	42	24	21(g)	3	3(i)	5	0	0
United Kingdom	see particular table																			
United States of America	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0

* Cases are shown by year of confirmation.
... Not available

(a) **Canada:** 1 case diagnosed in Canada in May 2003 + 1 case diagnosed in the United States of America in December 2003 and confirmed as having been imported from Canada.
Finland: date of confirmation of the case: 7 December 2001.
France: includes 1 imported case (confirmed on 13 August 1999).
Ireland: includes imported cases: 5 in 1989, 1 in 1990, 2 in 1991 and 1992, 1 in 1994 and 1995.
Italy: includes 2 imported cases.
Liechtenstein : date of the last confirmation of a case: 30 September 1998.
Portugal: includes 1 imported case.
Slovenia: includes 1 imported case.

(b) Imported case(s).

(c) **Ireland** - Data as of 31 March 2009. Cases detected by the active surveillance programme = 4.

Luxembourg - Data as of 28 February 2009.

(d) **France year 2000** - Clinical cases = 101. Cases detected within the framework of the research programme launched on 8 June 2000 = 60.
Ireland year 2000 - Clinical cases = 138. Cases identified by active surveillance of at risk cattle populations = 7. Cases identified by examination of depopulated BSE positive herds, birth cohorts and progeny animals = 4.
Switzerland year 2000 - Clinical cases = 17. Cases detected within the framework of the investigation programme = 16.

(e) **France year 2001** - Clinical cases = 91. Cases detected at rendering (bovines at risk) = 100 (out of 139,500 bovines tested). Cases detected as result of routine screening at the abattoir = 83 (out of 2,373,000 bovines tested).
Ireland year 2001 - Clinical cases = 123. Cases identified by systematic active surveillance of all adult bovines = 119. Cases identified by examination of depopulated BSE positive herds, birth cohorts and progeny animals = 4.
Japan year 2001 - Clinical cases = 1. Cases detected as result of screening at the abattoir = 2.

(f) **France year 2002** - Clinical cases = 41. Cases detected at rendering (bovines at risk) = 124 (out of 274,143 bovines tested). Cases detected as result of systematic screening at the abattoir = 74 (out of 2,915,103 bovines tested). The active BSE surveillance programmes implemented in France in 2002 led to routine examination of cattle aged over 24 months, which were slaughtered for consumption purposes, were euthanised or died due to other reasons.
Ireland year 2002 - Clinical cases = 108. Cases detected by the active surveillance programme = 221. Cases identified by examination of depopulated BSE positive herds, birth cohorts and progeny animals = 4.
Poland year 2002 - Clinical cases = 1. Cases detected as result of routine screening at the abattoir (cattle over 30 months) = 3.

(g) **France year 2003** - Clinical cases = 13. Cases detected at rendering (bovines at risk) = 87. Cases detected as result of systematic screening at the abattoir = 37.
Japan year 2003 - The 9th case was a bullock aged 21 months.
Ireland year 2003 - Clinical cases = 41. Cases detected by the active surveillance programme = 140.
Switzerland year 2003 - Clinical cases: 8. Cases detected within the framework of the official surveillance programme: 11. Cases detected through voluntary testing following routine slaughter: 2.

(h) **France year 2004** - Clinical cases = 8. Cases detected at rendering (bovines at risk) = 29. Cases detected as result of systematic screening at the abattoir = 17.
Ireland year 2004 - Clinical cases = 31. Cases detected by the active surveillance programme = 94. Cases identified by examination of depopulated BSE positive herds, birth cohorts and progeny animals = 1.

(i) **Ireland year 2005** - Cases detected by the passive surveillance programme = 13. Cases detected by the active surveillance programme = 56.
Switzerland year 2005 - Cases detected by the passive surveillance programme = 1. Cases detected within the framework of the official surveillance programme: 1. Cases detected through voluntary testing following routine slaughter = 1.

(j) **Ireland year 2006** - Cases detected by the passive surveillance programme = 5. Cases detected by the active surveillance programme = 36.

(k) **Ireland year 2007** - Cases detected by the passive surveillance programme = 5. Cases detected by the active surveillance programme = 20.

(l) **Ireland year 2008**- Cases detected by the passive surveillance programme = 3. Cases detected by the active surveillance programme = 20.
Slovakia - Data as of 30 June 2008.
Sweden - Data as of 30 June 2008.

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Last update : 07-Avr-2009 (fr)

別紙様式第2-1

No. 26

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. 4. 15	該当なし	
一般的名称	人赤血球濃厚液		研究報告の公表状況	OIE - World Organisation for Animal Health. Available from: http://www.oie.int/eng/info/en_esbru.htm.	公表国 OIE	
販売名(企業名)	赤血球濃厚液-LR「日赤」(日本赤十字社) 照射赤血球濃厚液-LR「日赤」(日本赤十字社)					

研究報告の概要

○英国の畜牛におけるウシ海綿状脳症(BSE)症例の報告数
1987年以前から2008年までに、英国から国際獣疫事務局(OIE)に報告されたウシ海綿状脳症の報告数である。2008年にはグレートブリテン島で33頭、北アイルランドで4頭の計37頭が報告された。

使用上の注意記載状況・その他参考事項等

赤血球濃厚液-LR「日赤」
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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

1987年以前から2008年までに、英国から国際獣疫事務局(OIE)に報告されたウシ海綿状脳症の報告数である。

今後の対応

日本赤十字社は、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より1980～96年に1日以上の英国滞在歴のある人の献血を制限している。今後もCJD等プリオン病に関する新たな知見及び情報の収集に努める。

(14)

undefined

Number of cases of bovine spongiform encephalopathy (BSE) reported in the United Kingdom [1]

■ Number of cases in the United Kingdom ■ Number of reported cases worldwide (excluding the United Kingdom) ■ Cases in imported animals only ■ Annual incidence rate

	Alderney	Great Britain	Guernsey [3]	Isle of Man [2]	Jersey	Northern Ireland	Total United Kingdom
1987 and before[4]	0	442	4	0	0	0	446
1988[4]	0	2 469	34	6	1	4	2 514
1989	0	7 137	52	6	4	29	7 228
1990	0	14 181	83	22	8	113	14 407
1991	0	25 032	75	67	15	170	25 359
1992	0	36 682	92	109	23	374	37 280
1993	0	34 370	115	111	35	459	35 090
1994	2	23 945	69	55	22	345	24 438
1995	0	14 302	44	33	10	173	14 562
1996	0	8 016	36	11	12	74	8 149
1997	0	4 312	44	9	5	23	4 393
1998	0	3 179	25	5	8	18	3 235
1999	0	2 274	11	3	6	7	2 301
2000	0	1 355	13	0	0	75	1 443
2001	0	1,113	2	0	0	87	1,202
2002	0	1,044	1	0	1	98	1,144
2003	0	549	0	0	0	62	611
2004	0	309	0	0	0	34	343
2005	0	203	0	0	0	22	225
2006	0	104	0	0	0	10	114
2007	0	53	0	0	0	14	67
2008	0	33	0	0	0	4	37

[1] Cases are shown by year of restriction.

[2] In the Isle of Man BSE is confirmed on the basis of a laboratory examination of tissues for the first case on a farm and thereafter by clinical signs only. However, all cases in animals born after the introduction of the feed ban have been subjected to histopathological/scrapie-associated fibrils analysis. To date, a total of 277 animals have been confirmed on clinical grounds only.

[3] In Guernsey BSE is generally confirmed on the basis of clinical signs only. To date, a total of 600 animals have been confirmed without laboratory examination.

[4] Cases prior to BSE being made notifiable are shown by year of report, apart from cases in Great Britain which are shown by year of clinical onset of disease.

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Last update :22-Jan-2009 (fr)

別紙様式第2-1

No. 20

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. 3. 15	該当なし	
一般的名称	解凍人赤血球濃厚液		研究報告の公表状況	Dorsey K, Zou S, Schonberger LB, Sullivan M, Kessler D, Notari E 4th, Fang CT, Dodd RY. Transfusion. Epub 2009 Jan 5.	公表国 米国	
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社) 解凍赤血球-LR「日赤」(日本赤十字社) 照射解凍赤血球-LR「日赤」(日本赤十字社)					

研究報告の概要

○米国の調査試験においてクロイツフェルト・ヤコブ病の輸血による伝播についてのエビデンスは得られなかった

背景:2004年以降、英国では輸血により伝播した変異型クロイツフェルト・ヤコブ病(vCJD)が複数報告され、古典的CJDの同様な伝播リスクについて懸念が再び浮上した。

調査デザインおよび方法:CJDと診断された患者および患者の供血歴がコーディネータに報告された。血液供給と病院記録の調査を通して、これら供血者に由来する血液成分の受血者を特定した。その後、各受血者の生存状況を調べ、死亡している場合には、受血者のIDとCDCのNational Death Indexデータベースとを適合させて、死因を特定した。この調査は受血者の登録後と、それ以降生存する者に対して毎年実施した。

結果:後にCJDを発症した供血者36名と受血者436名が対象となった。2006年までの期間、受血者のうち生存者91名、死亡者329名、追跡不能者16名となった。これら3群の輸血後の生存期間は合計2096.0人年であった。合計144名の受血者が5年以上生存し、そのうち68名は、供血後60ヶ月以内にCJDを発症した供血者の血液の輸血を受けた。輸血後にCJDを発症した受血者は特定されなかった。

結論:現在も実施中のこの大規模ルックバック調査の現在までの結果は、CJDの輸血伝播の証拠を示していない。これによりCJD供血者によるプリオン病の輸血による伝播リスクは、もしあったとしても、vCJD供血者による伝播リスクよりも非常に低いという結論が強まった。

使用上の注意記載状況・その他参考事項等

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

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
米国の大規模ルックバック調査において、古典的CJDの輸血伝播の証拠は示されず、CJD供血者によるプリオン病の輸血による伝播リスクは、vCJD供血者による伝播リスクよりも非常に低いとの報告である。	日本赤十字社は、vCJDの血液を介する感染防止の目的から、献血時に過去の海外渡航歴(旅行及び居住)を確認し、欧州36ヶ国に一定期間滞在したドナーを無期限に献血延期としている。また、英国滞在歴を有するvCJD患者が国内で発生したことから、平成17年6月1日より1980～96年に1日以上の英国滞在歴のある人の献血を制限している。今後もCJD等プリオン病に関する新たな知見及び情報の収集に努める。

TRANSFUSION COMPLICATIONS

Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study

Kerri Dorsey, Shimian Zou, Lawrence B. Schonberger, Marian Sullivan, Debra Kessler, Edward Notari IV, Chyang T. Fang, and Roger Y. Dodd

BACKGROUND: Since 2004, several reported transfusion transmissions of variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom have reawakened concerns about the possible risk of similar transmissions of nonvariant or classic forms of CJD.

STUDY DESIGN AND METHODS: Patients with a CJD diagnosis and a history of donating blood were reported to the study coordinator. Through review of blood distribution and hospital records, the recipients of blood components from these donors were identified. We then determined each recipient's vital status and, if deceased, the cause(s) of death identified by matching the recipient's personal identifiers with the Centers for Disease Control and Prevention's National Death Index database. We conducted such searches after recipients were enrolled in this study and annually thereafter for those who remained alive.

RESULTS: The study included a total of 36 blood donors who subsequently developed CJD and 436 recipients. Through 2006, 91 of these recipients were still alive, 329 were deceased, and 16 were lost to follow-up. After transfusion, these three groups had survived a total of 2096.0 person-years. A total of 144 recipients survived 5 years or longer after transfusion and 68 of them had received blood donated 60 or fewer months before the onset of CJD in the donor. We identified no recipient with CJD.

CONCLUSIONS: The current results of this large, ongoing lookback study show no evidence of transfusion transmission of CJD. They reinforce the conclusion that the risk, if any, of transfusion transmission of prion disease by CJD donors is significantly lower than the comparable risk of such transmission by vCJD donors.

Variant Creutzfeldt-Jakob disease (vCJD) and the nonvariant or classic forms of Creutzfeldt-Jakob disease (CJD) of humans belong to a group of transmissible, fatal degenerative neurologic diseases called transmissible spongiform encephalopathies (TSEs). These diseases are also called prion diseases because of the formation and accumulation of an abnormal form of the prion protein (PrP^{Dz}) that is hypothesized to play a central etiologic role in the disease process.[1] TSEs affect both humans and animals (e.g., bovine spongiform encephalopathy [commonly known as mad cow disease] in cattle; scrapie in sheep and goats; and chronic wasting disease in deer, elk, and moose).

Prion diseases in humans have been reported to occur sporadically without an apparent environmental source, through an inherited genetic mutation, or iatrogenically. Cases of familial CJD have occurred due to a mutated prion protein gene (PRNP) located on chromosome 20. More than 30 different mutations of the PRNP

ABBREVIATIONS: NDI = National Death Index; TMER = Transfusion Medicine Epidemiological Review; TSE(s) = transmissible spongiform encephalopathy(-ies); vCJD = variant Creutzfeldt-Jakob disease.

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have been linked to familial human prion diseases. The most common familial CJD haplotypes are E200K-129M and D178N-129V.[2] Cases of iatrogenic CJD have been associated with exposures to contaminated neurosurgical equipment, human-derived pituitary growth hormone injections, cadaver-derived dura mater grafts, and corneal grafts.[3]

Surveillance of CJD in the United States has shown approximately one case annually per million people in the general population. Over many years, these rates have remained reasonably stable and the median age at death has consistently been approximately 68 years.[4,5]

Since the late 1980s, efforts have been made to minimize the potential risk of transfusion transmission of CJD, and in the 1990s the Food and Drug Administration (FDA) convened a TSE advisory committee, consisting of public interest advocates, ethicists, caregivers, and technical experts. Further, the FDA has issued a number of guidances for industry. These guidances attempt to balance the benefits of reducing the uncertain risks of prion disease transmission by blood products and the potential adverse impact that such preventive policies might have on product availability.[6]

Since 2004, transfusion transmission of the vCJD agent has been well documented. To date, the investigators conducting the UK Transfusion Medicine Epidemiological Review (TMER) study have linked three symptomatic cases of vCJD and one asymptomatic vCJD infection to receipt of blood transfusions from donors who subsequently developed vCJD (vCJD donor).[7,8] One blood donor was linked to two of the vCJD transmissions through donations, 21 and 17 months before the donors' onset of vCJD. These data suggest that once vCJD infectivity appears in blood it probably persists there. In addition to increasing concerns about the transmissibility of vCJD, these transfusion transmissions reawakened concerns and interest in blood safety and CJD. Both vCJD and CJD are invariably fatal and are caused by similar unconventional agents that are unusually resistant to inactivation. Incubation periods for vCJD and iatrogenic CJD are measured in years; there is no practical, licensed screening test to identify those who may be incubating these diseases.[9,10] Because CJD is far more common than vCJD, CJD might potentially affect even more recipients if, in fact, CJD were transmitted by blood transfusion.[11,12]

Surveillance and epidemiologic studies have provided the most reassuring data about blood safety and CJD, although very little long-term lookback data on donations from CJD donors have been reported.[8,13,14] Surveillance of high-exposure recipients, such as persons with hemophilia, and case-control studies show no evidence for transfusion transmission of CJD in humans.[15-17] In contrast, animal models have demonstrated that prion diseases can be transmitted by blood, a finding that aggravates concern about blood safety and CJD.[18,19] For example, studies comparing the infectivity in murine models of vCJD and Gerstmann-Straussler-Scheinker disease, a genetically inherited, classic (not bovine spongiform encephalopathy related) form of prion disease, revealed similarly low levels of infectivity in blood components during both the preclinical and the clinical phases of disease.[19]

In late 1994, a report of CJD in an American Red Cross 10-gallon donor heightened public health concerns in the United States about the possible transfusion transmission risk of CJD. Because of these concerns, in 1995 the Red Cross in collaboration with the Centers for Disease Control and Prevention (CDC) initiated a long-term lookback investigation of blood donors who were later diagnosed with CJD (CJD donors). The purpose of this collaborative study was to provide further epidemiologic data to assess the recurring concerns about the possibility of CJD transmission by blood transfusion. This article reports on the follow-up of the recipients of blood products from reported CJD donors. This study is the largest of its kind reported to date in terms of the number of such recipients identified and the period of time that they were documented to have survived after transfusion.

MATERIALS AND METHODS

CJD patients with a history of blood donation

The study coordinator identified CJD blood donors from reports provided by collaborating blood centers, family members, the CDC, and the FDA. Through searches of blood establishment records on donations made by the CJD donor and with the cooperation of hospitals, we identified recipients of the CJD donors' blood components.

Criteria for inclusion of a CJD donor in the study included a diagnosis of CJD made by a neurologist (and preferably confirmed by neuropathologic study of brain tissue at autopsy or biopsy) and a history of at least one documented allogeneic blood donation. (Autologous and therapeutic donations were not included.) We collected results of available diagnostic laboratory tests, cerebrospinal fluid studies, and electroencephalograms on the reported CJD donors. We notified the blood centers about the CJD donors and requested that each center review its records for each of the CJD donor's donations to identify the recipients of each donor's labile blood components. A CJD donor was entered in the study when at least one of these recipients was identified and could be documented to have survived for at least 1 day after receiving the blood components.

Recipients of blood products from donors who developed CJD

We requested that the transfusion service personnel send us information on each recipient of blood from a CJD donor. This information included the recipient's name and social security number; data on the transfusion of concern, including date of transfusion and the volume and type of components transfused; and data on the last known vital status of the patient, including the date and cause of death if a recipient was deceased. The institutional review boards of the CDC and the Red Cross approved this protocol. No study-related recipient notification was required by the institutional review boards because of the absence of: 1) compelling evidence of transfusion transmission of CJD in humans, 2) any practical licensed test for preclinical CJD, and 3) any established treatment to prevent or cure CJD.

Follow-up of the recipients

For recipients for whom we had identifiers, we determined each recipient's vital status and cause(s) of death, if deceased, through searching the CDC's National Death Index (NDI) database (National Center for Health Statistics, Hyattsville, MD). We conducted such searches after a recipient was entered in this study and annually thereafter for those who remained alive. Whenever a match between the recipient's personal identifiers and the NDI database occurred, the NDI provided us with the date and codes for the cause(s) of death. The NDI database contains up to 20 codes describing the multiple causes of death. All codes describing the cause of death (underlying and additional contributing causes) were reviewed and recorded. When a code for a neurologic death was identified, the death certificate itself was obtained for review primarily to verify that CJD or some other mention of a prion disease was not listed on the certificate and possibly miscoded. In addition to enabling this verification, the death certificate may provide information on the duration of the illness and whether an autopsy was performed. Codes that triggered a request of the death certificate for a further review are listed in Table 1. The information received from NDI has an 18- to 24-month lag (e.g., the 2006 death index data first became available in 2008) because the vital statistics information is first compiled and coded by the states in which the death occurs, after which it is sent to NDI.

In addition to cross-matching recipient data with the NDI database, we annually queried AutotrackXP (Choicepoint, Inc., Boca Raton, FL) databases. AutotrackXP is a database that provides personal data sourced from multiple public and private databases. They enabled us to confirm the last known state of residence and the survival status of the recipients (e.g., a report of recent activity would indicate that the recipient was alive). For new recipients, we also used the Choicepoint databases to verify the recipients' names and social security numbers. Loss to follow-up occurred when a hospital did not provide us with identifying information for the recipient, but did provide us with the most recent health and vital status available (e.g., patient was alive and healthy at last visit, date of visit).

Statistical analysis

We analyzed the data in terms of the number of recipients of CJD donor blood components multiplied by each recipient's period in years of survival after the date of transfusion. Because the date of each donation was not collected, we used the transfusion date as a surrogate for it when determining the interval from the donation to onset of CJD in the donor. In the few situations where only the month and year were provided, the date was set as the 15th of the month and if only the year was provided the month and day was set to the middle of the year (July 1). Thus, this interval in months was calculated by determining the number of days between the date of onset of the CJD in the donor minus the date of transfusion in the recipient, dividing by 365 and multiplying by 12. This information, in turn, was categorized into seven groups: less than or equal to 12, 13 to 24, 25 to 36, 37 to 48, 49 to 60, 61 to 72, and 73 months and greater.

For recipients, their survival time was calculated by the interval between the date of transfusion and the last known date the recipient was alive or, if the recipient was known to be deceased, the interval between the date of transfusion and the date of death. Person-years were also determined for selected groups of recipients with different lengths of posttransfusion survival, such as recipients who had survived 5 or more years after transfusion ("long-term survivors").

We used Fisher's exact test to assess the difference in risk of blood transfusion transmission of CJD and vCJD among recipients who survived 5 years or longer after transfusion and received blood from a donor whose last donation occurred within 60 months of the onset of symptoms (donation-to-onset interval). The data on CJD were derived from the present study and the data on vCJD from the UK TMER study.[7] In the UK study, the three identified clinical cases of vCJD occurred among 21 recipients known to have survived 5 years or longer and whose donors had an onset-to-donation interval of 60 months or less (R.G. Will, personal communication, 2008).

RESULTS

Study donors

Forty-three blood donors who were subsequently diagnosed with CJD were reported for possible inclusion in this study. Of these 43, 7 were not included due to lack of response from the blood centers, absence of donations on file, or incomplete recipient records.

The CJD illness of all 36 identified study donors was diagnosed by a neurologist, and 58 percent (21/36) of

TABLE 1. Frequency for the top five ICD-9 and ICD-10 codes for the multiple causes of death and for codes that generated further investigation

Code	Grouping or frequency	Number
ICD-9 morbidity/mortality codes for deaths between 1978 and 1998		
ICD-9	*Five most frequent grouping of codes (total diagnosis codes 696 from 252 decedents*)*	
420.0-429.9	Other forms of heart disease	67
410.0-414.9	Ischemic heart disease	58
200.0-208.9	Malignant neoplasms of lymphatic and hematopoietic tissue	45
570.0-579.9	Other diseases of digestive system	37
280.0-289.9	Diseases of blood and blood-forming organs	34
	Frequency of codes that generated further investigation†	
046.1	CJD	0
310.9	Specific nonpsychotic mental disorders following organic brain damage, unspecified	1
331.9	Other cerebral degenerations, unspecified	0
341.9	Other demyelinating diseases of central nervous system, unspecified	0
348.8	Other conditions of brain	0
ICD-10 morbidity/mortality codes for deaths for 1999 through present		
ICD-10	*Five most frequent grouping of codes (total diagnosis codes 182 from 77 decedents*)*	
I30.0-I51.9	Other forms of heart disease (e.g., cardiac arrest, congestive heart failure, endocarditis)	21
I20.0-I25.9	Ischemic heart disease	18
N17.0-N19.9	Renal failure	15
I60.0-I69.9	Cerebrovascular disease	12
I10.0-I13.9	Hypertensive disease	8
	Frequency of codes that generated further investigation†	
A81.0	CJD	0
A81.2	Progressive multifocal leukoencephalopathy	0
A81.9	Atypical virus infection of central nervous system, unspecified	0
B94.8	Sequelae of other specified infectious and parasitic diseases	0
E85.2	Heredofamilial amyloidosis, unspecified	0
F03	Unspecified dementia	3
G20	Parkinson's disease	1
G30.0	Alzheimer's disease with early onset	0
G30.9	Alzheimer's disease, unspecified	1
G31.8	Other specified degenerative diseases of nervous system	0
G47.0	Disorders of initiating and maintaining sleep	0
G90	Disorders of the autonomic nervous system	0
G93.3	Postviral fatigue syndrome	0
G93.4	Encephalopathy, unspecified	0
G93.9	Disorder of brain, unspecified	0
G96.9	Disorder of central nervous system, unspecified	0
G98	Other disorders of nervous system, not elsewhere classified	0
R99	Other ill-defined and unspecified causes of mortality	0

* Mean number of multiple cause of death codes listed per decedent is 3 for both ICD-9 and ICD-10.
† Mean age at death for those decedents that triggered further investigation was 79.5 years (range, 64-101 years).

these diagnoses were autopsy and/or biopsy confirmed by examination of brain tissue. Of these 36 CJD donors, 34 (94%) were identified as sporadic CJD, 1 as familial CJD (E200K), and 1 as iatrogenic CJD.

These 36 donors donated blood in 16 states in the United States between 1970 and 2006. The mean age of these donors at onset of their CJD was 60 years (range, 39-74 years). The mean of reported donations made by the donors was 20 (range, 1-76). Not all of the donations yielded an enrolled recipient. Of the units linked to identified study recipients, red blood cells (238 units) were the most commonly received component, followed by platelets (75 units), and plasma (49 units) with the remaining units being other types of components such as whole blood, cryoprecipitate, and granulocytes (35 units).The transfusion service did not report the type of component received for 41 of the recipients.

Study recipients and the results of their follow-up

A total of 436 recipients were included in this lookback. Their median age at transfusion was 66.1 years (range, 4 days to 99 years). They received transfusions in 30 different states between 1970 and 2006.

As of the end of December 2006, 329 recipients (75.4%) were deceased, 91 (20.9%) were alive, and 16 (3.7%) were lost to follow-up. For those who died, the median age at death was 70.5 years (range, 8 months-101 years). None died with a diagnosis of CJD. The top five causes of death for the reported combined underlying cause and multiple causes of death groupings are listed in Table 1; ICD-9 codes were used for deaths occurring before 1999 and ICD-10 codes were used for deaths occurring for 1999 through present and the complete list can be found in Table 1. On average, the decedents had three multiple causes of death

TABLE 2. Distribution of recipients by vital status and the interval between their transfusion and their donor's onset of CJD

Interval between recipient's transfusion and donor's onset of CJD symptoms (months)	Alive	Deceased	Lost to follow-up	Total
≤12	17	44	5	66 (15.1%)
13-24	5	32	3	40 (9.2%)
25-36	12	50	1	63 (14.5%)
37-48	5	35	0	40 (9.2%)
49-60	8	43	0	51 (11.7%)
61-72	15	26	0	41 (9.4%)
≥73	29	99	7	135 (30.9%)
Total	91 (21%)	329 (75%)	16 (4%)	436 (100%)
Person-years followed	1199.25	832.25	64.5	2096.00

TABLE 3. Distribution of recipients by years of posttransfusion survival and the interval between transfusion and onset of CJD in donor

Interval between recipient's transfusion and donor's onset of CJD symptoms (months)	Posttransfusion survival (years)									
	≤4	5	6	7	8	9	10	≥11	≥5, subtotal	Total
≤12	47	2	0	0	7	1	3	6	19	66
13 to 24	31	0	0	1	1	1	2	4	9	40
25 to 36	51	0	2	1	0	0	1	8	12	63
37 to 48	27	0	2	2	0	1	2	6	13	40
49 to 60	36	1	3	2	0	1	0	8	15	51
61 to 72	19	1	3	0	2	2	2	12	22	41
≥73	81	3	1	5	4	4	1	36	54	135
Total	292	7	11	11	14	10	11	80	144	436

listed. Codes that triggered further investigation were 310.9, F03, G20, and G30.9 and occurred six times. Review of each of the six death certificates verified that none included any mention of prion diseases. The mean age of the six decedents was 79.5 years (range, 64-101 years; Table 1). Almost half (49%) of the recipients died within the first year after transfusion. The 2006 NDI results indicated that 91 recipients (all but 2 were adults) were still alive at the end December 31, 2006. Of these 89 adults, AutotrackXP subsequently provided further evidence that at least 85 percent of them were alive.

Recipients in the study were documented to have survived for a total of 2096.0 person-years after receipt of a blood component from a CJD donor (Table 2). The 329 deceased recipients contributed 832.25 of these person-years and the 91 recipients who were alive as of December 2006 contributed 1199.25 person-years. The remaining 16 recipients who were lost to follow-up had contributed 64.5 person-years.

A majority (60%) of the 436 recipients in this study received blood and components from CJD donors that were donated 60 months or less before their onset of CJD (Table 2). A total of 66 recipients received their units within 12 months or less of the donor's onset of CJD. Of the 260 recipients who received blood from donors 60 months or less before their donor's onset of CJD, 47 (18%) were still alive as of 2006.

Approximately one-third of the recipients survived 5 or more years after transfusion (Table 3). Within this group of long-term survivors, 68 recipients (46.8%) received blood that had been donated 60 months or less before onset of CJD in the donor.

We compared the risk associated with receipt of blood components donated 60 months or less before the onset of the prion disease in the CJD donors in the United States and the vCJD donors in the United Kingdom. Whereas in the United States, no case of CJD was identified among the 68 long-term surviving recipients of the blood components donated by the CJD donors within the 60-month period before their onset, in the United Kingdom 3 cases of vCJD (14%) were identified among 21 long-term surviving recipients of the blood components donated by the vCJD donors ($p = 0.012$, Fisher's exact test).

DISCUSSION

This study evaluates the risk of transfusion transmission of CJD in US blood recipients and compares the risk to that reported for vCJD in the United Kingdom. Overall, the US recipients survived for a total of 2096.0 person-years after receipt of a blood component from a CJD donor. No recipient was found to have been diagnosed with CJD. These results indicate that for the period studied, the risk, if any of transfusion transmission of CJD by CJD donors is significantly lower than the risk of transfusion transmission of vCJD by vCJD donors.

Although the incubation period for prion diseases can be very long, about 30 years or longer as observed

when environmental exposures can be reasonably estimated (e.g., Kuru, dural graft-associated CJD, and pituitary hormone-associated CJD), it is noteworthy that at least one case for each of these prion diseases has been observed within 10 years of an exposure. The present plan for evaluating transfusion transmission of CJD is to continue the current surveillance efforts and to continue to identify new recipients for at least another 5 years.

There could be a variety of reasons for not seeing a case of CJD in our recipient population. One of the most likely reasons is that CJD may not be transmitted by blood transfusion, unlike its variant counterpart. If the agent that causes CJD were present in human blood, its concentration might be too low to transmit an infection by the intravenous route. It is also possible that this study has not yet included enough donors and recipients to observe an infection or followed up on the study recipients long enough for them to have completed their incubation period.

The observation of zero cases of CJD among recipients in this study is consistent with the considerable additional data in the medical literature on the risk of transfusion transmission of human prion diseases that has recently been reviewed.[6] In addition to the UK TMER study, we are aware of a German lookback investigation of one blood donor who died of CJD. The donor had 27 definite recipients and 8 probable recipients (total, 35). None of the deceased recipients died from dementia or neurologic causes. Of the 14 who were alive at publication, none exhibited signs of dementia; the longest period of follow-up was 21 years.[14]

Through 2007, the proportion of vCJD cases among the long-term surviving recipients who received blood from a vCJD donor 60 months or less before onset of the donors' illness was 14 percent in the United Kingdom. In contrast, the present study identified no case of CJD among the 68 long-term surviving recipients of the blood components donated by the CJD donors within the 60-month period before their onset. In addition, the smaller UK study of blood components donated by CJD donors in the United Kingdom revealed no transfusion transmissions of CJD. Thus, the results of the present study in combination with the results from the TMER study in the United Kingdom strongly support the conclusion that the risk, if any, associated with receipt of blood components from CJD donors is significantly lower than that associated with receipt of blood components from vCJD donors.

The limitations of this study include the fact that 15 (42%) of the CJD donors enrolled in this study did not have their diagnosis confirmed neuropathologically. The CJD illness of each of these 15 donors was diagnosed by a neurologist and at least 11 of these donors had an electroencephalogram characteristic of CJD and/or a positive cerebrospinal fluid test for the neuron-specific enolase or 14-3-3 proteins. Nevertheless, it is possible that not all the recipients received blood from a true CJD donor.

Another limitation of this study is that we relied upon the US multiple cause of death data to identify CJD in recipients. The sensitivity of such data was assessed by a CDC study conducted in 1996, shortly after vCJD was first announced in the United Kingdom. Although this latter study did not allow for sufficient time for complete filing of all death records, it nevertheless found that the sensitivity of the death records compared to very active, alternative surveillance efforts was 86 percent.[4] In addition to this study, Davanipour and colleagues[20] found the false-positive rate of the death certificates to be 8.3 percent.

Assessment of risks of blood-borne transmission of diseases with potentially long latent periods is inherently limited by the poor survival of transfusion recipients. In the present study, for example, approximately 26 percent[21] of the recipients were alive 10 years after transfusion. Although this survival rate is low, it is consistent with another report of lookback investigations in which only 26 percent of the recipients had survived 10 or more years posttransfusion. Lookback investigations may be more inclined to have lower posttransfusion survival rates because they overrepresent recipients that receive multiple transfusions.[22,23] This relatively low survival rate contributes to the limited statistical power of the present study despite its being the largest study of its kind reported to date to assess the risk of transfusion transmission of CJD. Further detection and enrollment of donor/recipient clusters will continue to increase the power, and, if recipients remain free of CJD, will continue to provide the most direct evidence for the absence of CJD transmission by transfusion. Finally, another limitation encountered in this and other lookback investigations is the increasing difficulty in obtaining identifying information on all recipients. As hospital personnel have become more concerned about remaining in compliance with the federal medical privacy rule of the Health Insurance Portability and Accountability Act (HIPAA), our ability to obtain patient information has been reduced.

In addition to providing public health surveillance data on CJD and blood transfusions, our study provides important evidence demonstrating that compared to vCJD donors, CJD donors pose much less of a risk, if any, to blood safety. Precisely why this difference exists, however, is not fully understood, although clearly CJD and vCJD are different prion diseases. They are most prevalent in different age groups, their pathology and etiologic prion disease agents differ, and they are characterized by a different pattern and duration of clinical signs and symptoms.[5,6] As pointed out by the authors of the TMER study, the observed increased lymphoreticular involvement in vCJD compared to CJD is consistent with an increased transfusion-transmissibility of vCJD.[7,24] Further research may shed additional light on the pathophysiologic mechanisms that account for the greater transfusion transmissibility of vCJD compared to CJD.

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REFERENCES

1. Prusiner SB. Novel proteinaceous infectious particles causes scrapie. Science 1982;216:136-44.
2. Gambetti P, Kong Q, Zou W, Parchi P, Chen S. Sporadic and familial CJD: classification and characterisation. Br Med Bull 2003;66:213-39.
3. Belay ED, Schonberger LB. The public health impact of prion diseases. Annu Rev Public Health 2005;26: 191-212.
4. Centers for Disease Control and Prevention (CDC). Surveillance for Creutzfeldt-Jakob disease—United States. MMWR Morb Mortal Wkly Rep 1996;45:665-8.
5. Centers for Disease Control and Prevention. CJD (Creutzfeldt-Jakob disease, classic). Atlanta (GA): Centers for Disease Control and Prevention; 2008. [cited 2008 Apr 8]. Retrieved from: http://www.cdc.gov/ncidod/dvrd/cjd/
6. Food and Drug Administration: Center for Biologics Evaluation and Research (CBER). Guidance for industry-revised preventive measures to reduce the possible risk of transmission of Creutzfeldt-Jakob disease (CJD) and variant Creutzfeldt-Jakob disease (vCJD) by blood and blood products. [PDF file] Rockville (MD): U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER); 2002. [cited 2008 Jan 22]. Retrieved from: http://www.fda.gov/cber/gdlns/cjdvcjd.pdf
7. Hewitt PE, Llewelyn CA, Mackenzie RG. Creutzfeldt-Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiological Review study (TMER). Vox Sang 2006;91:221-30.
8. Zou S, Fang CT, Schonberger LB. Transfusion transmission of human prion diseases. Transfus Med Rev 2008;22:58-69.
9. Huillard d'Aignaux J, Costagliola D, Maccario J, Billette de Villemeur T, Brandel JP, Deslys JP, Hauw JJ, Chaussain JL, Agid Y, Dormont D, Alperovitch A. Incubation period of Creutzfeldt-Jakob disease in human growth hormone recipients in France. Neurology 1999;53:1197-201.
10. Preusser M, Strobel T, Gelpi E, Eller M, Broessner G, Schmutzhard E, Budka H. Alzheimer-type neuropathology in a 28 year old patient with iatrogenic Creutzfeldt-Jakob disease after dural grafting. J Neurol Neurosurg Psychiatry 2006;77:413-6.
11. The National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU). CJD statistics. Edinburgh: NCJDSU; 2008. [cited 2008 Apr 24]. Retrieved from: http://www.cjd.ed.ac.uk/figures.htm
12. National Prion Disease Pathology Surveillance Center. National prion disease pathology surveillance center: cases examined. Cleveland (OH): National Prion Disease Pathology Surveillance Center; 2007. [cited 2008 Apr 24]. Retrieved from: http://www.cjdsurveillance.com/pdf/case-table.pdf
13. Brown P. Pathogensis and transfusion risk of transmissible spongiform encephalopathies. Dev Biol Adv Transfus Saf 2005;120:27-33.
14. Heye N, Hensen S, Müller N. Creutzfeldt-Jakob disease and blood transfusion. Lancet (Comment) 1994;343: 298-9.
15. Wilson K, Code C, Ricketts M. Risk of acquiring Creutzfeldt-Jakob disease from blood transfusion: systematic review of case-control studies. Br J Med 2000; 231:17-9.
16. Bvatt B, Austin H, Barnhart E, Schonberger L, Sharer L, Jones R, DeArmond S. Surveillance for Creutzfeldt-Jakob disease among persons with hemophilia. Transfusion 1998; 38:817-20.
17. Lee CA, Ironside JW, Bell JE, Glangrande P, Ludlam C, Esiri MM, McLaughlin JE. Retrospective neuropathological review of prion disease in UK haemophilic patients. Thromb Haemost 1998;80:909-11.
18. Hunter N, Foster J, Chong A, McCutcheon S, Parnham D, Eaton S, MacKenzie C, Houston F. Transmission of prion diseases by blood transfusion. J Gen Virol 2002;83:2897-905.
19. Cervenakova L, Yakovlena O, McKenzie C, Kolchinsky S, McShane L, Drohan WN, Brown P. Similar levels of infectivity in the blood of mice infected with human-derived vCJD and GSS strains of transmissible spongiform encephalopathy. Transfusion 2003;43:1687-94.
20. Davanipour Z, Smoak C, Bohr T, Sobel E, Liwnicz B, Chang S. Death certificates: an efficient source of ascertainment of Creutzfeldt-Jakob disease cases. Neuroepidemiology 1995;14:1-6.
21. Dorsey KA, Zou S, Notari E IV, Fang C, Schonberger L. Survival Analysis of Blood Transfusion Recipients. The 135th Annual Meeting & Exposition of the American Public Health Association (APHA), November 3-7, 2007, Washington, DC. Abstract no. 157850. [cited 2008 Dec 10]. Retrieved from: http://apha.confex.com/apha/135am/techprogram/paper_157850.htm

22. Vamvakas EC. Ten-year survival of transfusion recipients identified by hepatitis C lookback. Transfusion 2003;43: 418.
23. Vamvakas EC. Uses and sources of data on long-term survival after blood transfusion. Transfus Med Rev 2003;17: 194-208.
24. Herzog C, Riviere J, Lescoutra-Etchegaray N, Charbonnier A, Leblanc V, Salès N, Deslys JP, Lasmézas CI. PrPTSE distribution in a primate model of variant, sporadic and iatrogenic Creutzfeldt-Jakob disease. J Virol 2005;79:14339-45.

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一般的名称	乾燥濃縮人アンチトロンビンIII					
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研究報告の概要 102	問題点（米国調査研究：輸血によるCJD伝播のエビデンス欠如） 米国赤十字社の報告である。2004年以降、英国でのvCJDの輸血による伝播が報告され、古典的CJDの伝播のリスクについての懸念が高まってきた。1995年に米国赤十字社は米国疾病対策センター（CDC）と共同して、輸血によるCJD伝播の懸念を評価する詳細な疫学データを得るために、供血後にCJDと診断された供血者（CJD donor）の長期遡及調査を開始し、CJD donorの供血から製造された血液製剤の受血者の追跡調査を実施した。調査コーディネーターは、共同している血液センター、患者家族、CDCやFDAからの情報によりCJD donorを特定した。血液事業者の記録調査及び医療施設との協力により、CJD donorの血液成分を投与された受血者を特定した。少なくとも受血者の一人が特定され、投与後少なくとも1日以上の生存記録があれば、そのCJD donorは本調査に登録される。受血者の生存状況また死亡の場合は死因を、CDCのNational Death Index (NDI)データベースで調査した。 36人の特定されたCJD donor（供血期間：1970年から2006年まで）のCJDの診断は、神経科医により行われ、その58%（21/36）は脳組織の剖検、生検が実施された。36人のCJD donorのうち、34人（94%）が孤発性CJD、1人が家族性CJD、1人が医原性CJDと特定された。 436人の受血者が本調査に登録され、2006年12月時点で329人（75.4%）が死亡、91人（20.9%）が生存、16人（3.7%）が脱落した。死亡者の平均年齢は70.5歳で、CJDの診断で死亡した人はなかった。 供血後60ヶ月未満にCJDを発症した供血者の血液を投与された受血者260人のうち、47人（18%）が2006年時点で生存していた。 受血者の約三分の一(144人)が輸血後5年以上生存していた。この長期生存者中60人の受血者(46.8%)がCJD発症60ヶ月未満に供血された血液を投与されていた。 米国のCJD発症60ヶ月未満に供血された血液成分を輸血された68人の長期生存者と英国でのvCJD donorの血液成分を輸血された21人の長期生存者のリスクを比較した。米国では死亡例がなく、英国では3例（14%）で有意に差があった（p=0.012、Fisher's exact test）。 CJD Donorは、血液の安全性にとって例えリスクがあったとしても、vCJD Donorと比較してリスクはより少ない。

報告企業の意見	今後の対応
当社製品を製造する原料血漿は、ドイツ、米国、オーストリア由来であり、またCJDの家族歴、英国等の滞在期間等に基づき供血停止基準を設けて収集している。 製造工程において異常プリオンを低減し得るとの報告があるものの、理論的なvCJD等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与することを添付文書に記載し、注意喚起している。	今後とも新しい感染症に関する情報収集に努める所存である。

使用上の注意記載状況・その他参考事項等

Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study

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BACKGROUND: Since 2004, several reported transfusion transmissions of variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom have reawakened concerns about the possible risk of similar transmissions of nonvariant or classic forms of CJD.

STUDY DESIGN AND METHODS: Patients with a CJD diagnosis and a history of donating blood were reported to the study coordinator. Through review of blood distribution and hospital records, the recipients of blood components from these donors were identified. We then determined each recipient's vital status and, if deceased, the cause(s) of death identified by matching the recipient's personal identifiers with the Centers for Disease Control and Prevention's National Death Index database. We conducted such searches after recipients were enrolled in this study and annually thereafter for those who remained alive.

RESULTS: The study included a total of 36 blood donors who subsequently developed CJD and 436 recipients. Through 2006, 91 of these recipients were still alive, 329 were deceased, and 16 were lost to follow-up. After transfusion, these three groups had survived a total of 2096.0 person-years. A total of 144 recipients survived 5 years or longer after transfusion and 68 of them had received blood donated 60 or fewer months before the onset of CJD in the donor. We identified no recipient with CJD.

CONCLUSIONS: The current results of this large, ongoing lookback study show no evidence of transfusion transmission of CJD. They reinforce the conclusion that the risk, if any, of transfusion transmission of prion disease by CJD donors is significantly lower than the comparable risk of such transmission by vCJD donors.

Variant Creutzfeldt-Jakob disease (vCJD) and the nonvariant or classic forms of Creutzfeldt-Jakob disease (CJD) of humans belong to a group of transmissible, fatal degenerative neurologic diseases called transmissible spongiform encephalopathies (TSEs). These diseases are also called prion diseases because of the formation and accumulation of an abnormal form of the prion protein (PrP^{sc}) that is hypothesized to play a central etiologic role in the disease process.[1] TSEs affect both humans and animals (e.g., bovine spongiform encephalopathy [commonly known as mad cow disease] in cattle; scrapie in sheep and goats; and chronic wasting disease in deer, elk, and moose).

Prion diseases in humans have been reported to occur sporadically without an apparent environmental source, through an inherited genetic mutation, or iatrogenically. Cases of familial CJD have occurred due to a mutated prion protein gene (PRNP) located on chromosome 20. More than 30 different mutations of the PRNP have been linked to familial human prion diseases. The most common familial CJD haplotypes are E200K-129M and D178N-129V.[2] Cases of iatrogenic CJD have been associated with exposures to contaminated neurosurgical equipment, human-derived pituitary growth hormone injections, cadaver-derived dura mater grafts, and corneal grafts.[3]

Surveillance of CJD in the United States has shown approximately one case annually per million people in the general population. Over many years, these rates have remained reasonably stable and the median age at death has consistently been approximately 68 years.[4,5]

Since the late 1980s, efforts have been made to minimize the potential risk of transfusion transmission of CJD, and in the 1990s the Food and Drug Administration (FDA) convened a TSE advisory committee, consisting of public interest advocates, ethicists, caregivers, and technical experts. Further, the FDA has issued a number of guidances for industry. These guidances attempt to balance the benefits of reducing the uncertain risks of prion disease transmission by blood products and the potential adverse impact that such preventive policies might have on product availability.[6]

Since 2004, transfusion transmission of the vCJD agent has been well documented. To date, the investigators conducting the UK Transfusion Medicine Epidemiological Review (TMER) study have linked three symptomatic cases of vCJD and one asymptomatic vCJD infection to receipt of blood transfusions from donors who subsequently developed vCJD (vCJD donor).[7,8] One blood donor was linked to two of the vCJD transmissions through donations, 21 and 17 months before the donors' onset of vCJD. These data suggest that once vCJD infectivity appears in blood it probably persists there. In addition to increasing concerns about the transmissibility of vCJD, these transfusion transmissions reawakened concerns and interest in blood safety and CJD. Both vCJD and CJD are invariably fatal and are caused by similar unconventional agents that are unusually resistant to inactivation. Incubation periods for vCJD and iatrogenic CJD are measured in years; there is no practical, licensed screening test to identify those who may be incubating these diseases.[9,10] Because CJD is far more common than vCJD, CJD might potentially affect even more recipients if, in fact, CJD were transmitted by blood transfusion.[11,12]

Surveillance and epidemiologic studies have provided the most reassuring data about blood safety and CJD, although very little long-term lookback data on donations from CJD donors have been reported.[8,13,14] Surveillance of high-exposure recipients, such as persons with hemophilia, and case-control studies show no evidence for transfusion transmission of CJD in humans.[15-17] In contrast, animal models have demonstrated that prion diseases can be transmitted by blood, a finding that aggravates concern about blood safety and CJD.[18,19] For example, studies comparing the infectivity in murine models of vCJD and Gerstmann-Straussler-Scheinker disease, a genetically inherited, classic (not bovine spongiform encephalopathy related) form of prion disease, revealed similarly low levels of infectivity in blood components during both the preclinical and the clinical phases of disease.[19]

In late 1994, a report of CJD in an American Red Cross 10-gallon donor heightened public health concerns in the United States about the possible transfusion transmission risk of CJD. Because of these concerns, in 1995 the Red Cross in collaboration with the Centers for Disease Control and Prevention (CDC) initiated a long-term lookback investigation of blood donors who were later diagnosed with CJD (CJD donors). The purpose of this collaborative study was to provide further epidemiologic data to assess the recurring concerns about the possibility of CJD transmission by blood transfusion. This article reports on the follow-up of the recipients of blood products from reported CJD donors. This study is the largest of its kind reported to date in terms of the number of such recipients identified and the period of time that they were documented to have survived after transfusion.

MATERIALS AND METHODS

CJD patients with a history of blood donation

The study coordinator identified CJD blood donors from reports provided by collaborating blood centers, family members, the CDC, and the FDA. Through searches of blood establishment records on donations made by the CJD donor and with the cooperation of hospitals, we identified recipients of the CJD donors' blood components.

Criteria for inclusion of a CJD donor in the study included a diagnosis of CJD made by a neurologist (and preferably confirmed by neuropathologic study of brain tissue at autopsy or biopsy) and a history of at least one documented allogeneic blood donation. (Autologous and therapeutic donations were not included.) We collected results of available diagnostic laboratory tests, cerebrospinal fluid studies, and electroencephalograms on the reported CJD donors. We notified the blood centers about the CJD donors and requested that each center review its records for each of the CJD donor's donations to identify the recipients of each donor's labile blood components. A CJD donor was entered in the study when at least one of these recipients was identified and could be documented to have survived for at least 1 day after receiving the blood components.

Recipients of blood products from donors who developed CJD

We requested that the transfusion service personnel send us information on each recipient of blood from a CJD

ABBREVIATIONS: NDI = National Death Index; TMER = Transfusion Medicine Epidemiological Review; TSE(s) = transmissible spongiform encephalopathy(-ies); vCJD = variant Creutzfeldt-Jakob disease.

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donor. This information included the recipient's name and social security number; data on the transfusion of concern, including date of transfusion and the volume and type of components transfused; and data on the last known vital status of the patient, including the date and cause of death if a recipient was deceased. The institutional review boards of the CDC and the Red Cross approved this protocol. No study-related recipient notification was required by the institutional review boards because of the absence of: 1) compelling evidence of transfusion transmission of CJD in humans, 2) any practical licensed test for preclinical CJD, and 3) any established treatment to prevent or cure CJD.

Follow-up of the recipients

For recipients for whom we had identifiers, we determined each recipient's vital status and cause(s) of death, if deceased, through searching the CDC's National Death Index (NDI) database (National Center for Health Statistics, Hyattsville, MD). We conducted such searches after a recipient was entered in this study and annually thereafter for those who remained alive. Whenever a match between the recipient's personal identifiers and the NDI database occurred, the NDI provided us with the date and codes for the cause(s) of death. The NDI database contains up to 20 codes describing the multiple causes of death. All codes describing the cause of death (underlying and additional contributing causes) were reviewed and recorded. When a code for a neurologic death was identified, the death certificate itself was obtained for review primarily to verify that CJD or some other mention of a prion disease was not listed on the certificate and possibly miscoded. In addition to enabling this verification, the death certificate may provide information on the duration of the illness and whether an autopsy was performed. Codes that triggered a request of the death certificate for a further review are listed in Table 1. The information received from NDI has an 18- to 24-month lag (e.g., the 2006 death index data first became available in 2008) because the vital statistics information is first compiled and coded by the states in which the death occurs, after which it is sent to NDI.

In addition to cross-matching recipient data with the NDI database, we annually queried AutotrackXP (Choicepoint, Inc., Boca Raton, FL) databases. AutotrackXP is a database that provides personal data sourced from multiple public and private databases. They enabled us to confirm the last known state of residence and the survival status of the recipients (e.g., a report of recent activity would indicate that the recipient was alive). For new recipients, we also used the Choicepoint databases to verify the recipients' names and social security numbers. Loss to follow-up occurred when a hospital did not provide us with identifying information for the recipient, but did provide us with the most recent health and vital status available (e.g., patient was alive and healthy at last visit, date of visit).

Statistical analysis

We analyzed the data in terms of the number of recipients of CJD donor blood components multiplied by each recipient's period in years of survival after the date of transfusion. Because the date of each donation was not collected, we used the transfusion date as a surrogate for it when determining the interval from the donation to onset of CJD in the donor. In the few situations where only the month and year were provided, the date was set as the 15th of the month and if only the year was provided the month and day was set to the middle of the year (July 1). Thus, this interval in months was calculated by determining the number of days between the date of onset of the CJD in the donor minus the date of transfusion in the recipient, dividing by 365 and multiplying by 12. This information, in turn, was categorized into seven groups: less than or equal to 12, 13 to 24, 25 to 36, 37 to 48, 49 to 60, 61 to 72, and 73 months and greater.

For recipients, their survival time was calculated by the interval between the date of transfusion and the last known date the recipient was alive or, if the recipient was known to be deceased, the interval between the date of transfusion and the date of death. Person-years were also determined for selected groups of recipients with different lengths of posttransfusion survival, such as recipients who had survived 5 or more years after transfusion ("long-term survivors").

We used Fisher's exact test to assess the difference in risk of blood transfusion transmission of CJD and vCJD among recipients who survived 5 years or longer after transfusion and received blood from a donor whose last donation occurred within 60 months of the onset of symptoms (donation-to-onset interval). The data on CJD were derived from the present study and the data on vCJD from the UK TMER study.[7] In the UK study, the three identified clinical cases of vCJD occurred among 21 recipients known to have survived 5 years or longer and whose donors had an onset-to-donation interval of 60 months or less (R.G. Will, personal communication, 2008).

RESULTS

Study donors

Forty-three blood donors who were subsequently diagnosed with CJD were reported for possible inclusion in this study. Of these 43, 7 were not included due to lack of response from the blood centers, absence of donations on file, or incomplete recipient records.

The CJD illness of all 36 identified study donors was diagnosed by a neurologist, and 58 percent (21/36) of these diagnoses were autopsy and/or biopsy confirmed by examination of brain tissue. Of these 36 CJD donors, 34 (94%) were identified as sporadic CJD, 1 as familial CJD (E200K), and 1 as iatrogenic CJD.

These 36 donors donated blood in 16 states in the United States between 1970 and 2006. The mean age of these donors at onset of their CJD was 60 years (range, 39-74 years). The mean of reported donations made by the donors was 20 (range, 1-76). Not all of the donations yielded an enrolled recipient. Of the units linked to identified study recipients, red blood cells (238 units) were the most commonly received component, followed by platelets (75 units), and plasma (49 units) with the remaining units being other types of components such as whole blood, cryoprecipitate, and granulocytes (35 units).The transfusion service did not report the type of component received for 41 of the recipients.

TABLE 1. Frequency for the top five ICD-9 and ICD-10 codes for the multiple causes of death and for codes that generated further investigation

Code	Grouping or frequency	Number
ICD-9 morbidity/mortality codes for deaths between 1978 and 1998		
ICD-9	*Five most frequent grouping of codes (total diagnosis codes 696 from 252 decedents*)*	
420.0-429.9	Other forms of heart disease	67
410.0-414.9	Ischemic heart disease	58
200.0-208.9	Malignant neoplasms of lymphatic and hematopoietic tissue	45
570.0-579.9	Other diseases of digestive system	37
280.0-289.9	Diseases of blood and blood-forming organs	34
	Frequency of codes that generated further investigation†	
046.1	CJD	0
310.9	Specific nonpsychotic mental disorders following organic brain damage, unspecified	1
331.9	Other cerebral degenerations, unspecified	0
341.9	Other demyelinating diseases of central nervous system, unspecified	0
348.8	Other conditions of brain	0
ICD-10 morbidity/mortality codes for deaths for 1999 through present		
ICD-10	*Five most frequent grouping of codes (total diagnosis codes 182 from 77 decedents*)*	
I30.0-I51.9	Other forms of heart disease (e.g., cardiac arrest, congestive heart failure, endocarditis)	21
I20.0-I25.9	Ischemic heart disease	18
N17.0-N19.9	Renal failure	15
I60.0-I69.9	Cerebrovasular disease	12
I10.0-I13.9	Hypertensive disease	8
	Frequency of codes that generated further investigation†	
A81.0	CJD	0
A81.2	Progressive multifocal leukoencephalopathy	0
A81.9	Atypical virus infection of central nervous system, unspecified	0
B94.8	Sequelae of other specified infectious and parasitic diseases	0
E85.2	Heredofamilial amyloidosis, unspecified	0
F03	Unspecified dementia	3
G20	Parkinson's disease	1
G30.0	Alzheimer's disease with early onset	0
G30.9	Alzheimer's disease, unspecified	1
G31.8	Other specified degenerative diseases of nervous system	0
G47.0	Disorders of initiating and maintaining sleep	0
G90	Disorders of the autonomic nervous system	0
G93.3	Postviral fatigue syndrome	0
G93.4	Encephalopathy, unspecified	0
G93.9	Disorder of brain, unspecified	0
G96.9	Disorder of central nervous system, unspecified	0
G98	Other disorders of nervous system, not elsewhere classified	0
R99	Other ill-defined and unspecified causes of mortality	0

* Mean number of multiple cause of death codes listed per decedent is 3 for both ICD-9 and ICD-10.
† Mean age at death for those decedents that triggered further investigation was 79.5 years (range, 64-101 years).

Study recipients and the results of their follow-up

A total of 436 recipients were included in this lookback. Their median age at transfusion was 66.1 years (range, 4 days to 99 years). They received transfusions in 30 different states between 1970 and 2006.

As of the end of December 2006, 329 recipients (75.4%) were deceased, 91 (20.9%) were alive, and 16 (3.7%) were lost to follow-up. For those who died, the median age at death was 70.5 years (range, 8 months-101 years). None died with a diagnosis of CJD. The top five causes of death for the reported combined underlying cause and multiple causes of death groupings are listed in Table 1; ICD-9 codes were used for deaths occurring before 1999 and ICD-10 codes were used for deaths occurring for 1999 through present and the complete list can be found in Table 1. On average, the decedents had three multiple causes of death

TABLE 2. Distribution of recipients by vital status and the interval between their transfusion and their donor's onset of CJD

Interval between recipient's transfusion and donor's onset of CJD symptoms (months)	Alive	Deceased	Lost to follow-up	Total
≤12	17	44	5	66 (15.1%)
13-24	5	32	3	40 (9.2%)
25-36	12	50	1	63 (14.5%)
37-48	5	35	0	40 (9.2%)
49-60	8	43	0	51 (11.7%)
61-72	15	26	0	41 (9.4%)
≥73	29	99	7	135 (30.9%)
Total	91 (21%)	329 (75%)	16 (4%)	436 (100%)
Person-years followed	1199.25	832.25	64.5	2096.00

TABLE 3. Distribution of recipients by years of posttransfusion survival and the interval between transfusion and onset of CJD in donor

Interval between recipient's transfusion and donor's onset of CJD symptoms (months)	Posttransfusion survival (years)									
	≤4	5	6	7	8	9	10	≥11	≥5, subtotal	Total
≤12	47	2	0	0	7	1	3	6	19	66
13 to 24	31	0	0	1	1	1	2	4	9	40
25 to 36	51	0	2	1	0	0	1	8	12	63
37 to 48	27	0	2	2	0	1	2	6	13	40
49 to 60	36	1	3	2	0	1	0	8	15	51
61 to 72	19	1	3	0	2	2	2	12	22	41
≥73	81	3	1	5	4	4	1	36	54	135
Total	292	7	11	11	14	10	11	80	144	436

listed. Codes that triggered further investigation were 310.9, F03, G20, and G30.9 and occurred six times. Review of each of the six death certificates verified that none included any mention of prion diseases. The mean age of the six decedents was 79.5 years (range, 64-101 years; Table 1). Almost half (49%) of the recipients died within the first year after transfusion. The 2006 NDI results indicated that 91 recipients (all but 2 were adults) were still alive at the end December 31, 2006. Of these 89 adults, AutotrackXP subsequently provided further evidence that at least 85 percent of them were alive.

Recipients in the study were documented to have survived for a total of 2096.0 person-years after receipt of a blood component from a CJD donor (Table 2). The 329 deceased recipients contributed 832.25 of these person-years and the 91 recipients who were alive as of December 2006 contributed 1199.25 person-years. The remaining 16 recipients who were lost to follow-up had contributed 64.5 person-years.

A majority (60%) of the 436 recipients in this study received blood and components from CJD donors that were donated 60 months or less before their onset of CJD (Table 2). A total of 66 recipients received their units within 12 months or less of the donor's onset of CJD. Of the 260 recipients who received blood from donors 60 months or less before their donor's onset of CJD, 47 (18%) were still alive as of 2006.

Approximately one-third of the recipients survived 5 or more years after transfusion (Table 3). Within this group of long-term survivors, 68 recipients (46.8%) received blood that had been donated 60 months or less before onset of CJD in the donor.

We compared the risk associated with receipt of blood components donated 60 months or less before the onset of the prion disease in the CJD donors in the United States and the vCJD donors in the United Kingdom. Whereas in the United States, no case of CJD was identified among the 68 long-term surviving recipients of the blood components donated by the CJD donors within the 60-month period before their onset, in the United Kingdom 3 cases of vCJD (14%) were identified among 21 long-term surviving recipients of the blood components donated by the vCJD donors ($p = 0.012$, Fisher's exact test).

DISCUSSION

This study evaluates the risk of transfusion transmission of CJD in US blood recipients and compares the risk to that reported for vCJD in the United Kingdom. Overall, the US recipients survived for a total of 2096.0 person-years after receipt of a blood component from a CJD donor. No recipient was found to have been diagnosed with CJD. These results indicate that for the period studied, the risk, if any of transfusion transmission of CJD by CJD donors is significantly lower than the risk of transfusion transmission of vCJD by vCJD donors.

Although the incubation period for prion diseases can be very long, about 30 years or longer as observed

when environmental exposures can be reasonably estimated (e.g., Kuru, dural graft-associated CJD, and pituitary hormone-associated CJD), it is noteworthy that at least one case for each of these prion diseases has been observed within 10 years of an exposure. The present plan for evaluating transfusion transmission of CJD is to continue the current surveillance efforts and to continue to identify new recipients for at least another 5 years.

There could be a variety of reasons for not seeing a case of CJD in our recipient population. One of the most likely reasons is that CJD may not be transmitted by blood transfusion, unlike its variant counterpart. If the agent that causes CJD were present in human blood, its concentration might be too low to transmit an infection by the intravenous route. It is also possible that this study has not yet included enough donors and recipients to observe an infection or followed up on the study recipients long enough for them to have completed their incubation period.

The observation of zero cases of CJD among recipients in this study is consistent with the considerable additional data in the medical literature on the risk of transfusion transmission of human prion diseases that has recently been reviewed.[8] In addition to the UK TMER study, we are aware of a German lookback investigation of one blood donor who died of CJD. The donor had 27 definite recipients and 8 probable recipients (total, 35). None of the deceased recipients died from dementia or neurologic causes. Of the 14 who were alive at publication, none exhibited signs of dementia; the longest period of follow-up was 21 years.[14]

Through 2007, the proportion of vCJD cases among the long-term surviving recipients who received blood from a vCJD donor 60 months or less before onset of the donors' illness was 14 percent in the United Kingdom. In contrast, the present study identified no case of CJD among the 68 long-term surviving recipients of the blood components donated by the CJD donors within the 60-month period before their onset. In addition, the smaller UK study of blood components donated by CJD donors in the United Kingdom revealed no transfusion transmissions of CJD. Thus, the results of the present study in combination with the results from the TMER study in the United Kingdom strongly support the conclusion that the risk, if any, associated with receipt of blood components from CJD donors is significantly lower than that associated with receipt of blood components from vCJD donors.

The limitations of this study include the fact that 15 (42%) of the CJD donors enrolled in this study did not have their diagnosis confirmed neuropathologically. The CJD illness of each of these 15 donors was diagnosed by a neurologist and at least 11 of these donors had an electroencephalogram characteristic of CJD and/or a positive cerebrospinal fluid test for the neuron-specific enolase or 14-3-3 proteins. Nevertheless, it is possible that not all the recipients received blood from a true CJD donor.

Another limitation of this study is that we relied upon the US multiple cause of death data to identify CJD in recipients. The sensitivity of such data was assessed by a CDC study conducted in 1996, shortly after vCJD was first announced in the United Kingdom. Although this latter study did not allow for sufficient time for complete filing of all death records, it nevertheless found that the sensitivity of the death records compared to very active, alternative surveillance efforts was 86 percent.[4] In addition to this study, Davanipour and colleagues[20] found the false-positive rate of the death certificates to be 8.3 percent.

Assessment of risks of blood-borne transmission of diseases with potentially long latent periods is inherently limited by the poor survival of transfusion recipients. In the present study, for example, approximately 26 percent[21] of the recipients were alive 10 years after transfusion. Although this survival rate is low, it is consistent with another report of lookback investigations in which only 26 percent of the recipients had survived 10 or more years posttransfusion. Lookback investigations may be more inclined to have lower posttransfusion survival rates because they overrepresent recipients that receive multiple transfusions.[22,23] This relatively low survival rate contributes to the limited statistical power of the present study despite its being the largest study of its kind reported to date to assess the risk of transfusion transmission of CJD. Further detection and enrollment of donor/recipient clusters will continue to increase the power, and, if recipients remain free of CJD, will continue to provide the most direct evidence for the absence of CJD transmission by transfusion. Finally, another limitation encountered in this and other lookback investigations is the increasing difficulty in obtaining identifying information on all recipients. As hospital personnel have become more concerned about remaining in compliance with the federal medical privacy rule of the Health Insurance Portability and Accountability Act (HIPAA), our ability to obtain patient information has been reduced.

In addition to providing public health surveillance data on CJD and blood transfusions, our study provides important evidence demonstrating that compared to vCJD donors, CJD donors pose much less of a risk, if any, to blood safety. Precisely why this difference exists, however, is not fully understood, although clearly CJD and vCJD are different prion diseases. They are most prevalent in different age groups, their pathology and etiologic prion disease agents differ, and they are characterized by a different pattern and duration of clinical signs and symptoms.[5,6] As pointed out by the authors of the TMER study, the observed increased lymphoreticular involvement in vCJD compared to CJD is consistent with an increased transfusion-transmissibility of vCJD.[7,24] Further research may shed additional light on the pathophysiologic

mechanisms that account for the greater transfusion transmissibility of vCJD compared to CJD.

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REFERENCES

1. Prusiner SB. Novel proteinaceous infectious particles causes scrapie. Science 1982;216:136-44.
2. Gambetti P, Kong Q, Zou W, Parchi P, Chen S. Sporadic and familial CJD: classification and characterisation. Br Med Bull 2003;66:213-39.
3. Belay ED, Schonberger LB. The public health impact of prion diseases. Annu Rev Public Health 2005;26: 191-212.
4. Centers for Disease Control and Prevention (CDC). Surveillance for Creutzfeldt-Jakob disease—United States. MMWR Morb Mortal Wkly Rep 1996;45:665-8.
5. Centers for Disease Control and Prevention. CJD (Creutzfeldt-Jakob disease, classic). Atlanta (GA): Centers for Disease Control and Prevention; 2008. [cited 2008 Apr 8]. Retrieved from: http://www.cdc.gov/ncidod/dvrd/cjd/
6. Food and Drug Administration: Center for Biologics Evaluation and Research (CBER). Guidance for industry-revised preventive measures to reduce the possible risk of transmission of Creutzfeldt-Jakob disease (CJD) and variant Creutzfeldt-Jakob disease (vCJD) by blood and blood products. [PDF file] Rockville (MD): U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER); 2002. [cited 2008 Jan 22]. Retrieved from: http://www.fda.gov/cber/gdlns/cjdvcjd.pdf
7. Hewitt PE, Llewelyn CA, Mackenzie RG. Creutzfeldt-Jakob disease and blood transfusion: results of the UK Transfusion Medicine Epidemiological Review study (TMER). Vox Sang 2006;91:221-30.
8. Zou S, Fang CT, Schonberger LB. Transfusion transmission of human prion diseases. Transfus Med Rev 2008;22:58-69.
9. Huillard d'Aignaux J, Costagliola D, Maccario J, Billette de Villemeur T, Brandel JP, Deslys JP, Hauw JJ, Chaussain JL, Agid Y, Dormont D, Alperovitch A. Incubation period of Creutzfeldt-Jakob disease in human growth hormone recipients in France. Neurology 1999;53:1197-201.
10. Preusser M, Strobel T, Gelpi E, Eller M, Broessner G, Schmutzhard E, Budka H. Alzheimer-type neuropathology in a 28 year old patient with iatrogenic Creutzfeldt-Jakob disease after dural grafting. J Neurol Neurosurg Psychiatry 2006;77:413-6.
11. The National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU). CJD statistics. Edinburgh: NCJDSU; 2008. [cited 2008 Apr 24]. Retrieved from: http://www.cjd.ed.ac.uk/figures.htm
12. National Prion Disease Pathology Surveillance Center. National prion disease pathology surveillance center: cases examined. Cleveland (OH): National Prion Disease Pathology Surveillance Center; 2007. [cited 2008 Apr 24]. Retrieved from: http://www.cjdsurveillance.com/pdf/case-table.pdf
13. Brown P. Pathogensis and transfusion risk of transmissible spongiform encephalopathies. Dev Biol Adv Transfus Saf 2005;120:27-33.
14. Heye N, Hensen S, Müller N. Creutzfeldt-Jakob disease and blood transfusion. Lancet (Comment) 1994;343: 298-9.
15. Wilson K, Code C, Ricketts M. Risk of acquiring Creutzfeldt-Jakob disease from blood transfusion: systematic review of case-control studies. Br J Med 2000; 231:17-9.
16. Evatt B, Austin H, Barnhart E, Schonberger L, Sharer L, Jones R, DeArmond S. Surveillance for Creutzfeldt-Jakob disease among persons with hemophilia. Transfusion 1998; 38:817-20.
17. Lee CA, Ironside JW, Bell JE, Giangrande P, Ludlam C, Esiri MM, McLaughlin JE. Retrospective neuropathological review of prion disease in UK haemophilic patients. Thromb Haemost 1998;80:909-11.
18. Hunter N, Foster J, Chong A, McCutcheon S, Parnham D, Eaton S, MacKenzie C, Houston F. Transmission of prion diseases by blood transfusion. J Gen Virol 2002;83:2897-905.
19. Cervenakova L, Yakovlena O, McKenzie C, Kolchinsky S, McShane L, Drohan WN, Brown P. Similar levels of infectivity in the blood of mice infected with human-derived vCJD and GSS strains of transmissible spongiform encephalopathy. Transfusion 2003;43:1687-94.
20. Davanipour Z, Smoak C, Bohr T, Sobel E, Liwnicz B, Chang S. Death certificates: an efficient source of ascertainment of Creutzfeldt-Jakob disease cases. Neuroepidemiology 1995;14:1-6.
21. Dorsey KA, Zou S, Notari E IV, Fang C, Schonberger L. Survival Analysis of Blood Transfusion Recipients. The 135th Annual Meeting & Exposition of the American Public Health Association (APHA), November 3-7, 2007, Washington, DC. Abstract no. 157850. [cited 2008 Dec 10]. Retrieved from: http://apha.confex.com/apha/135am/techprogram/paper_157850.htm

22. Vamvakas EC. Ten-year survival of transfusion recipients identified by hepatitis C lookback. Transfusion 2003;43: 418.
23. Vamvakas EC. Uses and sources of data on long-term survival after blood transfusion. Transfus Med Rev 2003;17: 194-208.
24. Herzog C, Riviere J, Lescoutra-Etchegaray N, Charbonnier A, Leblanc V, Salès N, Deslys JP, Lasmézas CI. PrPTSE distribution in a primate model of variant, sporadic, and iatrogenic Creutzfeldt-Jakob disease. J Virol 2005;79:14339-45.